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(54) Title: THERAPEUTIC COMBINATIONS OF A BTK INHIBITOR, A PI3K INHIBITOR, A JAK-2 INHIBITOR AND/OR A CDK 4/6 INHIBITOR

(57) Abstract: Therapeutic combinations of a phosphoinositide 3-kinase (PI3K) inhibitor, including PI3K inhibitors selective for the γ- and δ-isoforms and selective for both γ- and δ-isoforms (PI3Kγ-δ, PI3Kγ, and PI3Kδ, a Janus kinase-2 (JAK-2) inhibitor, a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor, and/or a Bruton's tyrosine kinase (BTK) inhibitor) are described. In certain embodiments, the invention includes therapeutic combinations of a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor and a BTK inhibitor, a PI3K-δ inhibitor and a BTK inhibitor, a JAK-2 and a BTK inhibitor, and a JAK-2, PI3K-δ, and BTK inhibitor.

![Graph](image-url)
THERAPEUTIC COMBINATIONS OF A BTK INHIBITOR, A PI3K INHIBITOR, A JAK-2 INHIBITOR, AND/OR A CDK4/6 INHIBITOR

CROSS-REFERENCE TO RELATED APPLICATIONS

[001] This application claims the benefit of U.S. Provisional Application No. 62/035,806 filed on August 11, 2014; U.S. Provisional Application No. 62/088,371 filed on December 5, 2014; U.S. Provisional Application No. 62/115,512 filed on February 12, 2015; and U.S. Provisional Application No. 62/181,163 filed on June 17, 2015, all of which are herein incorporated by reference in their entireties.

FIELD OF THE INVENTION

[002] Therapeutic combinations of a Bruton’s tyrosine kinase (BTK) inhibitor, a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor, a phosphoinositide 3-kinase (PI3K) inhibitor, and/or a Janus kinase-2 (JAK-2) inhibitor, and uses of the therapeutic combinations are disclosed herein.

BACKGROUND OF THE INVENTION

[003] PI3K kinases are members of a unique and conserved family of intracellular lipid kinases that phosphorylate the 3’-OH group on phosphatidylinositols or phosphoinositides. PI3K kinases are key signaling enzymes that relay signals from cell surface receptors to downstream effectors. The PI3K family comprises 15 kinases with distinct substrate specificities, expression patterns, and modes of regulation. The class I PI3K kinases (p110α, p110β, p110δ, and p110γ) are typically activated by tyrosine kinases or G-protein coupled receptors to generate PIP3, which engages downstream effectors such as those in the Akt/PDK1 pathway, mTOR, the Tec family kinases, and the Rho family GTPases.

[004] The PI3K signaling pathway is known to be one of the most highly mutated in human cancers. PI3K signaling is also a key factor in disease states including hematologic malignancies, non-Hodgkin lymphoma (such as diffuse large B-cell lymphoma), allergic contact dermatitis, rheumatoid arthritis, osteoarthritis, inflammatory bowel diseases, chronic obstructive pulmonary disorder, psoriasis, multiple sclerosis, asthma, disorders related to diabetic complications, and inflammatory complications of the cardiovascular system such as acute coronary syndrome. The role of PI3K in cancer has been discussed, for example, in Engleman,

[005] The delta (δ) isoform of class I PI3K (PI3K-δ) is involved in mammalian immune system functions such as T-cell function, B-cell activation, mast cell activation, dendritic cell function, and neutrophil activity. Due to its role in immune system function, PI3K-δ is also involved in a number of diseases related to undesirable immune response such as allergic reactions, inflammatory diseases, inflammation mediated angiogenesis, rheumatoid arthritis, auto-immune diseases such as lupus, asthma, emphysema and other respiratory diseases. The gamma (γ) isoform of class I PI3K (PI3K-γ) is also involved in immune system functions and plays a role in leukocyte signaling and has been implicated in inflammation, rheumatoid arthritis, and autoimmune diseases such as lupus.

[006] Downstream mediators of the PI3K signal transduction pathway include Akt and mammalian target of rapamycin (mTOR). One important function of Akt is to augment the activity of mTOR, through phosphorylation of TSC2 and other mechanisms. mTOR is a serine-threonine kinase related to the lipid kinases of the PI3K family and has been implicated in a wide range of biological processes including cell growth, cell proliferation, cell motility and survival. Disregulation of the mTOR pathway has been reported in various types of cancer.

[007] In view of the above, PI3K inhibitors are prime targets for drug development, as described in Kurt and Ray-Coquard, Anticancer Res. 2012, 32, 2463-70. Several PI3K inhibitors are known, including those those that are PI3K-δ inhibitors, PI3K-γ inhibitors and those that are PI3K-δ,γ inhibitors.

[008] Bruton’s Tyrosine Kinase (BTK) is a Tec family non-receptor protein kinase expressed in B cells and myeloid cells. The function of BTK in signaling pathways activated by the engagement of the B cell receptor (BCR) and FCER1 on mast cells is well established. Functional mutations in BTK in humans result in a primary immunodeficiency disease characterized by a defect in B cell development with a block between pro- and pre-B cell stages. The result is an almost complete absence of B lymphocytes, causing a pronounced reduction of serum immunoglobulin of all classes. These findings support a key role for BTK in the regulation of the production of auto-antibodies in autoimmune diseases.
[009] Other diseases with an important role for dysfunctional B cells are B cell malignancies. The reported role for BTK in the regulation of proliferation and apoptosis of B cells indicates the potential for BTK inhibitors in the treatment of B cell lymphomas. BTK inhibitors have thus been developed as potential therapies, as described in D’Cruz and Uckun, *OncoTargets and Therapy* 2013, 6, 161-176.

[0010] JAK-2 is an enzyme that is a member of the Janus kinase family of four cytoplasmic tyrosine kinases that also includes JAK-1, JAK-3, and Tyk2 (tyrosine kinase 2). The Janus kinase family transduces cytokine-mediated signals as part of the JAK-STAT signalling pathway (where STAT is an acronym for “signal transducer and activator of transcription”), as described in Ghoreschi, et al., Janus kinases in immune cell signaling. *Immunol. Rev.* 2009, 228, 273-287. The JAK-STAT pathway mediates signalling by cytokines that affects proliferation, differentiation, and survival in many cell types, and is commonly expressed in leukocytes. The Janus kinase family of enzymes is required for signaling by cytokine and growth factor receptors that lack intrinsic kinase activity. JAK-2 is implicated in signaling processes by members of the type II cytokine receptor family (such as interferon receptors), the GM-CSF receptor family (IL-3R, IL-5R and GM-CSF-R), the gp130 receptor family (e.g. IL-6R), and the single chain receptors (e.g. Epo-R, Tpo-R, GH-R, PRL-R), as described in U.S. Patent Application Publication No. 2012/0157500, the disclosure of which is incorporated herein by reference. JAK-2 signaling is activated downstream from the prolactin receptor. JAK-2 inhibitors were developed after discovery of an activating tyrosine kinase mutation (the V617F mutation) in myeloproliferative cancers and disorders. JAK-2 inhibitors have been developed as potential therapies for myeloproliferative neoplasms, polycythemia vera, essential thrombocythemia, and primary myelofibrosis, as discussed in Verstovsek, Therapeutic potential of JAK2 inhibitors, *Hematology (American Society of Hematology Education Book)*, 2009, 636-642. JAK-2 inhibitors may reverse hyperphosphorylation of JAK-2 and effectively treat myeloproliferative cancers and disorders.

[0011] Cyclin-dependent kinase 4 (CDK-4), which is also known as cell division protein kinase 4 is an enzyme encoded by the CDK-4 gene, while cyclin-dependent kinase 6 (CDK-6) is similarly encoded by the CDK-6 gene. Both CDK-4 and 6 are catalytic subunits of the protein kinase complex and are important during the cell cycle including during the G1 phase progression and the G1/S transition. CDK4/6 are known to be unbalanced in many tumors, as
described in Aarts et al., Cur. Opin. Pharmacol., 2013, 13, 529–535. As a result, CDK4/6 inhibitors have been explored for treatment of diseases such as breast cancer, as described in Finn et al., Breast Cancer Res. 2009, 11, R77.

[0012] In many solid tumors, the supportive microenvironment (which may make up the majority of the tumor mass) is a dynamic force that enables tumor survival. The tumor microenvironment is generally defined as a complex mixture of “cells, soluble factors, signaling molecules, extracellular matrices, and mechanical cues that promote neoplastic transformation, support tumor growth and invasion, protect the tumor from host immunity, foster therapeutic resistance, and provide niches for dominant metastases to thrive,” as described in Swartz et al., Cancer Res., 2012, 72, 2473. Although tumors express antigens that should be recognized by T cells, tumor clearance by the immune system is rare because of immune suppression by the microenvironment. Addressing the tumor cells themselves with e.g. chemotherapy has also proven to be insufficient to overcome the protective effects of the microenvironment. New approaches are thus urgently needed for more effective treatment of solid tumors that take into account the role of the microenvironment.

[0013] The present invention provides the unexpected finding that combinations of a PI3K inhibitor, a CDK4/6 inhibitor, and/or a BTK inhibitor is effective in the treatment of any of several types of cancers such as leukemia, lymphoma and solid tumor cancers. The present invention provides the unexpected finding that the combination of a CDK4/6 inhibitor and a BTK inhibitor is effective in the treatment of any of several types of cancers such as leukemia, lymphoma and solid tumor cancers. The present invention also provides the unexpected finding that the combination of a JAK-2 inhibitor and a BTK inhibitor is effective in the treatment of any of several types of cancers such as leukemia, lymphoma and solid tumor cancers. The present invention further provides the unexpected discovery that the combination of a JAK-2 inhibitor, a PI3K inhibitor, and/or a BTK inhibitor is effective in the treatment of any of several types of cancers such as leukemia, lymphoma and solid tumor cancers.

SUMMARY OF THE INVENTION

[0014] In one embodiment, the invention provides a composition comprising (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, and (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a
pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. This composition is typically a pharmaceutical composition.

[0015] In one embodiment, the invention provides a composition comprising (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (3) a phosphoinositide 3-kinase (PI3K) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. This composition is typically a pharmaceutical composition.

[0016] In one embodiment, the invention provides a composition comprising (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (3) a PI3K-δ inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. This composition is typically a pharmaceutical composition.

[0017] In one embodiment, the invention provides a composition comprising (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (3) an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof. This composition is typically a pharmaceutical composition.

[0018] In one embodiment, the invention provides a composition comprising (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a phosphoinositide 3-kinase (PI3K) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (4) an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab,
and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof. This composition is typically a pharmaceutical composition.

[0019] In one embodiment, the invention provides a composition comprising (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a PI3K-δ inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (4) an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof. This composition is typically a pharmaceutical composition.

[0020] In one embodiment, the invention provides a composition comprising (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (3) a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. This composition is typically a pharmaceutical composition.

[0021] In one embodiment, the invention provides a composition comprising (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a phosphoinositide 3-kinase (PI3K) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (4) a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. This composition is typically a pharmaceutical composition.

[0022] In one embodiment, the invention provides a composition comprising (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a PI3K-δ inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof;
and (4) a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. This composition is typically a pharmaceutical composition.

[0023] In one embodiment, the invention provides a composition comprising (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof; and (4) a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. This composition is typically a pharmaceutical composition.

[0024] In one embodiment, the invention provides a composition comprising (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a phosphoinositide 3-kinase (PI3K) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (4) an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof; and (5) a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. This composition is typically a pharmaceutical composition.

[0025] In one embodiment, the invention provides a composition comprising (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a PI3K-δ inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (4) an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof; and (5) a JAK-2 inhibitor or a
pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. This composition is typically a pharmaceutical composition.

[0026] In one embodiment, the invention provides a composition comprising (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (2) a BTK inhibitor having the structure:

![Chemical structure](image)

or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof. This composition is typically a pharmaceutical composition.

[0027] In one embodiment, the invention provides a composition comprising (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a BTK inhibitor having the structure:
or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof; and (3) a PI3K inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. This composition is typically a pharmaceutical composition.

[0028] In one embodiment, the invention provides a composition comprising (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a BTK inhibitor having the structure:
or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof; and (3) a PI3K-δ inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. This composition is typically a pharmaceutical composition.

[0029] In one embodiment, the invention provides a composition comprising (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a BTK inhibitor having the structure:
or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (3) an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof. This composition is typically a pharmaceutical composition.

[0030] In one embodiment, the invention provides a composition comprising (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (2) a BTK inhibitor having the structure:
or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a phosphoinositide 3-kinase (PI3K) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (4) an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof. This composition is typically a pharmaceutical composition.

[0031] In one embodiment, the invention provides a composition comprising (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate,
cocrystal, or prodrug thereof; and (2) a BTK inhibitor having the structure:

![BTK Inhibitor Structure]

[0032] or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a PI3K-δ inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (4) an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof. This composition is typically a pharmaceutical composition.

[0033] In one embodiment, the invention provides a composition comprising (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (2) a BTK inhibitor having the structure:
or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (3) a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. This composition is typically a pharmaceutical composition.

[0034] In one embodiment, the invention provides a composition comprising (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (2) a BTK inhibitor having the structure:
or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a phosphoinositide 3-kinase (PI3K) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (4) a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

This composition is typically a pharmaceutical composition.

[0035] In one embodiment, the invention provides a composition comprising (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (2) a BTK inhibitor having the structure:
or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a PI3K-δ inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (4) a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. This composition is typically a pharmaceutical composition.

[0036] In one embodiment, the invention provides a composition comprising (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (2) a BTK inhibitor having the structure:
or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof; and (4) a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. This composition is typically a pharmaceutical composition.

[0037] In one embodiment, the invention provides a composition comprising (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (2) a BTK inhibitor having the structure:
or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof; (2) a
Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate,
cocrystal, or prodrug thereof; (3) a phosphoinositide 3-kinase (PI3K) inhibitor or a
pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (4) an anti-
CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab,
veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants,
radioisotope-labeled complexes, and biosimilars thereof; and (5) a JAK-2 inhibitor or a
pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. This
composition is typically a pharmaceutical composition.

[0038] In one embodiment, the invention provides a composition comprising (1) a cyclin-
dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate,
cocrystal, or prodrug thereof; and (2) a BTK inhibitor having the structure:
or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a PI3K-δ inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (4) an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof; and (5) a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. This composition is typically a pharmaceutical composition.

[0039] In one embodiment, the invention provides a composition comprising (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, and (2) a BTK inhibitor is selected from the group consisting of ibrutinib:
and pharmaceutically-acceptable salts, cocrystals, hydrates, solvates, or prodrugs thereof. This composition is typically a pharmaceutical composition.

[0040] In one embodiment, the invention provides a composition comprising (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a BTK inhibitor is selected from the group consisting of ibrutinib:

![Chemical structures](image1)

and pharmaceutically-acceptable salts, cocrystals, hydrates, solvates, or prodrugs thereof; and (3) a phosphoinositide 3-kinase (PI3K) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. This composition is typically a pharmaceutical composition.
[0041] In one embodiment, the invention provides a composition comprising (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a BTK inhibitor is selected from the group consisting of ibrutinib:

\[ \text{Chemical Structures} \]

and pharmaceutically-acceptable salts, cocrystals, hydrates, solvates, or prodrugs thereof; and (3) a PI3K-δ inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. This composition is typically a pharmaceutical composition.

[0042] In one embodiment, the invention provides a composition comprising (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a BTK inhibitor is selected from the group consisting of ibrutinib:
and pharmaceutically-acceptable salts, cocrystals, hydrates, solvates, or prodrugs thereof; and (3) an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibrutinomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof. This composition is typically a pharmaceutical composition.

[0043] In one embodiment, the invention provides a composition comprising (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a BTK inhibitor is selected from the group consisting of ibrutinib:

pharmaceutically-acceptable salts, cocrystals, hydrates, solvates, or prodrugs thereof; (3) a
phosphoinositide 3-kinase (PI3K) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (4) an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof. This composition is typically a pharmaceutical composition.

[0044] In one embodiment, the invention provides a composition comprising (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a BTK inhibitor is selected from the group consisting of ibrutinib:

pharmaceutically-acceptable salts, cocrystals, hydrates, solvates, or prodrugs thereof; (3) a PI3K-δ inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (4) an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof. This composition is typically a pharmaceutical composition.

[0045] In one embodiment, the invention provides a composition comprising (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a BTK inhibitor is selected from the group consisting of ibrutinib:
(1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a BTK inhibitor is selected from the group consisting of ibrutinib:

(3) a phosphoinositide 3-kinase (PI3K) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (4) a JAK-2 inhibitor or a pharmaceutically acceptable salts, cocrystals, hydrates, solvates, or prodrugs thereof; and (3) a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. This composition is typically a pharmaceutical composition.

[0046] In one embodiment, the invention provides a composition comprising (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a BTK inhibitor is selected from the group consisting of ibrutinib:
acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. This composition is typically a pharmaceutical composition.

[0047] In one embodiment, the invention provides a composition comprising (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a BTK inhibitor is selected from the group consisting of ibrutinib:

![Chemical structures](image)

and pharmaceutically-acceptable salts, cocrystals, hydrates, solvates, or prodrugs thereof; (3) a PI3K-δ inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (4) a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. This composition is typically a pharmaceutical composition.

[0048] In one embodiment, the invention provides a composition comprising (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a BTK inhibitor is selected from the group consisting of ibrutinib:
(2) a BTK inhibitor is selected from the group consisting of ibrutinib:
pharmaceutically-acceptable salts, cocrystals, hydrates, solvates, or prodrugs thereof; (3) a phosphoinositide 3-kinase (PI3K) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (4) an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof; and (5) a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. This composition is typically a pharmaceutical composition.

In one embodiment, the invention provides a composition comprising (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a BTK inhibitor is selected from the group consisting of ibrutinib:
pharmaceutically-acceptable salts, cocrystals, hydrates, solvates, or prodrugs thereof; (3) a PI3K-δ inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (4) an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof; and (5) a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. This composition is typically a pharmaceutical composition.

[0051] In one embodiment, the invention provides a composition comprising (1) a CDK4/6 inhibitor selected from palbociclib:

c or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof; and (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. This composition is typically a pharmaceutical composition.

[0052] In one embodiment, the invention provides a composition comprising (1) a CDK4/6 inhibitor selected from palbociclib:
or a pharmaceutically-acceptable salt, cocrystal, hydate, solvate, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (3) a phosphoinositide 3-kinase (PI3K) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. This composition is typically a pharmaceutical composition.

[0053] In one embodiment, the invention provides a composition comprising (1) a CDK4/6 inhibitor selected from palbociclib:

or a pharmaceutically-acceptable salt, cocrystal, hydate, solvate, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (3) a PI3K-δ inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. This composition is typically a pharmaceutical composition.

[0054] In one embodiment, the invention provides a composition comprising (1) a CDK4/6 inhibitor selected from palbociclib:
(1) a CDK4/6 inhibitor selected from palbociclib; or a pharmaceutically-acceptable salt, cocrystal, hydate, solvate, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (3) an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof. This composition is typically a pharmaceutical composition.

[0055] In one embodiment, the invention provides a composition comprising (1) a CDK4/6 inhibitor selected from palbociclib:
and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof. This composition is typically a pharmaceutical composition.

[0056] In one embodiment, the invention provides a composition comprising (1) a CDK4/6 inhibitor selected from palbociclib:

![Chemical structure of a CDK4/6 inhibitor](image)

or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a PI3K-δ inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (4) an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof. This composition is typically a pharmaceutical composition.

[0057] In one embodiment, the invention provides a composition comprising (1) a CDK4/6 inhibitor selected from palbociclib:
or a pharmaceutically-acceptable salt, cocrystal, hydate, solvate, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate,hydrate, cocrystal, or prodrug thereof; and (3) a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. This composition is typically a pharmaceutical composition.

[0058] In one embodiment, the invention provides a composition comprising (1) a CDK4/6 inhibitor selected from palbociclib:

or a pharmaceutically-acceptable salt, cocrystal, hydate, solvate, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a phosphoinositide 3-kinase (PI3K) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (4) a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. This composition is typically a pharmaceutical composition.
In one embodiment, the invention provides a composition comprising (1) a CDK4/6 inhibitor selected from palbociclib:

or a pharmaceutically-acceptable salt, cocrystal, hydate, solvate, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a PI3K-δ inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (4) a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. This composition is typically a pharmaceutical composition.

In one embodiment, the invention provides a composition comprising (1) a CDK4/6 inhibitor selected from palbociclib:

or a pharmaceutically-acceptable salt, cocrystal, hydate, solvate, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants,
radioisotope-labeled complexes, and biosimilars thereof; and (4) a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. This composition is typically a pharmaceutical composition.

[0061] In one embodiment, the invention provides a composition comprising (1) a CDK4/6 inhibitor selected from palbociclib:

![Chemical structure of palbociclib]

or a pharmaceutically-acceptable salt, cocrystal, hydate, solvate, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a phosphoinositide 3-kinase (PI3K) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (4) an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof; and (5) a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. This composition is typically a pharmaceutical composition.

[0062] In one embodiment, the invention provides a composition comprising (1) a CDK4/6 inhibitor selected from palbociclib:
(1) a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a PI3K-δ inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (4) an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof; and (5) a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. This composition is typically a pharmaceutical composition.

[0063] In one embodiment, the invention provides a composition comprising (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (3) a PI3K inhibitor selected from the group consisting of:
and pharmaceutically acceptable salts, solvates, hydrates, cocrystals, or prodrugs thereof. This composition is typically a pharmaceutical composition.

[0064] In one embodiment, the invention provides a composition comprising (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (3) a PI3K-δ inhibitor selected from the group consisting of:
and pharmaceutically acceptable salts, solvates, hydrates, cocrystals, or prodrugs thereof. This composition is typically a pharmaceutical composition.

[0065] In one embodiment, the invention provides a composition comprising (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a PI3K inhibitor selected from the group consisting of:
and pharmaceutically acceptable salts, solvates, hydrates, cocrystals, or prodrugs thereof; and (4) an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof. This composition is typically a pharmaceutical composition.
In one embodiment, the invention provides a composition comprising (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a PI3K-δ inhibitor selected from the group consisting of:

[Chemical Structures]
and pharmaceutically acceptable salts, solvates, hydrates, cocrystals, or prodrugs thereof; and (4) an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof. This composition is typically a pharmaceutical composition.

In one embodiment, the invention provides a composition comprising (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a PI3K inhibitor selected from the group consisting of:

![Chemical structures]
In one embodiment, the invention provides a composition comprising (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a PI3K inhibitor selected from the group consisting of: idelalisib and acalisib.
, and pharmaceutically acceptable salts, solvates, hydrates, cocrystals, or prodrugs thereof; and (4) a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. This composition is typically a pharmaceutical composition.

[0071] In one embodiment, the invention provides a composition comprising (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a PI3K inhibitor selected from the group consisting of:
and pharmaceutically acceptable salts, solvates, hydrates, cocrystals, or prodrugs thereof; (4) an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof; and (5) a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. This composition is typically a pharmaceutical composition.

[0072] In one embodiment, the invention provides a composition comprising (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a PI3K-δ inhibitor selected from the group consisting of:
and pharmaceutically acceptable salts, solvates, hydrates, cocrystals, or prodrugs thereof; (4) an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof; and (5) a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. This composition is typically a pharmaceutical composition.
[0073] In one embodiment, the invention provides a composition comprising (1) a cyclin-
dependent kinase-4/6 (CDK4/6) inhibitor or a pharmacologically acceptable salt, solvate, hydrate, 
cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a 
pharmacologically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (3) an 
anticoagulant or an antiplatelet active pharmaceutical ingredient. This composition is typically a 
pharmaceutical composition.

[0074] In one embodiment, the invention provides a composition comprising (1) a cyclin-
dependent kinase-4/6 (CDK4/6) inhibitor or a pharmacologically acceptable salt, solvate, hydrate, 
cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a 
pharmacologically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (3) a 
phosphoinositide 3-kinase (PI3K) inhibitor or a pharmacologically acceptable salt, solvate, 
hydrate, cocrystal, or prodrug thereof. This composition is typically a pharmaceutical 
composition.

[0075] In one embodiment, the invention provides a composition comprising (1) a cyclin-
dependent kinase-4/6 (CDK4/6) inhibitor or a pharmacologically acceptable salt, solvate, hydrate, 
cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a 
pharmacologically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a PI3K-δ 
inhibitor or a pharmacologically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; 
and (4) an anticoagulant or an antiplatelet active pharmaceutical ingredient. This composition is 
typically a pharmaceutical composition.

[0076] In one embodiment, the invention provides a composition comprising (1) a cyclin-
dependent kinase-4/6 (CDK4/6) inhibitor or a pharmacologically acceptable salt, solvate, hydrate, 
cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a 
pharmacologically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) an anti-
CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, 
veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, 
radiosotope-labeled complexes, and biosimilars thereof; and (4) an anticoagulant or an 
antiplatelet active pharmaceutical ingredient. This composition is typically a pharmaceutical 
composition.
In one embodiment, the invention provides a composition comprising (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a phosphoinositide 3-kinase (PI3K) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (4) an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof; and (5) an anticoagulant or an antiplatelet active pharmaceutical ingredient. This composition is typically a pharmaceutical composition.

In one embodiment, the invention provides a composition comprising (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a PI3K-δ inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (4) an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof; and (5) an anticoagulant or an antiplatelet active pharmaceutical ingredient. This composition is typically a pharmaceutical composition.

In one embodiment, the invention provides a composition comprising (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (4) an anticoagulant or an antiplatelet active pharmaceutical ingredient. This composition is typically a pharmaceutical composition.

In one embodiment, the invention provides a composition comprising (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a
pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a phosphoinositide 3-kinase (PI3K) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (4) a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (5) an anticoagulant or an antiplatelet active pharmaceutical ingredient. This composition is typically a pharmaceutical composition.

[0081] In one embodiment, the invention provides a composition comprising (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a PI3K-δ inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (4) a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (5) an anticoagulant or an antiplatelet active pharmaceutical ingredient. This composition is typically a pharmaceutical composition.

[0082] In one embodiment, the invention provides a composition comprising (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof; (4) a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (5) an anticoagulant or an antiplatelet active pharmaceutical ingredient. This composition is typically a pharmaceutical composition.

[0083] In one embodiment, the invention provides a composition comprising (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a phosphoinositide 3-kinase (PI3K) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (4) an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab,
and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof; and (5) a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (6) an anticoagulant or an antiplatelet active pharmaceutical ingredient. This composition is typically a pharmaceutical composition.

[0084] In one embodiment, the invention provides a composition comprising (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a PI3K-δ inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (4) an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof; (5) a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (6) an anticoagulant or an antiplatelet active pharmaceutical ingredient. This composition is typically a pharmaceutical composition.

[0085] In one embodiment, the invention provides a composition comprising (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (3) a JAK-2 inhibitor selected from the group consisting of ruxolitinib, pacritinib:

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&\text{NH}
\end{align*}
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pacritinib:
and pharmaceutically-acceptable salts, cocrystals, hydrates, solvates, or prodrugs thereof. This composition is typically a pharmaceutical composition.

[0086] In one embodiment, the invention provides a composition comprising (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a phosphoinositide 3-kinase (PI3K) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (4) a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. This composition is typically a pharmaceutical composition.

[0087] In one embodiment, the invention provides a composition comprising (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a PI3K-δ inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (4) a JAK-2 inhibitor selected from the group consisting of ruxolitinib:

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\text{\text{N}} & \text{\text{N}} \\
\text{\text{N}} & \text{\text{N}} \\
\text{\text{N}} & \text{\text{N}} \\
\end{align*}
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and pacritinib:
and pharmaceutically-acceptable salts, cocrystals, hydrates, solvates, or prodrugs thereof. This composition is typically a pharmaceutical composition.

[0088] In one embodiment, the invention provides a composition comprising (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a phosphoinositide 3-kinase (PI3K) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (4) an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof; and (5) a JAK-2 inhibitor selected from the group consisting of ruxolitinib:

and pacritinib:
and pharmaceutically-acceptable salts, cocrystals, hydrates, solvates, or prodrugs thereof. This composition is typically a pharmaceutical composition.

[0089] In one embodiment, the invention provides a composition comprising (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a PI3K-δ inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (4) an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibrutinomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof; and (5) a JAK-2 inhibitor selected from the group consisting of ruxolitinib, pacritinib:
and pharmaceutically-acceptable salts, cocrystals, hydrates, solvates, or prodrugs thereof. This composition is typically a pharmaceutical composition.

In one embodiment, the invention provides a kit comprising (1) a composition comprising a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a composition comprising a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. These compositions are typically pharmaceutical compositions. The kit is for co-administration of the CDK4/6 inhibitor and the BTK inhibitor, either simultaneously or separately.

In one embodiment, the invention provides a kit comprising (1) a composition comprising a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a composition comprising a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (3) a composition comprising a phosphoinositide 3-kinase (PI3K) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. These compositions are typically pharmaceutical compositions. The kit is for co-administration of the CDK4/6 inhibitor, the BTK inhibitor, and the PI3K inhibitor, either simultaneously or separately.

In one embodiment, the invention provides a kit comprising (1) a composition comprising a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a composition comprising a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (3) a composition comprising a PI3K-δ inhibitor or a pharmaceutically acceptable
salt, solvate, hydrate, cocrystal, or prodrug thereof. These compositions are typically pharmaceutical compositions. The kit is for co-administration of the CDK4/6 inhibitor, the BTK inhibitor, and the PI3K-δ inhibitor, either simultaneously or separately.

[0094] In one embodiment, the invention provides a kit comprising (1) a composition comprising a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a composition comprising a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (3) a composition comprising an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof. These compositions are typically pharmaceutical compositions. The kit is for co-administration of the CDK4/6 inhibitor, the BTK inhibitor, and the anti-CD20 antibody, either simultaneously or separately.

[0095] In one embodiment, the invention provides a kit comprising (1) a composition comprising a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a composition comprising a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a composition comprising a phosphoinositide 3-kinase (PI3K) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (4) a composition comprising an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof. These compositions are typically pharmaceutical compositions. The kit is for co-administration of the CDK4/6 inhibitor, the BTK inhibitor, the PI3K inhibitor, and the anti-CD20 antibody, either simultaneously or separately.

[0096] In one embodiment, the invention provides a kit comprising (1) a composition comprising a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a composition comprising a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a composition comprising a PI3K-δ inhibitor or a pharmaceutically acceptable salt,
solvate, hydrate, cocrystal, or prodrug thereof; and (4) a composition comprising an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibrutinomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof. These compositions are typically pharmaceutical compositions. The kit is for co-administration of the CDK4/6 inhibitor, the BTK inhibitor, the PI3K-δ inhibitor, and the anti-CD20 antibody, either simultaneously or separately.

[0097] In one embodiment, the invention provides a kit comprising (1) a composition comprising a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a composition comprising a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (3) a composition comprising a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. These compositions are typically pharmaceutical compositions. The kit is for co-administration of the CDK4/6 inhibitor, the BTK inhibitor, and the JAK-2 inhibitor, either simultaneously or separately.

[0098] In one embodiment, the invention provides a kit comprising (1) a composition comprising a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a composition comprising a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a composition comprising a phosphoinositide 3-kinase (PI3K) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (4) a composition comprising a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. These compositions are typically pharmaceutical compositions. The kit is for co-administration of the CDK4/6 inhibitor, the BTK inhibitor, the PI3K inhibitor, and the JAK-2 inhibitor, either simultaneously or separately.

[0099] In one embodiment, the invention provides a kit comprising (1) a composition comprising a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a composition comprising a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a composition comprising a PI3K-δ inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (4) a composition comprising a JAK-2
inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. These compositions are typically pharmaceutical compositions. The kit is for co-administration of the CDK4/6 inhibitor, the BTK inhibitor, the PI3K-δ inhibitor, and the JAK-2 inhibitor, either simultaneously or separately.

[00100] In one embodiment, the invention provides a kit comprising (1) a composition comprising a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a composition comprising a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a composition comprising an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof; and (4) a composition comprising a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. These compositions are typically pharmaceutical compositions. The kit is for co-administration of the CDK4/6 inhibitor, the BTK inhibitor, the anti-CD20 antibody, and the JAK-2 inhibitor, either simultaneously or separately.

[00101] In one embodiment, the invention provides a kit comprising (1) a composition comprising a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a composition comprising a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a composition comprising a phosphoinositide 3-kinase (PI3K) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (4) a composition comprising an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof; and (5) a composition comprising a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. These compositions are typically pharmaceutical compositions. The kit is for co-administration of the CDK4/6 inhibitor, the BTK inhibitor, the PI3K inhibitor, the anti-CD20 antibody, and the JAK-2 inhibitor, either simultaneously or separately.
[00102] In one embodiment, the invention provides a kit comprising (1) a composition comprising a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a composition comprising a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a composition comprising a PI3K-δ inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (4) a composition comprising an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof; and (5) a composition comprising a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. These compositions are typically pharmaceutical compositions. The kit is for co-administration of the CDK4/6 inhibitor, the BTK inhibitor, the PI3K-δ inhibitor, the anti-CD20 antibody, and the JAK-2 inhibitor, either simultaneously or separately.

[00103] In one embodiment, the invention provides a kit comprising (1) a composition comprising a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, and (2) a composition comprising a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. These compositions are typically pharmaceutical compositions. The kit is for co-administration of the CDK4/6 inhibitor and the BTK inhibitor, either simultaneously or separately, in the treatment of a cancer selected from the group consisting of bladder cancer, squamous cell carcinoma including head and neck cancer, pancreatic ductal adenocarcinoma (PDA), pancreatic cancer, colon carcinoma, mammary carcinoma, breast cancer, fibrosarcoma, mesothelioma, renal cell carcinoma, lung carcinoma, thyma, prostate cancer, colorectal cancer, ovarian cancer, acute myeloid leukemia, thymus cancer, brain cancer, squamous cell cancer, skin cancer, eye cancer, retinoblastoma, melanoma, intraocular melanoma, oral cavity and oropharyngeal cancers, gastric cancer, stomach cancer, cervical cancer, head, neck, renal cancer, kidney cancer, liver cancer, ovarian cancer, prostate cancer, colorectal cancer, esophageal cancer, testicular cancer, gynecological cancer, thyroid cancer, aquired immune deficiency syndrome (AIDS)-related cancers (e.g., lymphoma and Kaposi’s sarcoma), viral-induced cancer, glioblastoma, glioma, esophageal tumors, hematological neoplasms, non-small-cell lung cancer, chronic myelocytic leukemia, diffuse large B-cell lymphoma, esophagus tumor, follicle center

[00104] In one embodiment, the invention provides a kit comprising (1) a composition comprising a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a composition comprising a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (3) a composition comprising a phosphoinositide 3-kinase (PI3K) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. These compositions are typically pharmaceutical compositions. The kit is for co-administration of the CDK4/6 inhibitor, the BTK inhibitor, and the PI3K inhibitor, either simultaneously or separately, in the treatment of a cancer selected from the group consisting of bladder cancer, squamous cell carcinoma including head and neck cancer, pancreatic ductal adenocarcinoma (PDA), pancreatic cancer, colon carcinoma, mammary carcinoma, breast cancer, fibrosarcoma, mesothelioma, renal cell carcinoma, lung carcinoma, thyma, prostate cancer, colorectal cancer, ovarian cancer, acute myeloid leukemia, thymus cancer, brain cancer, squamous cell cancer, skin cancer, eye cancer, retinoblastoma, melanoma, intraocular melanoma, oral cavity and oropharyngeal cancers, gastric cancer, stomach cancer, cervical cancer, head, neck, renal cancer, kidney cancer, liver cancer, ovarian cancer, prostate cancer, colorectal cancer, esophageal cancer, testicular cancer, gynecological cancer, thyroid cancer, aquired immune deficiency syndrome (AIDS)-related cancers (e.g., lymphoma and Kaposi’s sarcoma), viral-induced cancer, glioblastoma, esophageal tumors, hematological neoplasms, non-small-cell lung cancer, chronic myelocytic leukemia, diffuse large B-cell lymphoma, esophagus tumor, follicle center lymphoma, head and neck tumor, hepatitis C virus infection, hepatocellular carcinoma, Hodgkin’s disease, metastatic colon cancer, multiple myeloma, non-Hodgkin’s lymphoma, indolent non-Hodgkin’s lymphoma, ovary tumor, pancreas tumor, renal cell carcinoma, small-cell lung cancer, stage IV melanoma, chronic lymphocytic leukemia, B-cell acute lymphoblastic
leukemia (ALL), mature B-cell ALL, follicular lymphoma, mantle cell lymphoma, and Burkitt’s lymphoma.

[00105] In one embodiment, the invention provides a kit comprising (1) a composition comprising a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a composition comprising a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (3) a composition comprising a PI3K-δ inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. These compositions are typically pharmaceutical compositions. The kit is for co-administration of the CDK4/6 inhibitor, the BTK inhibitor, and the PI3K-δ inhibitor, either simultaneously or separately, in the treatment of a cancer selected from the group consisting of bladder cancer, squamous cell carcinoma including head and neck cancer, pancreatic ductal adenocarcinoma (PDA), pancreatic cancer, colon carcinoma, mammary carcinoma, breast cancer, fibrosarcoma, mesothelioma, renal cell carcinoma, lung carcinoma, thyoma, prostate cancer, colorectal cancer, ovarian cancer, acute myeloid leukemia, thymus cancer, brain cancer, squamous cell cancer, skin cancer, eye cancer, retinoblastoma, melanoma, intraocular melanoma, oral cavity and oropharyngeal cancers, gastric cancer, stomach cancer, cervical cancer, head, neck, renal cancer, kidney cancer, liver cancer, ovarian cancer, prostate cancer, colorectal cancer, esophageal cancer, testicular cancer, gynecological cancer, thyroid cancer, acquired immune deficiency syndrome (AIDS)-related cancers (e.g., lymphoma and Kaposi’s sarcoma), viral-induced cancer, glioblastoma, esophageal tumors, hematological neoplasms, non-small-cell lung cancer, chronic myelocytic leukemia, diffuse large B-cell lymphoma, esophagus tumor, follicle center lymphoma, head and neck tumor, hepatitis C virus infection, hepatocellular carcinoma, Hodgkin’s disease, metastatic colon cancer, multiple myeloma, non-Hodgkin’s lymphoma, indolent non-Hodgkin’s lymphoma, ovary tumor, pancreas tumor, renal cell carcinoma, small-cell lung cancer, stage IV melanoma, chronic lymphocytic leukemia, B-cell acute lymphoblastic leukemia (ALL), mature B-cell ALL, follicular lymphoma, mantle cell lymphoma, and Burkitt’s lymphoma.

[00106] In one embodiment, the invention provides a kit comprising (1) a composition comprising a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a composition comprising a Bruton’s
tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (3) a composition comprising an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof. These compositions are typically pharmaceutical compositions. The kit is for co-administration of the CDK4/6 inhibitor, the BTK inhibitor, and the anti-CD20 antibody, either simultaneously or separately, in the treatment of a cancer selected from the group consisting of bladder cancer, squamous cell carcinoma including head and neck cancer, pancreatic ductal adenocarcinoma (PDA), pancreatic cancer, colon carcinoma, mammary carcinoma, breast cancer, fibrosarcoma, mesothelioma, renal cell carcinoma, lung carcinoma, thymoma, prostate cancer, colorectal cancer, ovarian cancer, acute myeloid leukemia, thymus cancer, brain cancer, squamous cell cancer, skin cancer, eye cancer, retinoblastoma, melanoma, intraocular melanoma, oral cavity and oropharyngeal cancers, gastric cancer, stomach cancer, cervical cancer, head, neck, renal cancer, kidney cancer, liver cancer, ovarian cancer, prostate cancer, colorectal cancer, esophageal cancer, testicular cancer, gynecological cancer, thyroid cancer, acquired immune deficiency syndrome (AIDS)-related cancers (e.g., lymphoma and Kaposi’s sarcoma), viral-induced cancer, glioblastoma, esophageal tumors, hematological neoplasms, non-small-cell lung cancer, chronic myelocytic leukemia, diffuse large B-cell lymphoma, esophagus tumor, follicle center lymphoma, head and neck tumor, hepatitis C virus infection, hepatocellular carcinoma, Hodgkin’s disease, metastatic colon cancer, multiple myeloma, non-Hodgkin’s lymphoma, indolent non-Hodgkin’s lymphoma, ovary tumor, pancreas tumor, renal cell carcinoma, small-cell lung cancer, stage IV melanoma, chronic lymphocytic leukemia, B-cell acute lymphoblastic leukemia (ALL), mature B-cell ALL, follicular lymphoma, mantle cell lymphoma, and Burkitt’s lymphoma.

[00107] In one embodiment, the invention provides a kit comprising (1) a composition comprising a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a composition comprising a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a composition comprising a phosphoinositide 3-kinase (PI3K) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (4) a composition comprising an anti-CD20 antibody selected from the group consisting of rituximab,
obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibrutinomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof. These compositions are typically pharmaceutical compositions. The kit is for co-administration of the CDK4/6 inhibitor, the BTK inhibitor, the PI3K inhibitor, and the anti-CD20 antibody, either simultaneously or separately, in the treatment of a cancer selected from the group consisting of bladder cancer, squamous cell carcinoma including head and neck cancer, pancreatic ductal adenocarcinoma (PDA), pancreatic cancer, colon carcinoma, mammary carcinoma, breast cancer, fibrosarcoma, mesothelioma, renal cell carcinoma, lung carcinoma, thymoma, prostate cancer, colorectal cancer, ovarian cancer, acute myeloid leukemia, thymus cancer, brain cancer, squamous cell cancer, skin cancer, eye cancer, retinoblastoma, melanoma, intraocular melanoma, oral cavity and oropharyngeal cancers, gastric cancer, stomach cancer, cervical cancer, head, neck, renal cancer, kidney cancer, liver cancer, ovarian cancer, prostate cancer, colorectal cancer, esophageal cancer, testicular cancer, gynecological cancer, thyroid cancer, acquired immune deficiency syndrome (AIDS)-related cancers (e.g., lymphoma and Kaposi’s sarcoma), viral-induced cancer, glioblastoma, esophageal tumors, hematological neoplasms, non-small-cell lung cancer, chronic myelocytic leukemia, diffuse large B-cell lymphoma, esophagus tumor, follicle center lymphoma, head and neck tumor, hepatitis C virus infection, hepatocellular carcinoma, Hodgkin’s disease, metastatic colon cancer, multiple myeloma, non-Hodgkin’s lymphoma, indolent non-Hodgkin’s lymphoma, ovary tumor, pancreas tumor, renal cell carcinoma, small-cell lung cancer, stage IV melanoma, chronic lymphocytic leukemia, B-cell acute lymphoblastic leukemia (ALL), mature B-cell ALL, follicular lymphoma, mantle cell lymphoma, and Burkitt’s lymphoma.

[00108] In one embodiment, the invention provides a kit comprising (1) a composition comprising a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a composition comprising a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a composition comprising a PI3K-δ inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (4) a composition comprising an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibrutinomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof. These compositions are

[00109] In one embodiment, the invention provides a kit comprising (1) a composition comprising a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a composition comprising a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (3) a composition comprising a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. These compositions are typically pharmaceutical compositions. The kit is for co-administration of the CDK4/6 inhibitor, the BTK inhibitor, and the JAK-2 inhibitor, either simultaneously or separately, in the treatment of a cancer selected from the group consisting of bladder cancer, squamous cell carcinoma including head and neck cancer, pancreatic ductal adenocarcinoma (PDA), pancreatic cancer, colon carcinoma, mammary carcinoma, breast cancer, fibrosarcoma, mesothelioma, renal cell cancer, etc.

[00110] In one embodiment, the invention provides a kit comprising (1) a composition comprising a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a composition comprising a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a composition comprising a phosphoinositide 3-kinase (PI3K) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (4) a composition comprising a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. These compositions are typically pharmaceutical compositions. The kit is for co-administration of the CDK4/6 inhibitor, the BTK inhibitor, the PI3K inhibitor, and the JAK-2 inhibitor, either simultaneously or separately, in the treatment of a cancer selected from the group consisting of bladder cancer, squamous cell carcinoma including head and neck cancer, pancreatic ductal adenocarcinoma (PDA), pancreatic cancer, colon carcinoma, mammary carcinoma, breast cancer, fibrosarcoma, mesothelioma, renal cell carcinoma, lung carcinoma, thyoma, prostate cancer, colorectal cancer, ovarian cancer, acute myeloid leukemia, thymus cancer, brain cancer, squamous cell cancer, skin cancer, eye cancer, retinoblastoma, melanoma, intraocular melanoma, oral cavity and oropharyngeal cancers, gastric cancer, stomach cancer, cervical cancer, head, neck, renal cancer, kidney cancer, liver cancer,

[00111] In one embodiment, the invention provides a kit comprising (1) a composition comprising a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocystal, or prodrug thereof; (2) a composition comprising a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocystal, or prodrug thereof; (3) a composition comprising a PI3K-δ inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocystal, or prodrug thereof; and (4) a composition comprising a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocystal, or prodrug thereof. These compositions are typically pharmaceutical compositions. The kit is for co-administration of the CDK4/6 inhibitor, the BTK inhibitor, the PI3K-δ inhibitor, and the JAK-2 inhibitor, either simultaneously or separately, in the treatment of a cancer selected from the group consisting of bladder cancer, squamous cell carcinoma including head and neck cancer, pancreatic ductal adenocarcinoma (PDA), pancreatic cancer, colon carcinoma, mammary carcinoma, breast cancer, fibrosarcoma, mesothelioma, renal cell carcinoma, lung carcinoma, thymoma, prostate cancer, colorectal cancer, ovarian cancer, acute myeloid leukemia, thymus cancer, brain cancer, squamous cell cancer, skin cancer, eye cancer, retinoblastoma, melanoma, intraocular melanoma, oral cavity and oropharyngeal cancers, gastric cancer, stomach cancer, cervical cancer, head, neck, renal cancer, kidney cancer, liver cancer, ovarian cancer, prostate cancer, colorectal cancer, esophageal cancer, testicular cancer, gynecological cancer, thyroid cancer, acquired immune deficiency syndrome (AIDS)-related cancers (e.g., lymphoma and Kaposi's sarcoma), viral-induced cancer, glioblastoma, esophageal tumors, hematological neoplasms, non-small-cell lung cancer, chronic myelocytic leukemia, diffuse large B-cell
lymphoma, esophagus tumor, follicle center lymphoma, head and neck tumor, hepatitis C virus
infection, hepatocellular carcinoma, Hodgkin’s disease, metastatic colon cancer, multiple
myeloma, non-Hodgkin’s lymphoma, indolent non-Hodgkin’s lymphoma, ovary tumor, pancreas
tumor, renal cell carcinoma, small-cell lung cancer, stage IV melanoma, chronic lymphocytic
leukemia, B-cell acute lymphoblastic leukemia (ALL), mature B-cell ALL, follicular lymphoma,
mantle cell lymphoma, and Burkitt’s lymphoma.

[00112] In one embodiment, the invention provides a kit comprising (1) a composition
comprising a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable
salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a composition comprising a Bruton’s
tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal,
or prodrug thereof; (3) a composition comprising an anti-CD20 antibody selected from the group
consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab,
and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, andbiosimilars
thereof; and (4) a composition comprising a JAK-2 inhibitor or a pharmaceutically acceptable
salt, solvate, hydrate, cocrystal, or prodrug thereof. These compositions are typically
pharmaceutical compositions. The kit is for co-administration of the CDK4/6 inhibitor, the BTK
inhibitor, the anti-CD20 antibody, and the JAK-2 inhibitor, either simultaneously or separately,
in the treatment of a cancer selected from the group consisting of bladder cancer, squamous cell
carcinoma including head and neck cancer, pancreatic ductal adenocarcinoma (PDA), pancreatic
cancer, colon carcinoma, mammary carcinoma, breast cancer, fibrosarcoma, mesothelioma, renal
cell carcinoma, lung carcinoma, thyma, prostate cancer, colorectal cancer, ovarian cancer, acute
myeloid leukemia, thymus cancer, brain cancer, squamous cell cancer, skin cancer, eye cancer,
retinoblastoma, melanoma, intraocular melanoma, oral cavity and oropharyngeal cancers, gastric
cancer, stomach cancer, cervical cancer, head, neck, renal cancer, kidney cancer, liver cancer,
ovarian cancer, prostate cancer, colorectal cancer, esophageal cancer, testicular cancer,
gynecological cancer, thyroid cancer, acquired immune deficiency syndrome (AIDS)-related
cancers (e.g., lymphoma and Kaposi's sarcoma), viral-induced cancer, glioblastoma, esophageal
tumors, hematological neoplasms, non-small-cell lung cancer, chronic myelocytic leukemia,
diffuse large B-cell lymphoma, esophagus tumor, follicle center lymphoma, head and neck
tumor, hepatitis C virus infection, hepatocellular carcinoma, Hodgkin’s disease, metastatic colon
cancer, multiple myeloma, non-Hodgkin’s lymphoma, indolent non-Hodgkin’s lymphoma, ovary
tumor, pancreas tumor, renal cell carcinoma, small-cell lung cancer, stage IV melanoma, chronic lymphocytic leukemia, B-cell acute lymphoblastic leukemia (ALL), mature B-cell ALL, follicular lymphoma, mantle cell lymphoma, and Burkitt’s lymphoma.

[00113] In one embodiment, the invention provides a kit comprising (1) a composition comprising a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a composition comprising a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a composition comprising a phosphoinositide 3-kinase (PI3K) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (4) a composition comprising an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof; and (5) a composition comprising a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. These compositions are typically pharmaceutical compositions. The kit is for co-administration of the CDK4/6 inhibitor, the BTK inhibitor, the PI3K inhibitor, the anti-CD20 antibody, and the JAK-2 inhibitor, either simultaneously or separately, in the treatment of a cancer selected from the group consisting of bladder cancer, squamous cell carcinoma including head and neck cancer, pancreatic ductal adenocarcinoma (PDA), pancreatic cancer, colon carcinoma, mammary carcinoma, breast cancer, fibrosarcoma, mesothelioma, renal cell carcinoma, lung carcinoma, thyma, prostate cancer, colorectal cancer, ovarian cancer, acute myeloid leukemia, thymus cancer, brain cancer, squamous cell cancer, skin cancer, eye cancer, retinoblastoma, melanoma, intraocular melanoma, oral cavity and oropharyngeal cancers, gastric cancer, stomach cancer, cervical cancer, head, neck, renal cancer, kidney cancer, liver cancer, ovarian cancer, prostate cancer, colorectal cancer, esophageal cancer, testicular cancer, gynecological cancer, thyroid cancer, acquired immune deficiency syndrome (AIDS)-related cancers (e.g., lymphoma and Kaposi’s sarcoma), viral-induced cancer, glioblastoma, esophageal tumors, hematological neoplasms, non-small-cell lung cancer, chronic myelocytic leukemia, diffuse large B-cell lymphoma, esophagus tumor, follicle center lymphoma, head and neck tumor, hepatitis C virus infection, hepatocellular carcinoma, Hodgkin’s disease, metastatic colon cancer, multiple myeloma, non-Hodgkin’s lymphoma, indolent non-Hodgkin’s lymphoma, ovary tumor, pancreas tumor, renal cell carcinoma, small-
cell lung cancer, stage IV melanoma, chronic lymphocytic leukemia, B-cell acute lymphoblastic leukemia (ALL), mature B-cell ALL, follicular lymphoma, mantle cell lymphoma, and Burkitt’s lymphoma.

[00114] In one embodiment, the invention provides a kit comprising (1) a composition comprising a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a composition comprising a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a composition comprising a PI3K-δ inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (4) a composition comprising an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof; and (5) a composition comprising a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. These compositions are typically pharmaceutical compositions. The kit is for co-administration of the CDK4/6 inhibitor, the BTK inhibitor, the PI3K-δ inhibitor, the anti-CD20 antibody, and the JAK-2 inhibitor, either simultaneously or separately, in the treatment of a cancer selected from the group consisting of bladder cancer, squamous cell carcinoma including head and neck cancer, pancreatic ductal adenocarcinoma (PDA), pancreatic cancer, colon carcinoma, mammary carcinoma, breast cancer, fibrosarcoma, mesothelioma, renal cell carcinoma, lung carcinoma, thyma, prostate cancer, colorectal cancer, ovarian cancer, acute myeloid leukemia, thymus cancer, brain cancer, squamous cell cancer, skin cancer, eye cancer, retinoblastoma, melanoma, intraocular melanoma, oral cavity and oropharyngeal cancers, gastric cancer, stomach cancer, cervical cancer, head, neck, renal cancer, kidney cancer, liver cancer, ovarian cancer, prostate cancer, colorectal cancer, esophageal cancer, testicular cancer, gynecological cancer, thyroid cancer, acquired immune deficiency syndrome (AIDS)-related cancers (e.g., lymphoma and Kaposi's sarcoma), viral-induced cancer, glioblastoma, esophageal tumors, hematological neoplasms, non-small-cell lung cancer, chronic myelocytic leukemia, diffuse large B-cell lymphoma, esophagus tumor, follicle center lymphoma, head and neck tumor, hepatitis C virus infection, hepatocellular carcinoma, Hodgkin’s disease, metastatic colon cancer, multiple myeloma, non-Hodgkin’s lymphoma, indolent non-Hodgkin’s lymphoma, ovary tumor, pancreas tumor, renal cell carcinoma, small-cell lung cancer, stage IV melanoma, chronic
lymphocytic leukemia, B-cell acute lymphoblastic leukemia (ALL), mature B-cell ALL, follicular lymphoma, mantle cell lymphoma, and Burkitt’s lymphoma.

[00115] In an embodiment, the invention provides a method of treating leukemia, lymphoma or a solid tumor cancer in a subject, comprising co-administering to a mammal in need thereof a therapeutically effective amount of a CDK4/6 inhibitor and a BTK inhibitor.

[00116] In an embodiment, the invention provides a method of treating leukemia, lymphoma or a solid tumor cancer in a subject, comprising co-administering to a mammal in need thereof a therapeutically effective amount of a PI3K-δ inhibitor, a CDK4/6 inhibitor, and a BTK inhibitor.

[00117] In an embodiment, the invention provides a method of treating leukemia, lymphoma or a solid tumor cancer in a subject, comprising co-administering to a mammal in need thereof a therapeutically effective amount of a PI3K-γ,δ inhibitor, a CDK4/6 inhibitor, and a BTK inhibitor.

[00118] In an embodiment, the invention provides a method of treating leukemia, lymphoma or a solid tumor cancer in a subject, comprising co-administering to a mammal in need thereof a therapeutically effective amount of a PI3K-γ inhibitor, a CDK4/6 inhibitor, and a BTK inhibitor.

[00119] In an embodiment, the invention provides a method of treating leukemia, lymphoma or a solid tumor cancer in a subject, comprising co-administering to a mammal in need thereof a therapeutically effective amount of a PI3K-γ inhibitor, a JAK-2 inhibitor, a CDK4/6 inhibitor, and a BTK inhibitor.

[00120] In an embodiment, the invention provides a method of treating leukemia, lymphoma or a solid tumor cancer in a subject, comprising co-administering to a mammal in need thereof a therapeutically effective amount of a PI3K-δ inhibitor, a JAK-2 inhibitor, a CDK4/6 inhibitor, and a BTK inhibitor.

[00121] In an embodiment, the invention provides a method of treating leukemia, lymphoma or a solid tumor cancer in a subject, comprising co-administering to a mammal in need thereof a therapeutically effective amount of a PI3K-γ,δ inhibitor, a JAK-2 inhibitor, a CDK4/6 inhibitor, and a BTK inhibitor.
In an embodiment, the invention provides a method of treating leukemia, lymphoma or a solid tumor cancer in a subject, comprising co-administering to a mammal in need thereof a therapeutically effective amount of a PI3K inhibitor and a BTK inhibitor.

In an embodiment, the invention provides a method of treating leukemia, lymphoma or a solid tumor cancer in a subject, comprising co-administering to a mammal in need thereof a therapeutically effective amount of a PI3K-γ,δ inhibitor and a BTK inhibitor.

In an embodiment, the invention provides a method of treating leukemia, lymphoma or a solid tumor cancer in a subject, comprising co-administering to a mammal in need thereof a therapeutically effective amount of a PI3K-δ inhibitor and a BTK inhibitor.

In an embodiment, the invention provides a method of treating leukemia, lymphoma or a solid tumor cancer in a subject, comprising co-administering to a mammal in need thereof a therapeutically effective amount of a PI3K-γ,δ inhibitor and a BTK inhibitor.

In an embodiment, the invention provides a method of treating leukemia, lymphoma or a solid tumor cancer in a subject, comprising co-administering to a mammal in need thereof a therapeutically effective amount of a JAK-2 inhibitor and a BTK inhibitor.

In an embodiment, the invention provides a method of treating leukemia, lymphoma or a solid tumor cancer in a subject, comprising co-administering to a mammal in need thereof a therapeutically effective amount of a PI3K inhibitor, a JAK-2 inhibitor, and a BTK inhibitor.

In an embodiment, the invention provides a method of treating leukemia, lymphoma or a solid tumor cancer in a subject, comprising co-administering to a mammal in need thereof a therapeutically effective amount of a PI3K-γ inhibitor, a JAK-2 inhibitor, and a BTK inhibitor.

In an embodiment, the invention provides a method of treating leukemia, lymphoma or a solid tumor cancer in a subject, comprising co-administering to a mammal in need thereof a therapeutically effective amount of a PI3K-δ inhibitor, a JAK-2 inhibitor, and a BTK inhibitor.

In an embodiment, the invention provides a method of treating leukemia, lymphoma or a solid tumor cancer in a subject, comprising co-administering to a mammal in need thereof a therapeutically effective amount of a PI3K-γ,δ inhibitor, a JAK-2 inhibitor, and a BTK inhibitor.
BRIEF DESCRIPTION OF THE DRAWINGS

[00131] The foregoing summary, as well as the following detailed description of the invention, will be better understood when read in conjunction with the appended drawings.

[00132] FIG. 1 illustrates the sensitivity of the TMD8 diffuse large B cell lymphoma (DLBCL) cell line to individual treatment with the BTK inhibitor of Formula (XVIII) (“Tested Btk Inhibitor”) and the PI3K inhibitor of Formula (IX) (“Tested PI3K Inhibitor”) and combined treatment with Formula (XVIII) and Formula (IX) (“Btki + PI3Ki”) at different concentrations. The concentration of the first agent in the combination (the BTK inhibitor) and the concentration of the individual agents is given on the x-axis, and the concentration of the added PI3K inhibitor in combination with the BTK inhibitor is given in the legend.

[00133] FIG. 2 illustrates the sensitivity of the MINO mantle cell lymphoma cell to individual treatment with the BTK inhibitor of Formula (XVIII) (“Tested Btk Inhibitor”) and the PI3K inhibitor of Formula (IX) (“Tested PI3K Inhibitor”) and combined treatment with Formula (XVIII) and Formula (IX) (“Btki + PI3Ki”) at different concentrations. The concentration of the first agent in the combination (the BTK inhibitor) and the concentration of the individual agents is given on the x-axis, and the concentration of the added PI3K inhibitor in combination with the BTK inhibitor is given in the legend.

[00134] FIG. 3 illustrates the proliferative activity in primary mantle cell lymphoma cells of Formula (XVIII) (“Tested Btki”) and Formula (IX) (“Tested PI3Ki”). The percentage viability of cells (“% viability”, y-axis) is plotted versus the concentration of the agent or agents. Single-agent BTK (“Tested Btki”) and PI3K inhibitors (“Tested PI3Ki”) are compared to four combinations of Formula (XVIII) and Formula (IX) (“(10 µM) Tested PI3Ki”, “(1.0 µM) Tested PI3Ki,” “(0.1 µM) Tested PI3Ki,” “(0.01 µM) Tested PI3Ki”).

[00135] FIG. 4 illustrates the interaction index of the combination of the BTK inhibitor of Formula (XVIII) and the PI3K inhibitor of Formula (IX) in primary mantle cell lymphoma cells from different patients (MCL-1 to MCL-5). Each symbol represents a concentration from 10 µM to 0.1 nM.

[00136] FIG. 5 illustrates the synergy observed in certain cell lines when the BTK inhibitor of Formula (XVIII) and the PI3K-δ inhibitor of Formula (IX) are combined. The tested cell lines
include Maver-1 (B cell lymphoma, mantle), Jeko (B cell lymphoma, mantle), CCRF (B lymphoblast, acute lymphoblastic leukemia), and SUP-B15 (B lymphoblast, acute lymphoblastic leukemia). The dose-effect curves for these cell lines are given in FIG. 6, FIG. 7, FIG. 8, and FIG. 9. ED25, ED50, ED75, and ED90 refer to the effective doses causing 25%, 50%, 75%, and 90% of the maximum biological effect (proliferation).

[00137] FIG. 6 illustrates the dose-effect curves obtained for the tested Maver-1 cell line (B cell lymphoma, mantle) using combined dosing of the BTK inhibitor of Formula (XVIII) (“Inh.1”) and the PI3K-δ inhibitor of Formula (IX) (“Inh.3”). The y-axis (“Effect”) is given in units of Fa (fraction affected) and the x-axis (“Dose”) is given in linear units of μM.

[00138] FIG. 7 illustrates the dose-effect curves obtained for the tested Jeko cell line (B cell lymphoma, mantle) using combined dosing of the BTK inhibitor of Formula (XVIII) (“Inh.1”) and the PI3K-δ inhibitor of Formula (IX) (“Inh.3”). The y-axis (“Effect”) is given in units of Fa (fraction affected) and the x-axis (“Dose”) is given in linear units of μM.

[00139] FIG. 8 illustrates the dose-effect curves obtained for the tested CCRF cell line (B lymphoblast, acute lymphoblastic leukemia) using combined dosing of the BTK inhibitor of Formula (XVIII) (“Inh.1”) and the PI3K-δ inhibitor of Formula (IX) (“Inh.3”). The y-axis (“Effect”) is given in units of Fa (fraction affected) and the x-axis (“Dose”) is given in linear units of μM.

[00140] FIG. 9 illustrates the dose-effect curves obtained for the tested SUP-B15 cell line (B lymphoblast, acute lymphoblastic leukemia) using combined dosing of the BTK inhibitor of Formula (XVIII) (“Inh.1”) and the PI3K-δ inhibitor of Formula (IX) (“Inh.3”). The y-axis (“Effect”) is given in units of Fa (fraction affected) and the x-axis (“Dose”) is given in linear units of μM.

[00141] FIG. 10 illustrates the synergy observed in certain cell lines when the BTK inhibitor of Formula (XVIII) and the PI3K-δ inhibitor of Formula (IX) are combined. The tested cell lines include Jeko (B cell lymphoma, mantle cell lymphoma) and SU-DHL-4 (activated B cell like (ABC) diffuse large B cell lymphoma). The dose-effect curves for these cell lines are given in FIG. 11 and FIG. 12.
FIG. 11 illustrates the dose-effect curves obtained for the tested Jeko cell line (B cell lymphoma, mantle) using combined dosing of the BTK inhibitor of Formula (XVIII) (“Inh.1”) and the PI3K-δ inhibitor of Formula (IX) (“Inh.3”). The y-axis (“Effect”) is given in units of Fa (fraction affected) and the x-axis (“Dose”) is given in linear units of µM.

FIG. 12 illustrates the dose-effect curves obtained for the tested SU-DHL-4 cell line (diffuse large B cell lymphoma, ABC) using combined dosing of the BTK inhibitor of Formula (XVIII) (“Inh.1”) and the PI3K-δ inhibitor of Formula (IX) (“Inh.3”). The y-axis (“Effect”) is given in units of Fa (fraction affected) and the x-axis (“Dose”) is given in linear units of µM.

FIG. 13 illustrates the synergy observed in certain cell lines when the BTK inhibitor of Formula (XVIII) and the PI3K-δ inhibitor of Formula (IX) are combined. The tested cell lines include CCRF (B lymphoblast, acute lymphoblastic leukemia), SUP-B15 (B lymphoblast, acute lymphoblastic leukemia), JVM-2 (prolymphocytic leukemia), Ramos (Burkitt’s lymphoma), and Mino (mantle cell lymphoma). The dose-effect curves for these cell lines are given in FIG. 14, FIG. 15, FIG. 16, and FIG. 17. No dose-effect curve is given for Ramos (Burkitt’s lymphoma) because of negative slope.

FIG. 14 illustrates the dose-effect curves obtained for the tested CCRF cell line (B lymphoblast, acute lymphoblastic leukemia) using combined dosing of the BTK inhibitor of Formula (XVIII) (“Inh.1”) and the PI3K-δ inhibitor of Formula (IX) (“Inh.3”). The y-axis (“Effect”) is given in units of Fa (fraction affected) and the x-axis (“Dose”) is given in linear units of µM.

FIG. 15 illustrates the dose-effect curves obtained for the tested SUP-B15 cell line (B lymphoblast, acute lymphoblastic leukemia) using combined dosing of the BTK inhibitor of Formula (XVIII) (“Inh.1”) and the PI3K-δ inhibitor of Formula (IX) (“Inh.3”). The y-axis (“Effect”) is given in units of Fa (fraction affected) and the x-axis (“Dose”) is given in linear units of µM.

FIG. 16 illustrates the dose-effect curves obtained for the tested JVM-2 cell line (prolymphocytic leukemia) using combined dosing of the BTK inhibitor of Formula (XVIII) (“Inh.1”) and the PI3K-δ inhibitor of Formula (IX) (“Inh.3”). The y-axis (“Effect”) is given in units of Fa (fraction affected) and the x-axis (“Dose”) is given in linear units of µM.
FIG. 17 illustrates the dose-effect curves obtained for the tested Mino cell line (mantle cell lymphoma) using combined dosing of the BTK inhibitor of Formula (XVIII) (“Inh.1”) and the PI3K-δ inhibitor of Formula (IX) (“Inh.3”). The y-axis (“Effect”) is given in units of Fa (fraction affected) and the x-axis (“Dose”) is given in linear units of µM.

FIG. 18 illustrates the synergy observed in certain cell lines when the BTK inhibitor of Formula (XVIII) and the PI3K-δ inhibitor of Formula (IX) are combined. The tested cell lines include Raji (B lymphocyte, Burkitt’s lymphoma), SU-DHL-1 (DLBCL-ABC), and Pfeiffer (follicular lymphoma). The dose-effect curves for these cell lines are given in FIG. 19, FIG. 20, and FIG. 21.

FIG. 19 illustrates the dose-effect curves obtained for the tested Raji cell line (B lymphocyte, Burkitt’s lymphoma) using combined dosing of the BTK inhibitor of Formula (XVIII) (“Inh.1”) and the PI3K-δ inhibitor of Formula (IX) (“Inh.3”). The y-axis (“Effect”) is given in units of Fa (fraction affected) and the x-axis (“Dose”) is given in linear units of µM.

FIG. 20 illustrates the dose-effect curves obtained for the tested SU-DHL-1 cell line (DLBCL-ABC) using combined dosing of the BTK inhibitor of Formula (XVIII) (“Inh.1”) and the PI3K-δ inhibitor of Formula (IX) (“Inh.3”). The y-axis (“Effect”) is given in units of Fa (fraction affected) and the x-axis (“Dose”) is given in linear units of µM.

FIG. 21 illustrates the dose-effect curves obtained for the tested Pfeiffer cell line (follicular lymphoma) using combined dosing of the BTK inhibitor of Formula (XVIII) (“Inh.1”) and the PI3K-δ inhibitor of Formula (IX) (“Inh.3”). The y-axis (“Effect”) is given in units of Fa (fraction affected) and the x-axis (“Dose”) is given in linear units of µM.

FIG. 22 illustrates the synergy observed in certain cell lines when the BTK inhibitor of Formula (XVIII) and the PI3K-δ inhibitor of Formula (IX) are combined. The tested cell lines include Ly1 (Germinal center B-cell like diffuse large B-cell lymphoma, DLBCL-GCB), Ly7 (DLBCL-GCB), Ly19 (DLBCL-GCB), SU-DHL-2 (Activated B-cell like diffuse large B-cell lymphoma, DLBCL-ABC), and DOHH2 (follicular lymphoma, FL). The dose-effect curves for these cell lines are given in FIG. 23, FIG. 24, FIG. 25, and FIG. 26, except for the Ly19 cell line, which is not graphed because of a negative slope.
FIG. 23 illustrates the dose-effect curves obtained for the tested Ly1 cell line (DLBCL-GCB) using combined dosing of the BTK inhibitor of Formula (XVIII) (“Inh.1”) and the PI3K-δ inhibitor of Formula (IX) (“Inh.3”). The y-axis (“Effect”) is given in units of Fa (fraction affected) and the x-axis (“Dose”) is given in linear units of µM.

FIG. 24 illustrates the dose-effect curves obtained for the tested Ly7 cell line (DLBCL-GCB) using combined dosing of the BTK inhibitor of Formula (XVIII) (“Inh.1”) and the PI3K-δ inhibitor of Formula (IX) (“Inh.3”). The y-axis (“Effect”) is given in units of Fa (fraction affected) and the x-axis (“Dose”) is given in linear units of µM.

FIG. 25 illustrates the dose-effect curves obtained for the tested DOHH2 cell line (FL) using combined dosing of the BTK inhibitor of Formula (XVIII) (“Inh.1”) and the PI3K-δ inhibitor of Formula (IX) (“Inh.3”). The y-axis (“Effect”) is given in units of Fa (fraction affected) and the x-axis (“Dose”) is given in linear units of µM.

FIG. 26 illustrates the dose-effect curves obtained for the tested SU-DHL-2 cell line (DLBCL-ABC) using combined dosing of the BTK inhibitor of Formula (XVIII) (“Inh.1”) and the PI3K-δ inhibitor of Formula (IX) (“Inh.3”). The y-axis (“Effect”) is given in units of Fa (fraction affected) and the x-axis (“Dose”) is given in linear units of µM.

FIG. 27 illustrates the synergy observed in certain cell lines when Formula (XVIII) and Formula (IX) are combined. The tested cell lines include U937 (histiocytic lymphoma and/or myeloid), K562 (leukemia, myeloid, and/or chronic myelogenous leukemia), Daudi (human Burkitt's lymphoma), and SU-DHL-6 (DLBCL-GCB and/or peripheral T-cell lymphoma, PTCL). The dose-effect curves for these cell lines are given in FIG. 28, FIG. 29, FIG. 30, and FIG. 31.

FIG. 28 illustrates the dose-effect curves obtained for the tested U937 cell line (histiocytic lymphoma and/or myeloid) using combined dosing of the BTK inhibitor of Formula (XVIII) (“Inh.1”) and the PI3K-δ inhibitor of Formula (IX) (“Inh.3”). The y-axis (“Effect”) is given in units of Fa (fraction affected) and the x-axis (“Dose”) is given in linear units of µM.

FIG. 29 illustrates the dose-effect curves obtained for the tested K562 cell line (leukemia, myeloid, and/or chronic myelogenous leukemia) using combined dosing of the BTK inhibitor of Formula (XVIII) (“Inh.1”) and the PI3K-δ inhibitor of Formula (IX) (“Inh.3”).
y-axis (“Effect”) is given in units of $F_a$ (fraction affected) and the x-axis (“Dose”) is given in linear units of $\mu$M.

[00161] FIG. 30 illustrates the dose-effect curves obtained for the tested Daudi cell line (human Burkitt’s lymphoma) using combined dosing of the BTK inhibitor of Formula (XVIII) (“Inh.1”) and the PI3K-δ inhibitor of Formula (IX) (“Inh.3”). The y-axis (“Effect”) is given in units of $F_a$ (fraction affected) and the x-axis (“Dose”) is given in linear units of $\mu$M.

[00162] FIG. 31 illustrates the dose-effect curves obtained for the tested SU-DHL-6 cell line (DLBCL-GCB and/or PTCL) using combined dosing of the BTK inhibitor of Formula (XVIII) (“Inh.1”) and the PI3K-δ inhibitor of Formula (IX) (“Inh.3”). The y-axis (“Effect”) is given in units of $F_a$ (fraction affected) and the x-axis (“Dose”) is given in linear units of $\mu$M.

[00163] FIG. 32 illustrates the synergy observed in certain cell lines when the BTK inhibitor of Formula (XVIII) and the PI3K-δ inhibitor of Formula (IX) are combined. The tested cell lines include SU-DHL-6 (DLBCL-GCB or PTCL), TMD-8 (DLBCL-ABC), HBL-1 (DLBCL-ABC), and Rec-1 (follicular lymphoma). The dose-effect curves for these cell lines are given in FIG. 34, FIG. 35, FIG. 36, and FIG. 37.

[00164] FIG. 33 illustrates the synergy observed in certain cell lines when the BTK inhibitor of Formula (XVIII) and the PI3K-δ inhibitor of Formula (IX) are combined. The tested cell lines include SU-DHL-6 (DLBCL-GCB or PTCL), TMD-8 (DLBCL-ABC), HBL-1 (DLBCL-ABC), and Rec-1 (follicular lymphoma). All corresponding CIs are shown for each of the combinations tested as listed on the x-axis.

[00165] FIG. 34 illustrates the dose-effect curves obtained for the tested SU-DHL-6 cell line (DLBCL-GCB or PTCL) cell line using combined dosing of the BTK inhibitor of Formula (XVIII) (“Inh.1”) and the PI3K-δ inhibitor of Formula (IX) (“Inh.3”). The y-axis (“Effect”) is given in units of $F_a$ (fraction affected) and the x-axis (“Dose”) is given in linear units of $\mu$M.

[00166] FIG. 35 illustrates the dose-effect curves obtained for the tested TMD-8 cell line (DLBCL-ABC) using combined dosing of the BTK inhibitor of Formula (XVIII) (“Inh.1”) and the PI3K-δ inhibitor of Formula (IX) (“Inh.3”). The y-axis (“Effect”) is given in units of $F_a$ (fraction affected) and the x-axis (“Dose”) is given in linear units of $\mu$M.
[00167] FIG. 36 illustrates the dose-effect curves obtained for the tested HBL-1 cell line (DLBCL-ABC) using combined dosing of the BTK inhibitor of Formula (XVIII) (“Inh.1”) and the PI3K-δ inhibitor of Formula (IX) (“Inh.3”). The y-axis (“Effect”) is given in units of Fa (fraction affected) and the x-axis (“Dose”) is given in linear units of µM.

[00168] FIG. 37 illustrates the dose-effect curves obtained for the tested Rec-1 cell line (follicular lymphoma) using combined dosing of the BTK inhibitor of Formula (XVIII) (“Inh.1”) and the PI3K-δ inhibitor of Formula (IX) (“Inh.3”). The y-axis (“Effect”) is given in units of Fa (fraction affected) and the x-axis (“Dose”) is given in linear units of µM.

[00169] FIG. 38 illustrates the synergy observed in certain cell lines when the BTK inhibitor of Formula (XVIII) and the JAK-2 inhibitor of Formula XXX (ruxolitinib) are combined. The tested cell lines included Maver-1 (B cell lymphoma, mantle), Jeko (B cell lymphoma, mantle), SUP-B15 (B lymphoblast, acute lymphoblastic leukemia), and CCRF (B lymphoblast, acute lymphoblastic leukemia). The dose-effect curves for these cell lines are given in FIG. 39, FIG. 40, FIG. 41, and FIG. 42.

[00170] FIG. 39 illustrates the dose-effect curves obtained for the tested Maver-1 cell line (B cell lymphoma, mantle) using combined dosing of the BTK inhibitor of Formula (XVIII) (“Inh.1”) and the JAK-2 inhibitor of Formula XXX (“Inh.2”) (ruxolitinib). The y-axis (“Effect”) is given in units of Fa (fraction affected) and the x-axis (“Dose”) is given in linear units of µM.

[00171] FIG. 40 illustrates the dose-effect curves obtained for the tested Jeko cell line (B cell lymphoma, mantle) using combined dosing of the BTK inhibitor of Formula (XVIII) (“Inh.1”) and the JAK-2 inhibitor of Formula XXX (“Inh.2”) (ruxolitinib). The y-axis (“Effect”) is given in units of Fa (fraction affected) and the x-axis (“Dose”) is given in linear units of µM.

[00172] FIG. 41 illustrates the dose-effect curves obtained for the tested SUP-B15 cell line (B lymphoblast, acute lymphoblastic leukemia) using combined dosing of the BTK inhibitor of Formula (XVIII) (“Inh.1”) and the JAK-2 inhibitor of Formula XXX (“Inh.2”) (ruxolitinib). The y-axis (“Effect”) is given in units of Fa (fraction affected) and the x-axis (“Dose”) is given in linear units of µM.

[00173] FIG. 42 illustrates the dose-effect curves obtained for the tested CCRF cell line (B lymphoblast, acute lymphoblastic leukemia) using combined dosing of the BTK inhibitor of
Formula (XVIII) (“Inh.1”) and the JAK-2 inhibitor of Formula XXX (“Inh.2”) (ruxolitinib). The y-axis (“Effect”) is given in units of Fa (fraction affected) and the x-axis (“Dose”) is given in linear units of µM.

[00174] FIG. 43 illustrates the synergy observed in certain cell lines when the BTK inhibitor of Formula (XVIII) and the JAK-2 inhibitor of Formula XXX (ruxolitinib) are combined. Repeat experiments for two of the cell lines previously shown in FIG. 38 are shown, including SUP-B15 (B lymphoblast, acute lymphoblastic leukemia) and CCRF (B lymphoblast, acute lymphoblastic leukemia).

[00175] FIG. 44 illustrates the synergy observed in certain cell lines when the BTK inhibitor of Formula (XVIII) and the JAK-2 inhibitor of Formula XXX (ruxolitinib) are combined. The tested cell lines included JVM-2 (prolymphocytic leukemia), Raji (B lymphocyte, Burkitt’s lymphoma), Ramos (B lymphocyte, Burkitt’s lymphoma), and Mino (mantle cell lymphoma). The dose-effect curves for these cell lines are given in FIG. 45, FIG. 46, FIG. 47, and FIG. 48.

[00176] FIG. 45 illustrates the dose-effect curves obtained for the tested JVM-2 cell line (prolymphocytic leukemia) using combined dosing of the BTK inhibitor of Formula (XVIII) (“Inh.1”) and the JAK-2 inhibitor of Formula XXX (“Inh.2”) (ruxolitinib). The y-axis (“Effect”) is given in units of Fa (fraction affected) and the x-axis (“Dose”) is given in linear units of µM.

[00177] FIG. 46 illustrates the dose-effect curves obtained for the tested Raji cell line (B lymphocyte, Burkitt’s lymphoma) using combined dosing of the BTK inhibitor of Formula (XVIII) (“Inh.1”) and the JAK-2 inhibitor of Formula XXX (“Inh.2”) (ruxolitinib). The y-axis (“Effect”) is given in units of Fa (fraction affected) and the x-axis (“Dose”) is given in linear units of µM.

[00178] FIG. 47 illustrates the dose-effect curves obtained for the tested Ramos cell line (B lymphocyte, Burkitt’s lymphoma) using combined dosing of the BTK inhibitor of Formula (XVIII) (“Inh.1”) and the JAK-2 inhibitor of Formula XXX (“Inh.2”) (ruxolitinib). The y-axis (“Effect”) is given in units of Fa (fraction affected) and the x-axis (“Dose”) is given in linear units of µM.

[00179] FIG. 48 illustrates the dose-effect curves obtained for the tested Mino cell line (mantle cell lymphoma) using combined dosing of the BTK inhibitor of Formula (XVIII) (“Inh.1”) and
the JAK-2 inhibitor of Formula XXX ("Inh.2") (ruxolitinib). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of \( \mu M \).

**[00180]** FIG. 49 illustrates the synergy observed in certain cell lines when the BTK inhibitor of Formula (XVIII) and the JAK-2 inhibitor of Formula XXX (ruxolitinib) are combined. The tested cell lines included Pfeiffer (follicular lymphoma) and SU-DHL-1 (DLBCL-ABC). The dose-effect curves for these cell lines are given in FIG. 50 and FIG. 51.

**[00181]** FIG. 50 illustrates the dose-effect curves obtained for the tested Pfeiffer cell line (follicular lymphoma) using combined dosing of the BTK inhibitor of Formula (XVIII) ("Inh.1") and the JAK-2 inhibitor of Formula XXX ("Inh.2") (ruxolitinib). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of \( \mu M \).

**[00182]** FIG. 51 illustrates the dose-effect curves obtained for the tested SU-DHL-1 cell line (follicular lymphoma) using combined dosing of the BTK inhibitor of Formula (XVIII) ("Inh.1") and the JAK-2 inhibitor of Formula XXX ("Inh.2") (ruxolitinib). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of \( \mu M \).

**[00183]** FIG. 52 illustrates the synergy observed in certain cell lines when the BTK inhibitor of Formula (XVIII) and the JAK-2 inhibitor of Formula XXX (ruxolitinib) are combined. The tested cell lines included DOHH2 (follicular lymphoma), SU-DHL-1 (DLBCL-ABC), Ly1 (DLBCL-GCB), Ly7 (DLBCL-GCB), and Ly19 (DLBCL-GCB). The dose-effect curves for these cell lines are given in FIG. 53, FIG. 54, FIG. 55, and FIG. 56, except for the Ly19 cell line, which is not graphed because of a negative slope.

**[00184]** FIG. 53 illustrates the dose-effect curves obtained for the tested DOHH2 cell line (follicular lymphoma) using combined dosing of the BTK inhibitor of Formula (XVIII) ("Inh.1") and the JAK-2 inhibitor of Formula XXX ("Inh.2") (ruxolitinib). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of \( \mu M \).

**[00185]** FIG. 54 illustrates the dose-effect curves obtained for the tested SU-DHL-1 cell line (DLBCL-ABC) using combined dosing of the BTK inhibitor of Formula (XVIII) ("Inh.1") and the JAK-2 inhibitor of Formula XXX ("Inh.2") (ruxolitinib). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of \( \mu M \).
FIG. 55 illustrates the dose-effect curves obtained for the tested Ly1 cell line (DLBCL-GCB) using combined dosing of the BTK inhibitor of Formula (XVIII) (“Inh.1”) and the JAK-2 inhibitor of Formula XXX (“Inh.2”) (ruxolitinib). The y-axis (“Effect”) is given in units of Fa (fraction affected) and the x-axis (“Dose”) is given in linear units of µM.

FIG. 56 illustrates the dose-effect curves obtained for the tested Ly7 cell line (DLBCL-GCB) using combined dosing of the BTK inhibitor of Formula (XVIII) (“Inh.1”) and the JAK-2 inhibitor of Formula XXX (“Inh.2”) (ruxolitinib). The y-axis (“Effect”) is given in units of Fa (fraction affected) and the x-axis (“Dose”) is given in linear units of µM.

FIG. 57 illustrates the synergy observed in certain cell lines when the BTK inhibitor of Formula (XVIII) and the JAK-2 inhibitor of Formula XXX (ruxolitinib) are combined. The tested cell lines included U937 (histiocytic lymphoma), Daudi (human Burkitt’s lymphoma), and K562 (leukemia, myeloid, and/or chronic myelogenous leukemia). The dose-effect curves for these cell lines are given in FIG. 58, FIG. 59, and FIG. 60.

FIG. 58 illustrates the dose-effect curves obtained for the tested U937 cell line (histiocytic lymphoma) using combined dosing of the BTK inhibitor of Formula (XVIII) (“Inh.1”) and the JAK-2 inhibitor of Formula XXX (“Inh.2”) (ruxolitinib). The y-axis (“Effect”) is given in units of Fa (fraction affected) and the x-axis (“Dose”) is given in linear units of µM.

FIG. 59 illustrates the dose-effect curves obtained for the tested Daudi cell line (human Burkitt’s lymphoma) using combined dosing of the BTK inhibitor of Formula (XVIII) (“Inh.1”) and the JAK-2 inhibitor of Formula XXX (“Inh.2”) (ruxolitinib). The y-axis (“Effect”) is given in units of Fa (fraction affected) and the x-axis (“Dose”) is given in linear units of µM.

FIG. 60 illustrates the dose-effect curves obtained for the tested K562 cell line (leukemia, myeloid, and/or chronic myelogenous leukemia) using combined dosing of the BTK inhibitor of Formula (XVIII) (“Inh.1”) and the JAK-2 inhibitor of Formula XXX (“Inh.2”) (ruxolitinib). The y-axis (“Effect”) is given in units of Fa (fraction affected) and the x-axis (“Dose”) is given in linear units of µM.

FIG. 61 illustrates the synergy observed in certain cell lines when the BTK inhibitor of Formula (XVIII) and the JAK-2 inhibitor of Formula XXX (ruxolitinib) are combined. The tested cell lines include SU-DHL-6 (DLBCL-GCB or PTCL), TMD-8 (DLBCL-ABC), HBL-1.
(DLBCL-ABC), and Rec-1 (follicular lymphoma). The dose-effect curves for these cell lines are given in FIG. 62, FIG. 63, FIG. 64, and FIG. 65.

[00193] FIG. 62 illustrates the dose-effect curves obtained for the tested SU-DHL-6 cell line (DLBCL-GCB or PTCL) using combined dosing of the BTK inhibitor of Formula (XVIII) ("Inh.1") and the JAK-2 inhibitor of Formula XXX ("Inh.2") (ruxolitinib). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of µM.

[00194] FIG. 63 illustrates the dose-effect curves obtained for the tested TMD-8 cell line (DLBCL-ABC) using combined dosing of the BTK inhibitor of Formula (XVIII) ("Inh.1") and the JAK-2 inhibitor of Formula XXX ("Inh.2") (ruxolitinib). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of µM.

[00195] FIG. 64 illustrates the dose-effect curves obtained for the tested HBL-1 cell line (DLBCL-ABC) using combined dosing of the BTK inhibitor of Formula (XVIII) ("Inh.1") and the JAK-2 inhibitor of Formula XXX ("Inh.2") (ruxolitinib). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of µM.

[00196] FIG. 65 illustrates the dose-effect curves obtained for the tested Rec-1 cell line (follicular lymphoma) using combined dosing of the BTK inhibitor of Formula (XVIII) ("Inh.1") and the JAK-2 inhibitor of Formula XXX ("Inh.2") (ruxolitinib). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of µM.

[00197] FIG. 66 illustrates the synergy observed in certain cell lines when the BTK inhibitor of Formula (XVIII) and the CDK4/6 inhibitor of Formula (100-I) (palbociclib, denoted "Inh.4") are combined. The tested cell lines include Jeko (B cell lymphoma, mantle), Maver-1 (B cell lymphoma, mantle), Pfeiffer (Follicular lymphoma), SU-DHL-1 (DLBCL-ABC), SU-DHL-2 (DLBCL-ABC), TMD-8 (DLBCL-ABC), HBL-1 (DLBCL-ABC), and Raji (B lymphocyte, Burkitt’s lymphoma).

[00198] FIG. 67 illustrates dose-effect curves for SU-DHL-1 cell line as modulated by treatment with each of BTK inhibitor of Formula (XVIII) ("Inh.1") and the CDK4/6 inhibitor of Formula (100-I) (palbociclib, denoted “Inh.4”) separately and in combination with each other.
FIG. 68 illustrates dose-effect curves for SU-DHL-2 cell line as modulated by treatment with each of BTK inhibitor of Formula (XVIII) (“Inh.1”) and the CDK4/6 inhibitor of Formula (100-I) (palbociclib, denoted “Inh.4”) separately and in combination with each other.

FIG. 69 illustrates dose-effect curves for TMD-8 cell line as modulated by treatment with each of BTK inhibitor of Formula (XVIII) (“Inh.1”) and the CDK4/6 inhibitor of Formula (100-I) (palbociclib, denoted “Inh.4”) separately and in combination with each other.

FIG. 70 illustrates dose-effect curves for HBL-1 cell line as modulated by treatment with each of BTK inhibitor of Formula (XVIII) (“Inh.1”) and the CDK4/6 inhibitor of Formula (100-I) (palbociclib, denoted “Inh.4”) separately and in combination with each other.

FIG. 71 illustrates dose-effect curves for Jeko cell line as modulated by treatment with each of BTK inhibitor of Formula (XVIII) (“Inh.1”) and the CDK4/6 inhibitor of Formula (100-I) (palbociclib, denoted “Inh.4”) separately and in combination with each other.

FIG. 72 illustrates dose-effect curves for Maver-1 cell line as modulated by treatment with each of BTK inhibitor of Formula (XVIII) (“Inh.1”) and the CDK4/6 inhibitor of Formula (100-I) (palbociclib, denoted “Inh.4”) separately and in combination with each other.

FIG. 73 illustrates dose-effect curves for Pfeiffer cell line as modulated by treatment with each of BTK inhibitor of Formula (XVIII) (“Inh.1”) and the CDK4/6 inhibitor of Formula (100-I) (palbociclib, denoted “Inh.4”) separately and in combination with each other.

FIG. 74 illustrates dose-effect curves for Raji cell line as modulated by treatment with each of BTK inhibitor of Formula (XVIII) (“Inh.1”) and the CDK4/6 inhibitor of Formula (100-I) (palbociclib, denoted “Inh.4”) separately and in combination with each other.

FIG. 75 illustrates tumor growth suppression in an orthotopic pancreatic cancer model. Mice were dosed orally with 15 mg/kg of the BTK inhibitor of Formula (XVIII), 15 mg/kg of the PI3K inhibitor of Formula (IX) (referred to as “p110d”), or a combination of both drugs. The statistical p-value (presumption against null hypothesis) is shown for each tested single agent and for the combination against the vehicle.

FIG. 76 illustrates the effects of oral dosing with 15 mg/kg of the BTK inhibitor of Formula (XVIII), 15 mg/kg of the PI3K inhibitor of Formula (IX), or a combination of both inhibitors on myeloid tumor-associated macrophages (TAMs) in pancreatic tumor-bearing mice.
FIG. 77 illustrates the effects of oral dosing with 15 mg/kg of the BTK inhibitor of Formula (XVIII), 15 mg/kg of the PI3K inhibitor of Formula (IX), or a combination of both inhibitors on myeloid-derived suppressor cells (MDSCs) in pancreatic tumor-bearing mice.

FIG. 78 illustrates the effects of oral dosing with 15 mg/kg of the BTK inhibitor of Formula (XVIII), 15 mg/kg of the PI3K inhibitor of Formula (IX), or a combination of both inhibitors on regulatory T cells (Tregs) in pancreatic tumor-bearing mice.

FIG. 79 illustrates the synergy observed in certain cell lines when the BTK inhibitor of Formula (XVIII) and the JAK-2 inhibitor of Formula LIV (pacritinib) are combined. The tested cell lines include Mino (mantle cell lymphoma), Maver-1 (B cell lymphoma, mantle cell lymphoma), Raji (B lymphocyte, Burkitt's lymphoma), JVM-2 (prolymphocytic leukemia), Daudi (Human Burkitt's lymphoma), Rec-1 (follicular lymphoma), SUP-B15 (B lymphoblast, acute lymphoblastic leukemia), CCRF (B lymphoblast, acute lymphoblastic leukemia), and SU-DHL-4 (DLBCL-ABC). The dose-effect curves for these cell lines are given in FIG. 80, FIG. 81, FIG. 82, FIG. 83, FIG. 84, FIG. 85, FIG. 86, FIG. 87, and FIG. 88.

FIG. 80 illustrates the dose-effect curves obtained for the tested Mino cell line (mantle cell lymphoma) using combined dosing of the BTK inhibitor of Formula (XVIII) (“Inh.1”) and the JAK-2 inhibitor of Formula LIV (“Inh.4”) (pacritinib). The y-axis (“Effect”) is given in units of Fa (fraction affected) and the x-axis (“Dose”) is given in linear units of µM.

FIG. 81 illustrates the dose-effect curves obtained for the tested Maver-1 cell line (B cell lymphoma, mantle cell lymphoma) using combined dosing of the BTK inhibitor of Formula (XVIII) (“Inh.1”) and the JAK-2 inhibitor of Formula LIV (“Inh.4”) (pacritinib). The y-axis (“Effect”) is given in units of Fa (fraction affected) and the x-axis (“Dose”) is given in linear units of µM.

FIG. 82 illustrates the dose-effect curves obtained for the tested Raji cell line (B lymphocyte, Burkitt's lymphoma) using combined dosing of the BTK inhibitor of Formula (XVIII) (“Inh.1”) and the JAK-2 inhibitor of Formula LIV (“Inh.4”) (pacritinib). The y-axis (“Effect”) is given in units of Fa (fraction affected) and the x-axis (“Dose”) is given in linear units of µM.
FIG. 83 illustrates the dose-effect curves obtained for the tested JVM-2 cell line (prolymphocytic leukemia) using combined dosing of the BTK inhibitor of Formula (XVIII) (“Inh.1”) and the JAK-2 inhibitor of Formula LIV (“Inh.4”) (pacritinib). The y-axis (“Effect”) is given in units of Fa (fraction affected) and the x-axis (“Dose”) is given in linear units of µM.

FIG. 84 illustrates the dose-effect curves obtained for the tested Daudi cell line (Human Burkitt's lymphoma) using combined dosing of the BTK inhibitor of Formula (XVIII) (“Inh.1”) and the JAK-2 inhibitor of Formula LIV (“Inh.4”) (pacritinib). The y-axis (“Effect”) is given in units of Fa (fraction affected) and the x-axis (“Dose”) is given in linear units of µM.

FIG. 85 illustrates the dose-effect curves obtained for the tested Rec-1 cell line (follicular lymphoma) using combined dosing of the BTK inhibitor of Formula (XVIII) (“Inh.1”) and the JAK-2 inhibitor of Formula LIV (“Inh.4”) (pacritinib). The y-axis (“Effect”) is given in units of Fa (fraction affected) and the x-axis (“Dose”) is given in linear units of µM.

FIG. 86 illustrates the dose-effect curves obtained for the tested SUP-B15 cell line (B lymphoblast, acute lymphoblastic leukemia) using combined dosing of the BTK inhibitor of Formula (XVIII) (“Inh.1”) and the JAK-2 inhibitor of Formula LIV (“Inh.4”) (pacritinib). The y-axis (“Effect”) is given in units of Fa (fraction affected) and the x-axis (“Dose”) is given in linear units of µM.

FIG. 87 illustrates the dose-effect curves obtained for the tested CCRF cell line (B lymphoblast, acute lymphoblastic leukemia) using combined dosing of the BTK inhibitor of Formula (XVIII) (“Inh.1”) and the JAK-2 inhibitor of Formula LIV (“Inh.4”) (pacritinib). The y-axis (“Effect”) is given in units of Fa (fraction affected) and the x-axis (“Dose”) is given in linear units of µM.

FIG. 88 illustrates the dose-effect curves obtained for the tested SU-DHL-4 cell line (DLBCL-ABC) using combined dosing of the BTK inhibitor of Formula (XVIII) (“Inh.1”) and the JAK-2 inhibitor of Formula LIV (“Inh.4”) (pacritinib). The y-axis (“Effect”) is given in units of Fa (fraction affected) and the x-axis (“Dose”) is given in linear units of µM.

FIG. 89 illustrates the synergy observed in certain cell lines when the BTK inhibitor of Formula (XVIII) and the JAK-2 inhibitor of Formula LIV (pacritinib) are combined. The tested cell lines include EB3 (B lymphocyte, Burkitt's lymphoma), CA46 (B lymphocyte, Burkitt's
lymphoma), DB (B cell lymphoma, mantle cell lymphoma), Pfeiffer (follicular lymphoma), DOHH2 (follicular lymphoma), Namalwa (B lymphocyte, Burkitt’s lymphoma), JVM-13 (B cell lymphoma, mantle cell lymphoma), SU-DHL-1 (DLBCL-ABC), and SU-DHL-2 (DLBCL-ABC). The dose-effect curves for these cell lines are given in FIG. 90, FIG. 91, FIG. 92, FIG. 93, FIG. 94, FIG. 95, FIG. 96, FIG. 97, and FIG. 98.

[00221] FIG. 90 illustrates the dose-effect curves obtained for the tested EB3 cell line (B lymphocyte, Burkitt's lymphoma) using combined dosing of the BTK inhibitor of Formula (XVIII) (“Inh.1”) and the JAK-2 inhibitor of Formula LIV (“Inh.4”) (pacritinib). The y-axis (“Effect”) is given in units of Fa (fraction affected) and the x-axis (“Dose”) is given in linear units of µM.

[00222] FIG. 91 illustrates the dose-effect curves obtained for the tested CA46 cell line (B lymphocyte, Burkitt's lymphoma) using combined dosing of the BTK inhibitor of Formula (XVIII) (“Inh.1”) and the JAK-2 inhibitor of Formula LIV (“Inh.4”) (pacritinib). The y-axis (“Effect”) is given in units of Fa (fraction affected) and the x-axis (“Dose”) is given in linear units of µM.

[00223] FIG. 92 illustrates the dose-effect curves obtained for the tested DB cell line (B cell lymphoma, mantle cell lymphoma) using combined dosing of the BTK inhibitor of Formula (XVIII) (“Inh.1”) and the JAK-2 inhibitor of Formula LIV (“Inh.4”) (pacritinib). The y-axis (“Effect”) is given in units of Fa (fraction affected) and the x-axis (“Dose”) is given in linear units of µM.

[00224] FIG. 93 illustrates the dose-effect curves obtained for the tested Pfeiffer cell line (follicular lymphoma) using combined dosing of the BTK inhibitor of Formula (XVIII) (“Inh.1”) and the JAK-2 inhibitor of Formula LIV (“Inh.4”) (pacritinib). The y-axis (“Effect”) is given in units of Fa (fraction affected) and the x-axis (“Dose”) is given in linear units of µM.

[00225] FIG. 94 illustrates the dose-effect curves obtained for the tested DOHH2 cell line (follicular lymphoma) using combined dosing of the BTK inhibitor of Formula (XVIII) (“Inh.1”) and the JAK-2 inhibitor of Formula LIV (“Inh.4”) (pacritinib). The y-axis (“Effect”) is given in units of Fa (fraction affected) and the x-axis (“Dose”) is given in linear units of µM.
FIG. 95 illustrates the dose-effect curves obtained for the tested Namalwa cell line (B lymphocyte, Burkitt's lymphoma) using combined dosing of the BTK inhibitor of Formula (XVIII) (“Inh.1”) and the JAK-2 inhibitor of Formula LIV (“Inh.4”) (pacritinib). The y-axis (“Effect”) is given in units of Fa (fraction affected) and the x-axis (“Dose”) is given in linear units of µM.

FIG. 96 illustrates the dose-effect curves obtained for the tested JVM-13 cell line (B cell lymphoma, mantle cell lymphoma) using combined dosing of the BTK inhibitor of Formula (XVIII) (“Inh.1”) and the JAK-2 inhibitor of Formula LIV (“Inh.4”) (pacritinib). The y-axis (“Effect”) is given in units of Fa (fraction affected) and the x-axis (“Dose”) is given in linear units of µM.

FIG. 97 illustrates the dose-effect curves obtained for the tested SU-DHL-1 cell line (DLBCL-ABC) using combined dosing of the BTK inhibitor of Formula (XVIII) (“Inh.1”) and the JAK-2 inhibitor of Formula LIV (“Inh.4”) (pacritinib). The y-axis (“Effect”) is given in units of Fa (fraction affected) and the x-axis (“Dose”) is given in linear units of µM.

FIG. 98 illustrates the dose-effect curves obtained for the tested SU-DHL-2 cell line (DLBCL-ABC) using combined dosing of the BTK inhibitor of Formula (XVIII) (“Inh.1”) and the JAK-2 inhibitor of Formula LIV (“Inh.4”) (pacritinib). The y-axis (“Effect”) is given in units of Fa (fraction affected) and the x-axis (“Dose”) is given in linear units of µM.

FIG. 99 illustrates the synergy observed in certain cell lines when the BTK inhibitor of Formula (XVIII) and the JAK-2 inhibitor of Formula LIV (pacritinib) are combined. The tested cell lines include Jeko (B cell lymphoma, mantle cell lymphoma), TMD-8 (DLBCL-ABC), SU-DHL6 (DLBCL-GCB), Ramos (human Burkitt's lymphoma), HBL-1 (DLBCL-ABC), SU-DHL-10 (DLBCL-GCB), OCI-Ly7 (DLBCL-ABC), and OCI-Ly3 (DLBCL-ABC). The dose-effect curves for these cell lines are given in FIG. 100, FIG. 101, FIG. 102, FIG. 103, FIG. 104, FIG. 105, FIG. 106, and FIG. 107.

FIG. 100 illustrates the dose-effect curves obtained for the tested Jeko cell line (B cell lymphoma, mantle cell lymphoma) using combined dosing of the BTK inhibitor of Formula (XVIII) (“Inh.1”) and the JAK-2 inhibitor of Formula LIV (“Inh.4”) (pacritinib). The y-axis (“Effect”) is given in units of Fa (fraction affected) and the x-axis (“Dose”) is given in linear units of µM.
FIG. 101 illustrates the dose-effect curves obtained for the tested TMD-8 cell line (DLBCL-ABC) using combined dosing of the BTK inhibitor of Formula (XVIII) (“Inh.1”) and the JAK-2 inhibitor of Formula LIV (“Inh.4”) (pacritinib). The y-axis (“Effect”) is given in units of Fa (fraction affected) and the x-axis (“Dose”) is given in linear units of µM.

FIG. 102 illustrates the dose-effect curves obtained for the tested SU-DHL6 cell line (DLBCL-GCB) using combined dosing of the BTK inhibitor of Formula (XVIII) (“Inh.1”) and the JAK-2 inhibitor of Formula LIV (“Inh.4”) (pacritinib). The y-axis (“Effect”) is given in units of Fa (fraction affected) and the x-axis (“Dose”) is given in linear units of µM.

FIG. 103 illustrates the dose-effect curves obtained for the tested Ramos cell line (human Burkitt's lymphoma) using combined dosing of the BTK inhibitor of Formula (XVIII) (“Inh.1”) and the JAK-2 inhibitor of Formula LIV (“Inh.4”) (pacritinib). The y-axis (“Effect”) is given in units of Fa (fraction affected) and the x-axis (“Dose”) is given in linear units of µM.

FIG. 104 illustrates the dose-effect curves obtained for the tested HBL-1 cell line (DLBCL-ABC) using combined dosing of the BTK inhibitor of Formula (XVIII) (“Inh.1”) and the JAK-2 inhibitor of Formula LIV (“Inh.4”) (pacritinib). The y-axis (“Effect”) is given in units of Fa (fraction affected) and the x-axis (“Dose”) is given in linear units of µM.

FIG. 105 illustrates the dose-effect curves obtained for the tested SU-DHL-10 cell line (DLBCL-GCB) using combined dosing of the BTK inhibitor of Formula (XVIII) (“Inh.1”) and the JAK-2 inhibitor of Formula LIV (“Inh.4”) (pacritinib). The y-axis (“Effect”) is given in units of Fa (fraction affected) and the x-axis (“Dose”) is given in linear units of µM.

FIG. 106 illustrates the dose-effect curves obtained for the tested OCI-Ly7 cell line (DLBCL-ABC) using combined dosing of the BTK inhibitor of Formula (XVIII) (“Inh.1”) and the JAK-2 inhibitor of Formula LIV (“Inh.4”) (pacritinib). The y-axis (“Effect”) is given in units of Fa (fraction affected) and the x-axis (“Dose”) is given in linear units of µM.

FIG. 107 illustrates the dose-effect curves obtained for the tested OCI-Ly3 cell line (DLBCL-ABC) using combined dosing of the BTK inhibitor of Formula (XVIII) (“Inh.1”) and the JAK-2 inhibitor of Formula LIV (“Inh.4”) (pacritinib). The y-axis (“Effect”) is given in units of Fa (fraction affected) and the x-axis (“Dose”) is given in linear units of µM.
FIG. 108 illustrates the effects of vehicle on flux at two timepoints, as a control for comparison with FIG. 109, in the ID8 syngeneic orthotropic ovarian cancer model.

FIG. 109 illustrates the effects of the BTK inhibitor of Formula (XVIII) on flux at two timepoints, for comparison with FIG. 108, in the ID8 syngeneic orthotropic ovarian cancer model.

FIG. 110 illustrates tumor response to treatment with the BTK inhibitor of Formula (XVIII) correlates with a significant reduction in immunosuppressive tumor associated lymphocytes in tumor-bearing mice, in comparison to a control (vehicle).

FIG. 111 illustrates that treatment with the BTK inhibitor of Formula (XVIII) impairs ID8 ovarian cancer growth in the syngeneic murine model in comparison to a control (vehicle).

FIG. 112 illustrates that treatment with the BTK inhibitor of Formula (XVIII) induces a tumor response that correlates with a significant reduction in total B cells in tumor-bearing mice.

FIG. 113 illustrates that treatment with the BTK inhibitor of Formula (XVIII) induces a tumor response that correlates with a significant reduction in B regulatory cells (Bregs) in tumor-bearing mice.

FIG. 114 illustrates that treatment with the BTK inhibitor of Formula (XVIII) induces a tumor response that correlates with a significant reduction in immunosuppressive tumor associated Tregs.

FIG. 115 illustrates that treatment with the BTK inhibitor of Formula (XVIII) induces a tumor response that correlates with an increase in CD8⁺ T cells.

FIG. 116 illustrates the effects on tumor volume of vehicle (measured in mm³) of the BTK inhibitor of Formula (XVIII), a combination of the BTK inhibitor of Formula (XVIII) and gemcitabine (“Gem”), and gemcitabine alone.

FIG. 117 illustrates the effects on the amount of CD8⁺ T cells, given as a percentage of cells expressing the T cell receptor (CD3), of the BTK inhibitor of Formula (XVIII), a combination of the BTK inhibitor of Formula (XVIII) and gemcitabine (“Gem”), and gemcitabine alone.

FIG. 118 illustrates the effects on the percentage of CD4⁺, CD25⁺, and FoxP3⁺ T
regulatory cells ("Tregs"), given as a percentage of cells expressing the T cell receptor (CD3), of the BTK inhibitor of Formula (XVIII), a combination of the BTK inhibitor of Formula (XVIII) and gemcitabine ("Gem"), and gemcitabine alone.

[00250] FIG. 119 illustrates the effects on the percentage of CD11b\(^+\), LY6C\(^{hi}\), F4/80\(^-\), and Csf1r\(^+\) tumor-associated macrophages ("TAMs"), given as a percentage of cells expressing the T cell receptor (CD3), of the BTK inhibitor of Formula (XVIII), a combination of the BTK inhibitor of Formula (XVIII) and gemcitabine ("Gem"), and gemcitabine alone.

[00251] FIG. 120 illustrates the effects on the percentage of Gr1\(^\downarrow\) and LY6C\(^{hi}\), F4/80\(^-\), and Csf1r\(^+\) myeloid-derived suppressor cells ("MDSCs"), given as a percentage of cells expressing the T cell receptor (CD3), of the BTK inhibitor of Formula (XVIII), a combination of the BTK inhibitor of Formula (XVIII) and gemcitabine ("Gem"), and gemcitabine alone.

[00252] FIG. 121 illustrates representative photomicrographs and comparison of maximal thrombus size in laser injured arterioles of VWF HA1 mutant mice infused with human platelets in the absence or presence of various BTK inhibitors. Representative photomicrographs are given as a comparison of maximal thrombus size in laser-injured arterioles (1 µM concentrations shown).

[00253] FIG. 122 illustrates a quantitative comparison obtained by in vivo analysis of early thrombus dynamics in a humanized mouse laser injury model using three BTK inhibitors at a concentration 1 µM.

[00254] FIG. 123 illustrates the effect of the tested BTK inhibitors on thrombus formation. The conditions used were N=4, 3 mice per drug; anti-clotting agents < 2000 µM\(^2\). In studies with ibrutinib, 48% MCL bleeding events were observed with 560 mg QD and 63% CLL bleeding events were observed with 420 mg QD, where bleeding event is defined as subdural hematoma, ecchymoses, GI bleeding, or hematuria.

[00255] FIG. 124 illustrates the effect of the concentration of the tested BTK inhibitors on thrombus formation.

[00256] FIG. 125 illustrates the results of GPVI platelet aggregation studies of Formula XVIII (IC50 = 1.15 µM) and Formula XX-A (ibrutinib, IC50 = 0.13 µM).

[00257] FIG. 126 illustrates the results of GPVI platelet aggregation studies of Formula XVIII
and Formula XX-A (ibrutinib).

[00258] FIG. 127 illustrates the effects of treatment with single-active pharmaceutical ingredient Formula (XVIII) on tumor volumes in the KPC pancreatic cancer model.

[00259] FIG. 128 illustrates the results of analysis of tumor tissues showing that immunosuppressive TAMs (CD11b⁺Ly6ClowF4/80⁺Csf1r⁺) were significantly reduced with Formula (XVIII) treatment in the KPC pancreatic cancer model.

[00260] FIG. 129 illustrates the results of analysis of tumor tissues showing that immunosuppressive MDSCs (Gr1⁺Ly6CHi) were significantly reduced with Formula (XVIII) treatment in the KPC pancreatic cancer model.

[00261] FIG. 130 illustrates the results of analysis of tumor tissues showing that immunosuppressive Tregs (CD4⁻CD25⁺FoxP3⁻) were significantly reduced with Formula (XVIII) treatment in the KPC pancreatic cancer model.

[00262] FIG. 131 illustrates that the decrease in immunosuppressive TAMs, MDSCs, and Tregs in the KPC pancreatic cancer model correlated with a significant increase in CD8⁺ cells.

[00263] FIG. 132 shows *in vitro* analysis of antibody-dependent NK cell–mediated INF-γ release with BTK inhibitors. To evaluate NK cell function, purified NK cells were isolated from healthy peripheral blood mononuclear cells and cultured with 0.1 or 1 μM of ibrutinib or 1 μM of Formula (XVIII) for 4 hours together with rituximab-coated (10 μg/mL) lymphoma cells, DHL4, or trastuzumab-coated (10 μg/mL) HER2+ breast cancer cells, HER18, and supernatant was harvested and analyzed by enzyme-linked immunosorbent assay for interferon-γ (IFN-γ). All *in vitro* experiments were performed in triplicate. Labels are defined as follows: *p = 0.018, **p = 0.002, ***p = 0.001.

[00264] FIG. 133 shows *in vitro* analysis of antibody-dependent NK cell–mediated degranulation with BTK inhibitors. To evaluate NK cell function, purified NK cells were isolated from healthy peripheral blood mononuclear cells and cultured with 0.1 or 1 μM of ibrutinib or 1 μM of Formula (XVIII) for 4 hours together with rituximab-coated (10 μg/mL) lymphoma cells, DHL4, or trastuzumab-coated (10 μg/mL) HER2+ breast cancer cells, HER18, and NK cells isolated and analyzed for degranulation by flow cytometry for CD107a mobilization. All *in vitro* experiments were performed in triplicate. Labels are defined as
follows: *p = 0.01, **p = 0.002, ***p = 0.003, ****p = 0.0005.

[00265] FIG. 134 shows that ibrutinib antagonizes antibody-dependent NK cell–mediated cytotoxicity using the Raji cell line. NK cell cytotoxicity as percent lysis of tumor cells was analyzed in chromium release assays with purified NK cells incubated with chromium-labeled Raji cells for 4 hours at variable rituximab concentrations at a constant effector:target ratio of 25:1 and ibrutinib (1 µM), Formula (II) (1 µM), or other ITK sparing BTK inhibitors CGI-1746, inhibA (1 µM) and BGB-3111 (“inhib B,” 1 µM). All in vitro experiments were performed in triplicate. Labels are defined as follows: *p = 0.001.

[00266] FIG. 135 shows a summary of the results given in FIG. 134 at the highest concentration of rituximab (“Ab”) (10 µg/mL).

[00267] FIG. 136 shows that ibrutinib antagonizes antibody-dependent NK cell–mediated cytotoxicity in primary CLL cells, as with Raji cells in FIG. 134.

[00268] FIG. 137 illustrates in vivo potency of Formula (XVIII) (labeled “BTK inhibitor”) and ibrutinib. Mice were gavaged at increasing drug concentration and sacrificed at one time point (3 h post-dose). BCR is stimulated with IgM and the expression of activation markers CD69 and CD86 are monitored by flow cytometry to determine EC$_{50}$’s. The results show that Formula (XVIII) is more potent at inhibiting expression of activation makers than ibrutinib.

[00269] FIG. 138 illustrates the results of the clinical study of Formula (XVIII) (labeled “BTK inhibitor”) in CLL, which are shown in comparison to the results reported for ibrutinib in Figure 1A of Byrd, et al., N. Engl. J. Med. 2013, 369, 32-42. The results show that the BTK inhibitor of Formula (XVIII) causes a much smaller relative increase and much faster decrease in absolute lymphocyte count (ALC) relative to the BTK inhibitor ibrutinib. The sum of the product of greatest diameters (SPD) also decreases more rapidly during treatment with the BTK inhibitor than with the BTK inhibitor ibrutinib.

[00270] FIG. 139 shows overall response data shown by SPD of enlarged lymph nodes in CLL patients as a function of dose of the BTK inhibitor of Formula (XVIII).

[00271] FIG. 140 shows a comparison of progression-free survival (PFS) in CLL patients treated with the BTK inhibitor ibrutinib or the BTK inhibitor of Formula (XVIII). The ibrutinib
data is taken from Byrd, et al., *N. Engl. J. Med.* 2013, 369, 32-42. CLL patients treated with Formula (XVIII) for at least 8 days are included.

**FIG. 141** shows a comparison of number of patients at risk in CLL patients treated with the BTK inhibitor ibrutinib or the BTK inhibitor of Formula (XVIII). CLL patients treated with Formula (XVIII) for at least 8 days are included.

**FIG. 142** shows a comparison of progression-free survival (PFS) in CLL patients exhibiting the 17p deletion and treated with the BTK inhibitor ibrutinib or the BTK inhibitor of Formula (XVIII). The ibrutinib data is taken from Byrd, et al., *N. Engl. J. Med.* 2013, 369, 32-42.

**FIG. 143** shows a comparison of number of patients at risk in CLL patients exhibiting the 17p deletion and treated with the BTK inhibitor ibrutinib or the BTK inhibitor of Formula (XVIII). The ibrutinib data is taken from Byrd, et al., *N. Engl. J. Med.* 2013, 369, 32-42. CLL patients treated with Formula (XVIII) for at least 8 days are included.

**FIG. 144** shows improved BTK target occupancy of Formula (XVIII) at lower dosage versus ibrutinib in relapsed/refractory CLL patients.

**FIG. 145** shows the % change in myeloid-derived suppressor cell (MDSC) (monocytic) level over 28 days versus % ALC change at Cycle 1, day 28 (C1D28) with trendlines.

**FIG. 146** shows the % change in MDSC (monocytic) level over 28 days versus % ALC change at Cycle 2, day 28 (C2D28) with trendlines.

**FIG. 147** shows the % change in natural killer (NK) cell level over 28 days versus % ALC change at Cycle 1, day 28 (C2D28) with trendlines.

**FIG. 148** shows the % change in NK cell level over 28 days versus % ALC change at Cycle 2, day 28 (C2D28) with trendlines.

**FIG. 149** compares the % change in MDSC (monocytic) level and % change in NK cell level over 28 days versus % ALC change with the % change in level of CD4⁺ T cells, CD8⁺ T cells, CD4⁺/CD8⁺ T cell ratio, NK-T cells, PD-1⁺ CD4⁺ T cells, and PD-1⁺ CD8⁺ T cells, also versus % ALC change, at Cycle 1 day 28 (C1D28). Trendlines are shown for % change in MDSC (monocytic) level and % change in NK cell level.
FIG. 150 compares the % change in MDSC (monocytic) level and % change in NK cell level over 28 days versus % ALC change with the % change in level of CD4<sup>+</sup> T cells, CD8<sup>+</sup> T cells, CD4<sup>+</sup>/CD8<sup>+</sup> T cell ratio, NK-T cells, PD-1<sup>+</sup> CD4<sup>+</sup> T cells, and PD-1<sup>+</sup> CD8<sup>+</sup> T cells, also versus % ALC change, at Cycle 2 day 28 (C2D28). Trendlines are shown for % change in MDSC (monocytic) level and % change in NK cell level.

FIG. 151 shows additional results related to the data presented in FIG. 138.

FIG. 152 shows additional results related to the data presented in FIG. 144, and includes BID dosing results.

FIG. 153 illustrates PFS for patients with 17p deletion.

FIG. 154 illustrates PFS across relapsed/refractory patients with 17p deletion and with 11q deletion and no 17p deletion.

FIG. 155 illustrates PFS for patients with 11q deletion and no 17p deletion.

FIG. 156 illustrates additional SPD results from the clinical study of Formula (XVIII) in relapsed/refractory CLL patients.

FIG. 157 illustrates that treatment of CLL patients with Formula (XVIII) resulted in increased apoptosis.

FIG. 158 illustrates a decrease in CXCL12 levels observed in patients treated with Formula (XVIII).

FIG. 159 illustrates a decrease in CCL2 levels observed in patients treated with Formula (XVIII).

FIG. 160 illustrates BTK inhibitory effects on MDSCs.

FIG. 161 illustrates the dosing schema used with the KrasLA2 non-small cell lung cancer (NSCLC) model.

FIG. 162 illustrates tumor volume variation from baseline as assessed by microcomputerized tomography (microCT) in the KrasL2 NSCLC model.
FIG. 163 illustrates TAMs in the KrasL2 NSCLC model, and indicates that Formula (XVIII) induces a tumor response that correlates with a significant reduction in immunosuppressive tumor associated TAMs.

FIG. 164 illustrates MDSCs in the KrasL2 NSCLC model, and indicates that Formula (XVIII) induces a tumor response that correlates with a significant reduction in immunosuppressive tumor associated MDSCs.

FIG. 165 illustrates Tregs in the KrasL2 NSCLC model, and indicates that Formula (XVIII) induces a tumor response that correlates with a significant reduction in immunosuppressive tumor associated Tregs.

FIG. 166 illustrates CD8+ T cells in the KrasL2 NSCLC model.

FIG. 167 illustrates in vitro potency in whole blood of Formula (XVIII), ibrutinib and CC-292 in inhibition of signals through the B cell receptor.

FIG. 168 illustrates EGF receptor phosphorylation in vitro for Formula (XVIII) and ibrutinib.

FIG. 169 shows the results of the brain penetration study, demonstrating the surprising result that Formula (XVIII) crosses the blood-brain barrier.

FIG. 170 illustrates the synergy observed in certain cell lines when the BTK inhibitor of Formula (XXVIII-R) (ONO-4059) and the PI3K-δ inhibitor of Formula (XVI) (idelalisib) are combined. The tested cell lines include TMD-8 (DLBCL-ABC), Mino (MCL), RI-1 (NHL), DOHH-2 (follicular lymphoma), and SU-DHL-6 (DLBCL-GCB). The dose-effect curves for these cell lines are given in FIG. 171, FIG. 172, FIG. 173, FIG. 174, and FIG. 175.

FIG. 171 illustrates the dose-effect curves obtained for the tested TMD-8 cell line (DLBCL-ABC) using combined dosing of the BTK inhibitor of Formula (XXVIII-R) (ONO-4059) (“Inh.6”) and the PI3K-δ inhibitor of Formula (XVI) (idelalisib) (“Inh.7”). The y-axis (“Effect”) is given in units of Fa (fraction affected) and the x-axis (“Dose”) is given in linear units of µM.

FIG. 172 illustrates the dose-effect curves obtained for the tested Mino cell line (MCL) using combined dosing of the BTK inhibitor of Formula (XXVIII-R) (ONO-4059) (“Inh.6”) and
the PI3K-δ inhibitor of Formula (XVI) (idelalisib) (“Inh.7”). The y-axis (“Effect”) is given in units of Fa (fraction affected) and the x-axis (“Dose”) is given in linear units of µM.

[00304] FIG. 173 illustrates the dose-effect curves obtained for the tested RI-1 cell line (NHL) using combined dosing of the BTK inhibitor of Formula (XXVIII-R) (ONO-4059) (“Inh.6”) and the PI3K-δ inhibitor of Formula (XVI) (idelalisib) (“Inh.7”). The y-axis (“Effect”) is given in units of Fa (fraction affected) and the x-axis (“Dose”) is given in linear units of µM.

[00305] FIG. 174 illustrates the dose-effect curves obtained for the tested DOHH-2 cell line (follicular lymphoma) using combined dosing of the BTK inhibitor of Formula (XXVIII-R) (ONO-4059) (“Inh.6”) and the PI3K-δ inhibitor of Formula (XVI) (idelalisib) (“Inh.7”). The y-axis (“Effect”) is given in units of Fa (fraction affected) and the x-axis (“Dose”) is given in linear units of µM.

[00306] FIG. 175 illustrates the dose-effect curves obtained for the tested SU-DHL-6 cell line (DLBCL-GCB) using combined dosing of the BTK inhibitor of Formula (XXVIII-R) (ONO-4059) (“Inh.6”) and the PI3K-δ inhibitor of Formula (XVI) (idelalisib) (“Inh.7”). The y-axis (“Effect”) is given in units of Fa (fraction affected) and the x-axis (“Dose”) is given in linear units of µM.

BRIEF DESCRIPTION OF THE SEQUENCE LISTINGS

[00307] SEQ ID NO:1 is the heavy chain amino acid sequence of the anti-CD20 monoclonal antibody rituximab.

[00308] SEQ ID NO:2 is the light chain amino acid sequence of the anti-CD20 monoclonal antibody rituximab.

[00309] SEQ ID NO:3 is the heavy chain amino acid sequence of the anti-CD20 monoclonal antibody obinutuzumab.

[00310] SEQ ID NO:4 is the light chain amino acid sequence of the anti-CD20 monoclonal antibody obinutuzumab.

[00311] SEQ ID NO:5 is the variable heavy chain amino acid sequence of the anti-CD20 monoclonal antibody ofatumumab.

[00312] SEQ ID NO:6 is the variable light chain amino acid sequence of the anti-CD20.
monoclonal antibody ofatumumab.

[00313] SEQ ID NO:7 is the Fab fragment heavy chain amino acid sequence of the anti-CD20 monoclonal antibody ofatumumab.

[00314] SEQ ID NO:8 is the Fab fragment light chain amino acid sequence of the anti-CD20 monoclonal antibody ofatumumab.

[00315] SEQ ID NO:9 is the heavy chain amino acid sequence of the anti-CD20 monoclonal antibody veltuzumab.

[00316] SEQ ID NO:10 is the light chain amino acid sequence of the anti-CD20 monoclonal antibody veltuzumab.

[00317] SEQ ID NO:11 is the heavy chain amino acid sequence of the anti-CD20 monoclonal antibody tositumomab.

[00318] SEQ ID NO:12 is the light chain amino acid sequence of the anti-CD20 monoclonal antibody tositumomab.

[00319] SEQ ID NO:13 is the heavy chain amino acid sequence of the anti-CD20 monoclonal antibody ibritumomab.

[00320] SEQ ID NO:14 is the light chain amino acid sequence of the anti-CD20 monoclonal antibody ibritumomab.

DETAILED DESCRIPTION OF THE INVENTION

[00321] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs. All patents and publications referred to herein are incorporated by reference in their entireties.

[00322] The terms "co-administration," "co-administering," "administered in combination with," and "administering in combination with" as used herein, encompass administration of two or more active agents to a subject so that both the active agents and/or their metabolites are present in the subject at the same time. Co-administration includes simultaneous administration in separate compositions, administration at different times in separate compositions, or administration in a composition in which two or more active agents are present.
The term "effective amount" or "therapeutically effective amount" refers to that amount of a compound or combination of compounds as described herein that is sufficient to effect the intended application including, but not limited to, disease treatment. A therapeutically effective amount may vary depending upon the intended application (in vitro or in vivo), or the subject and disease condition being treated (e.g., the weight, age and gender of the subject), the severity of the disease condition, the manner of administration, etc. which can readily be determined by one of ordinary skill in the art. The term also applies to a dose that will induce a particular response in target cells, (e.g., the reduction of platelet adhesion and/or cell migration). The specific dose will vary depending on the particular compounds chosen, the dosing regimen to be followed, whether the compound is administered in combination with other compounds, timing of administration, the tissue to which it is administered, and the physical delivery system in which the compound is carried.

A "therapeutic effect" as that term is used herein, encompasses a therapeutic benefit and/or a prophylactic benefit as described herein. A prophylactic effect includes delaying or eliminating the appearance of a disease or condition, delaying or eliminating the onset of symptoms of a disease or condition, slowing, halting, or reversing the progression of a disease or condition, or any combination thereof.

The term "pharmacologically acceptable salt" refers to salts derived from a variety of organic and inorganic counter ions known in the art. Pharmacologically acceptable acid addition salts can be formed with inorganic acids and organic acids. Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid and phosphoric acid. Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid and salicylic acid. Pharmacologically acceptable base addition salts can be formed with inorganic and organic bases. Inorganic bases from which salts can be derived include, for example, sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese and aluminum. Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and
basic ion exchange resins. Specific examples include isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, and ethanolamine. In selected embodiments, the pharmaceutically acceptable base addition salt is chosen from ammonium, potassium, sodium, calcium, and magnesium salts. The term “cocrystal” refers to a molecular complex derived from a number of cocrystal formers known in the art. Unlike a salt, a cocrystal typically does not involve hydrogen transfer between the cocrystal and the drug, and instead involves intermolecular interactions, such as hydrogen bonding, aromatic ring stacking, or dispersive forces, between the cocrystal former and the drug in the crystal structure.

[00326] “Pharmaceutically acceptable carrier” or “pharmaceutically acceptable excipient” is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and inert ingredients. The use of such pharmaceutically acceptable carriers or pharmaceutically acceptable excipients for active pharmaceutical ingredients is well known in the art. Except insofar as any conventional pharmaceutically acceptable carrier or pharmaceutically acceptable excipient is incompatible with the active pharmaceutical ingredient, its use in the therapeutic compositions of the invention is contemplated. Additional active pharmaceutical ingredients, such as other drugs, can also be incorporated into the described compositions and methods.

[00327] "Prodrug" is intended to describe a compound that may be converted under physiological conditions or by solvolysis to a biologically active compound described herein. Thus, the term "prodrug" refers to a precursor of a biologically active compound that is pharmaceutically acceptable. A prodrug may be inactive when administered to a subject, but is converted in vivo to an active compound, for example, by hydrolysis. The prodrug compound often offers the advantages of solubility, tissue compatibility or delayed release in a mammalian organism (see, e.g., Bundgaard, H., Design of Prodrugs (1985) (Elsevier, Amsterdam). The term "prodrug" is also intended to include any covalently bonded carriers, which release the active compound in vivo when administered to a subject. Prodrugs of an active compound, as described herein, may be prepared by modifying functional groups present in the active compound in such a way that the modifications are cleaved, either in routine manipulation or in vivo, to yield the active parent compound. Prodrugs include, for example, compounds wherein a hydroxy, amino or mercapto group is bonded to any group that, when the prodrug of the active compound is
administered to a mammalian subject, cleaves to form a free hydroxy, free amino or free mercapto group, respectively. Examples of prodrugs include, but are not limited to, acetates, formates and benzoate derivatives of an alcohol, various ester derivatives of a carboxylic acid, or acetamide, formamide and benzamide derivatives of an amine functional group in the active compound.

[00328] As used herein, the term “warhead” or “warhead group” refers to a functional group present on a compound of the present invention wherein that functional group is capable of covalently binding to an amino acid residue (such as cysteine, lysine, histidine, or other residues capable of being covalently modified) present in the binding pocket of the target protein, thereby irreversibly inhibiting the protein.

[00329] The term "in vivo" refers to an event that takes place in a subject's body.

[00330] The term "in vitro" refers to an event that takes places outside of a subject's body. In vitro assays encompass cell-based assays in which cells alive or dead are employed and may also encompass a cell-free assay in which no intact cells are employed.

[00331] Unless otherwise stated, the chemical structures depicted herein are intended to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds where one or more hydrogen atoms is replaced by deuterium or tritium, or wherein one or more carbon atoms is replaced by \(^{13}\)C- or \(^{14}\)C-enriched carbons, are within the scope of this invention.

[00332] When ranges are used herein to describe, for example, physical or chemical properties such as weight or chemical formulae, all combinations and subcombinations of ranges and specific embodiments therein are intended to be included. Use of the term "about" when referring to a number or a numerical range means that the number or numerical range referred to is an approximation within experimental variability (or within statistical experimental error), and thus the number or numerical range may vary. The variation is typically from 0% to 15%, preferably from 0% to 10%, more preferably from 0% to 5% of the stated number or numerical range. The term "comprising" (and related terms such as "comprise" or "comprises" or "having" or "including") includes those embodiments such as, for example, an embodiment of any
composition of matter, method or process that "consist of" or "consist essentially of" the described features.

[00333] "Alkyl" refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing no unsaturation, having from one to ten carbon atoms (e.g., \( \text{C}_{1-10} \) alkyl or \( \text{C}_{1-10} \) alkyl). Whenever it appears herein, a numerical range such as "1 to 10" refers to each integer in the given range - e.g., "1 to 10 carbon atoms" means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, etc., up to and including 10 carbon atoms, although the definition is also intended to cover the occurrence of the term "alkyl" where no numerical range is specifically designated. Typical alkyl groups include, but are in no way limited to, methyl, ethyl, propyl, isopropyl, n-butyl, iso-butyl, sec-butyl isobutyl, tertiary butyl, pentyl, isopentyl, hexyl, heptyl, octyl, nonyl and decyl. The alkyl moiety may be attached to the rest of the molecule by a single bond, such as for example, methyl (Me), ethyl (Et), n-propyl (Pr), 1-methylethyl (iso-propyl), n-butyl, n-pentyl, 1,1-dimethylethyl (t-butyl) and 3-methylhexyl. Unless stated otherwise specifically in the specification, an alkyl group is optionally substituted by one or more of substituents which are independently heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroaryllalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, -OR', -SR', -OC(O)-R', -N(R')_2, -C(O)R', -C(O)OR', -OC(O)N(R')_2, -C(O)N(R')_2, -N(R')C(O)OR', -N(R')C(O)R', -N(R')C(O)N(R')_2, -N(R')C(NR')_2N(R')_2, -N(R')S(O)R' (where t is 1 or 2), -S(O)R' (where t is 1 or 2), -S(O)N(R')_2 (where t is 1 or 2), or PO_3(R')_2 where each R' is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroaryllalkyl.

[00334] "Alkylaryl" refers to an -(alkyl)aryl radical where aryl and alkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for aryl and alkyl respectively.

[00335] "Alkylhetaryl" refers to an -(alkyl)hetaryl radical where hetaryl and alkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for aryl and alkyl respectively.
"Alkylheterocycloalkyl" refers to an -(alkyl) heterocycyl radical where alkyl and heterocycloalkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heterocycloalkyl and alkyl respectively.

An "alkene" moiety refers to a group consisting of at least two carbon atoms and at least one carbon-carbon double bond, and an "alkyne" moiety refers to a group consisting of at least two carbon atoms and at least one carbon-carbon triple bond. The alkyl moiety, whether saturated or unsaturated, may be branched, straight chain, or cyclic.

"Alkenyl" refers to a straight or branched hydrocarbon chain radical group consisting solely of carbon and hydrogen atoms, containing at least one double bond, and having from two to ten carbon atoms (i.e., (C₂₋₁₀)alkenyl or C₂₋₁₀ alkenyl). Whenever it appears herein, a numerical range such as "2 to 10" refers to each integer in the given range - e.g., "2 to 10 carbon atoms" means that the alkenyl group may consist of 2 carbon atoms, 3 carbon atoms, etc., up to and including 10 carbon atoms. The alkenyl moiety may be attached to the rest of the molecule by a single bond, such as for example, ethenyl (i.e., vinyl), prop-1-enyl (i.e., allyl), but-1-enyl, pent-1-enyl and penta-1,4-dienyl. Unless stated otherwise specifically in the specification, an alkenyl group is optionally substituted by one or more substituents which are independently alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, etc.

"Alkenyl-cycloalkyl" refers to an -(alkenyl)cycloalkyl radical where alkenyl and cycloalkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for alkenyl and cycloalkyl respectively.

"Alkynyl" refers to a straight or branched hydrocarbon chain radical group consisting solely of carbon and hydrogen atoms, containing at least one triple bond, having from two to ten carbon atoms (i.e., (C₂₋₁₀)alkynyl or C₂₋₁₀ alkynyl). Whenever it appears herein, a numerical
range such as "2 to 10" refers to each integer in the given range - e.g., "2 to 10 carbon atoms" means that the alkynyl group may consist of 2 carbon atoms, 3 carbon atoms, etc., up to and including 10 carbon atoms. The alkynyl may be attached to the rest of the molecule by a single bond, for example, ethynyl, propynyl, butynyl, pentynyl and hexynyl. Unless stated otherwise specifically in the specification, an alkynyl group is optionally substituted by one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilyl, -OR′, -SR′, -OC(O)-R′, -N(R′)2, -C(O)R′, -C(O)OR′, -OC(O)N(R′)2, -C(O)N(R′)2, -N(R′)C(O)OR′, -N(R′)C(O)R′, -N(R′)C(O)N(R′)2, N(R′)C(NR′)N(R′)2, -N(R′)S(O)R′ (where t is 1 or 2), -S(O)OR′ (where t is 1 or 2), -S(O)N(R′)2 (where t is 1 or 2), or PO3(R′)2, where each R′ is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[00341] "Alkynyl-cycloalkyl" refers to an -(alkynyl)cycloalkyl radical where alkynyl and cycloalkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for alkynyl and cycloalkyl respectively.

[00342] "Carboxaldehyde" refers to a -(C=O)H radical.

[00343] "Carboxyl" refers to a -(C=O)OH radical.

[00344] "Cyano" refers to a -CN radical.

[00345] "Cycloalkyl" refers to a monocyclic or polycyclic radical that contains only carbon and hydrogen, and may be saturated, or partially unsaturated. Cycloalkyl groups include groups having from 3 to 10 ring atoms (i.e. C3−10 cycloalkyl or C3−10 cycloalkyl). Whenever it appears herein, a numerical range such as "3 to 10" refers to each integer in the given range - e.g., "3 to 10 carbon atoms" means that the cycloalkyl group may consist of 3 carbon atoms, etc., up to and including 10 carbon atoms. Illustrative examples of cycloalkyl groups include, but are not limited to the following moieties: cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, norbornyl, and the like. Unless stated otherwise specifically in the specification, a cycloalkyl group is optionally substituted by one or more substituents which independently are: alkyl, heteroalkyl, alkenyl,
alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroaryalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilyl, -OR, -SR, -OC(O)-R', -N(R')<sub>2</sub>, -C(O)R', -C(O)OR, -OC(O)N(R')<sub>2</sub>, -C(O)N(R')<sub>2</sub>, -N(R')C(O)OR', -N(R')C(O)R', -N(R')C(O)N(R')<sub>2</sub>, -N(R')C(NR')<sub>2</sub>, -N(R')C(NR'R'<sub>2</sub>), -C(O)N(R')<sub>2</sub>, -S(O)<sub>2</sub>-C(NR')<sub>2</sub>, -C(NR')<sub>2</sub>-S(O)-N(R')<sub>2</sub>, -S(O)-N(R')<sub>2</sub> (where t is 1 or 2), -S(O)<sub>2</sub>-R' (where t is 1 or 2), or PO<sub>3</sub>-R'<sub>2</sub>, where each R' is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroaryalkyl.

[00346] "Cycloalkyl-alkenyl" refers to a -(cycloalkyl)alkenyl radical where cycloalkyl and alkenyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for cycloalkyl and alkenyl, respectively.

[00347] "Cycloalkyl-heterocycloalkyl" refers to a -(cycloalkyl)heterocycloalkyl radical where cycloalkyl and heterocycloalkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for cycloalkyl and heterocycloalkyl, respectively.

[00348] "Cycloalkyl-heteroaryl" refers to a -(cycloalkyl)heteroaryl radical where cycloalkyl and heteroaryl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for cycloalkyl and heteroaryl, respectively.

[00349] The term "alkoxy" refers to the group -O-alkyl, including from 1 to 8 carbon atoms of a straight, branched, cyclic configuration and combinations thereof attached to the parent structure through an oxygen. Examples include, but are not limited to, methoxy, ethoxy, propoxy, isopropoxy, cyclopropoxy and cyclohexyloxy. "Lower alkoxy" refers to alkoxy groups containing one to six carbons.

[00350] The term "substituted alkoxy" refers to alkoxy wherein the alkyl constituent is substituted (i.e., -O-(substituted alkyl)). Unless stated otherwise specifically in the specification, the alkyl moiety of an alkoxy group is optionally substituted by one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroaryalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilyl, -OR, -SR, -OC(O)-R', -N(R')<sub>2</sub>, -C(O)R', -C(O)OR', -OC(O)N(R')<sub>2</sub>, -C(O)N(R')<sub>2</sub>, -N(R')C(O)OR', -N(R')C(O)R', -N(R')C(O)N(R')<sub>2</sub>, -N(R')C(NR')<sub>2</sub>, -N(R')C(NR'R'<sub>2</sub>), -C(O)N(R')<sub>2</sub>, -S(O)<sub>2</sub>-C(NR')<sub>2</sub>, -C(NR')<sub>2</sub>-S(O)-N(R')<sub>2</sub>, -S(O)-N(R')<sub>2</sub> (where t is 1 or 2), -S(O)<sub>2</sub>-R' (where t is 1 or 2), or PO<sub>3</sub>-R'<sub>2</sub>, where each R' is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroaryalkyl.
N(R')S(O)R (where t is 1 or 2), -S(O) t OR (where t is 1 or 2), -S(O) t N(R') (where t is 1 or 2), or PO₃(R')₂, where each R' is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocycllylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylylalkyl.

[00351] The term "alkoxycarbonyl" refers to a group of the formula (alkoxy)(C=O)- attached through the carbonyl carbon wherein the alkoxy group has the indicated number of carbon atoms. Thus a (C₃₋₆-)alkoxycarbonyl group is an alkoxy group having from 1 to 6 carbon atoms attached through its oxygen to a carbonyl linker. "Lower alkoxy carbonyl" refers to an alkoxy carbonyl group wherein the alkoxy group is a lower alkoxy group.

[00352] The term "substituted alkoxy carbonyl" refers to the group (substituted alkyl)-O-C(O)- wherein the group is attached to the parent structure through the carbonyl functionality. Unless stated otherwise specifically in the specification, the alkyl moiety of an alkoxy carbonyl group is optionally substituted by one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilyl, -OR', -SR', -OC(O)-R', -N(R')₂, -C(O)R', -C(O)OR', -OC(O)N(R')₂, -C(O)N(R')₂, -N(R')C(O)OR', -N(R')C(O)R', -N(R')C(O)N(R')₂, -N(R')C(NR')N(R')₂, -N(R')S(O)R (where t is 1 or 2), -S(O) t OR (where t is 1 or 2), -S(O) t N(R')₂ (where t is 1 or 2), or PO₃(R')₂, where each R' is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocycllylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylylalkyl.

[00353] "Acyl" refers to the groups (alkyl)-C(O)-, (aryl)-C(O)-, (heteroaryl)-C(O)-, (heteroarylalkyl)-C(O)- and (heterocycloalkyl)-C(O)-, wherein the group is attached to the parent structure through the carbonyl functionality. If the R radical is heteroaryl or heterocycloalkyl, the hetero ring or chain atoms contribute to the total number of chain or ring atoms. Unless stated otherwise specifically in the specification, the alkyl, aryl or heteroaryl moiety of the acyl group is optionally substituted by one or more substituents which are independently alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilyl, -OR', -SR', -OC(O)-R', -N(R')₂, -C(O)R', -C(O)OR', -OC(O)N(R')₂, -C(O)N(R')₂, -N(R')C(O)OR', -N(R')C(O)R', -N(R')C(O)N(R')₂, -N(R')C(NR')N(R')₂, -N(R')S(O)R (where t is 1 or 2), -
S(O)\textsubscript{i} OR\textsuperscript{t} (where t is 1 or 2), -S(O)\textsubscript{i} N(R\textsuperscript{t})\textsubscript{2} (where t is 1 or 2), or PO\textsubscript{3} (R\textsuperscript{t})\textsubscript{2}, where each R\textsuperscript{t} is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[00354] "Acyloxy" refers to a R(C=O)O- radical wherein "R" is alkyl, aryl, heteroaryl, heteroalkyl or heterocycloalkyl, which are as described herein. If the R radical is heteroaryl or heterocycloalkyl, the hetero ring or chain atoms contribute to the total number of chain or ring atoms. Unless stated otherwise specifically in the specification, the "R" of an acyloxy group is optionally substituted by one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilyl, -OR\textsuperscript{s}, -SR\textsuperscript{s}, -OC(O)-R\textsuperscript{s}, -C(O)R\textsuperscript{s}, -C(O)OR\textsuperscript{s}, -OC(O)N(R\textsuperscript{s})\textsubscript{2}, -C(O)N(R\textsuperscript{s})\textsubscript{2}, -N(R\textsuperscript{s})C(O)OR\textsuperscript{s}, -N(R\textsuperscript{s})C(O)R\textsuperscript{s}, -N(R\textsuperscript{s})C(NR\textsuperscript{r})\textsubscript{2}N(R\textsuperscript{r})\textsubscript{2}, -N(R\textsuperscript{s})S(O)\textsubscript{i} OR\textsuperscript{t} (where t is 1 or 2), -S(O)\textsubscript{i} OR\textsuperscript{t} (where t is 1 or 2), -S(O)\textsubscript{i} N(R\textsuperscript{t})\textsubscript{2} (where t is 1 or 2), or PO\textsubscript{3} (R\textsuperscript{t})\textsubscript{2}, where each R\textsuperscript{t} is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[00355] "Amino" or "amine" refers to a -N(R\textsuperscript{t})\textsubscript{2} radical group, where each R\textsuperscript{t} is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl, unless stated otherwise specifically in the specification. When a -N(R\textsuperscript{t})\textsubscript{2} group has two R\textsuperscript{t} substituents other than hydrogen, they can be combined with the nitrogen atom to form a 4-, 5-, 6- or 7-membered ring. For example, -N(R\textsuperscript{t})\textsubscript{2} is intended to include, but is not limited to, 1-pyrrolidinyl and 4-morpholiny1. Unless stated otherwise specifically in the specification, an amino group is optionally substituted by one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilyl, -OR\textsuperscript{s}, -SR\textsuperscript{s}, -OC(O)-R\textsuperscript{s}, -N(R\textsuperscript{s})\textsubscript{2}, -C(O)R\textsuperscript{s}, -C(O)OR\textsuperscript{s}, -OC(O)N(R\textsuperscript{s})\textsubscript{2}, -C(O)N(R\textsuperscript{s})\textsubscript{2}, -N(R\textsuperscript{s})C(O)OR\textsuperscript{s}, -N(R\textsuperscript{s})C(O)R\textsuperscript{s}, -N(R\textsuperscript{s})C(NR\textsuperscript{r})\textsubscript{2}N(R\textsuperscript{r})\textsubscript{2}, -N(R\textsuperscript{s})S(O)\textsubscript{i} OR\textsuperscript{t} (where t is 1 or 2), -S(O)\textsubscript{i} OR\textsuperscript{t} (where t is 1 or 2), -S(O)\textsubscript{i} N(R\textsuperscript{t})\textsubscript{2} (where t is 1 or 2), or PO\textsubscript{3} (R\textsuperscript{t})\textsubscript{2}, where each R\textsuperscript{t} is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.
The term "substituted amino" also refers to N-oxides of the groups -NHR\(^n\), and NR\(^n\)R\(^n\) each as described above. N-oxides can be prepared by treatment of the corresponding amino group with, for example, hydrogen peroxide or m-chloroperoxybenzoic acid.

"Amide" or "amido" refers to a chemical moiety with formula -C(O)N(R)\(_2\) or -NHC(O)R, where R is selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon), each of which moiety may itself be optionally substituted. The R\(_2\) of -N(R)\(_2\) of the amide may optionally be taken together with the nitrogen to which it is attached to form a 4-, 5-, 6- or 7-membered ring. Unless stated otherwise specifically in the specification, an amido group is optionally substituted independently by one or more of the substituents as described herein for alkyl, cycloalkyl, aryl, heteroaryl, or heterocycloalkyl. An amide may be an amino acid or a peptide molecule attached to a compound disclosed herein, thereby forming a prodrug. The procedures and specific groups to make such amides are known to those of skill in the art and can readily be found in seminal sources such as Greene and Wuts, Protective Groups in Organic Synthesis, 3\(^{rd}\) Ed., John Wiley & Sons, New York, N.Y., 1999, which is incorporated herein by reference in its entirety.

"Aromatic" or "aryl" or "Ar" refers to an aromatic radical with six to ten ring atoms (e.g., \(C_6\)-C\(_{10}\) aromatic or \(C_6\)-C\(_{10}\) aryl) which has at least one ring having a conjugated pi electron system which is carbocyclic (e.g., phenyl, fluorenyl, and naphthyl). Bivalent radicals formed from substituted benzene derivatives and having the free valences at ring atoms are named as substituted phenylene radicals. Bivalent radicals derived from univalent polycyclic hydrocarbon radicals whose names end in "-yl" by removal of one hydrogen atom from the carbon atom with the free valence are named by adding "-idene" to the name of the corresponding univalent radical, e.g., a naphthyl group with two points of attachment is termed naphthylidene. Whenever it appears herein, a numerical range such as "6 to 10" refers to each integer in the given range; e.g., "6 to 10 ring atoms" means that the aryl group may consist of 6 ring atoms, 7 ring atoms, etc., up to and including 10 ring atoms. The term includes monocyclic or fused-ring polycyclic (i.e., rings which share adjacent pairs of ring atoms) groups. Unless stated otherwise specifically in the specification, an aryl moiety is optionally substituted by one or more substituents which are independently alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl,
arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, -OR, -SR, -OC(O)-R, -N(R)2, -C(O)R, -C(O)OR, -OC(O)N(R)2, -C(O)N(R)2, -N(R)2, -N(R)C(O)R, -N(R)C(O)N(R)2, N(R)C(NR)N(R)2, N(R)S(O)R (where t is 1 or 2), -S(O)OR (where t is 1 or 2), -S(O)N(R)2 (where t is 1 or 2), or PO3(R)2, where each R is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[00359] "Aralkyl" or "arylalkyl" refers to an (aryl)alkyl-radical where aryl and alkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for aryl and alkyl respectively.

[00360] "Ester" refers to a chemical radical of formula -COOR, where R is selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon). The procedures and specific groups to make esters are known to those of skill in the art and can readily be found in seminal sources such as Greene and Wuts, Protective Groups in Organic Synthesis, 3rd Ed., John Wiley & Sons, New York, N.Y., 1999, which is incorporated herein by reference in its entirety. Unless stated otherwise specifically in the specification, an ester group is optionally substituted by one or more substituents which independently are: alkyl, heteroarylalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, aryalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, -OR, -SR, -OC(O)-R, -N(R)2, -C(O)R, -C(O)OR, -OC(O)N(R)2, -C(O)N(R)2, -N(R)2, -N(R)C(O)R, -N(R)C(O)N(R)2, N(R)C(NR)N(R)2, N(R)S(O)R (where t is 1 or 2), -S(O)OR (where t is 1 or 2), -S(O)N(R)2 (where t is 1 or 2), or PO3(R)2, where each R is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[00361] "Fluoroalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more fluoro radicals, as defined above, for example, trifluoromethyl, difluoromethyl, 2,2,2-trifluoroethyl, 1-fluoromethyl-2-fluoroethyl, and the like. The alkyl part of the fluoroalkyl radical may be optionally substituted as defined above for an alkyl group.
"Halo", "halide", or, alternatively, "halogen" is intended to mean fluoro, chloro, bromo or iodo. The terms "haloalkyl," "haloalkenyl," "haloalkynyl" and "haloalkoxy" include alkyl, alkenyl, alkynyl and alkoxy structures that are substituted with one or more halo groups or with combinations thereof. For example, the terms "fluoroalkyl" and "fluoroalkoxy" include haloalkyl and haloalkoxy groups, respectively, in which the halo is fluorine.

"Heteroalkyl", "heteroalkenyl" and "heteroalkynyl" refer to optionally substituted alkyl, alkenyl and alkynyl radicals and which have one or more skeletal chain atoms selected from an atom other than carbon, e.g., oxygen, nitrogen, sulfur, phosphorus or combinations thereof. A numerical range may be given - e.g., C_1-C_4 heteroalkyl which refers to the chain length in total, which in this example is 4 atoms long. A heteroalkyl group may be substituted with one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, nitro, oxo, thioxo, trimethylsilanyl, -OR, -SR, -OC(O)-R, -N(R')_2, -C(O)R, -C(O)OR, -OC(O)N(R')_2, -C(O)N(R')_2, -N(R')_2C(O)OR, -N(R')C(O)R, -N(R')_2C(O)N(R')_2, N(R')_2C(NR')_2N(R')_2, N(R')_2S(O)R (where t is 1 or 2), -S(O)OR (where t is 1 or 2), -S(O)_2N(R')_2 (where t is 1 or 2), or PO_3(R')_2, where each R' is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

"Heteroalkylaryl" refers to an -(heteroalkyl)aryl radical where heteroalkyl and aryl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heteroalkyl and aryl, respectively.

"Heteroalkylheteroaryl" refers to an -(heteroalkyl)heteroaryl radical where heteroalkyl and heteroaryl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heteroalkyl and heteroaryl, respectively.

"Heteroalkylheterocycloalkyl" refers to an -(heteroalkyl)heterocycloalkyl radical where heteroalkyl and heterocycloalkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heteroalkyl and heterocycloalkyl, respectively.
"Heteroalkylcycloalkyl" refers to a -(heteroalkyl)cycloalkyl radical where heteroalkyl and cycloalkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heteroalkyl and cycloalkyl, respectively.

"Heteroaryl" or "heteroaromatic" or "HetAr" refers to a 5- to 18-membered aromatic radical (e.g., C_5^-C_18 heteroaryl) that includes one or more ring heteroatoms selected from nitrogen, oxygen and sulfur, and which may be a monocyclic, bicyclic, tricyclic or tetracyclic ring system. Whenever it appears herein, a numerical range such as "5 to 18" refers to each integer in the given range - e.g., "5 to 18 ring atoms" means that the heteroaryl group may consist of 5 ring atoms, 6 ring atoms, etc., up to and including 18 ring atoms. Bivalent radicals derived from univalent heteroaryl radicals whose names end in "-yl" by removal of one hydrogen atom from the atom with the free valence are named by adding "-idene" to the name of the corresponding univalent radical - e.g., a pyridyl group with two points of attachment is a pyridyldiene. A N-containing "heteroaromatic" or "heteroaryl" moiety refers to an aromatic group in which at least one of the skeletal atoms of the ring is a nitrogen atom. The polycyclic heteroaryl group may be fused or non-fused. The heteroatom(s) in the heteroaryl radical are optionally oxidized. One or more nitrogen atoms, if present, are optionally quaternized. The heteroaryl may be attached to the rest of the molecule through any atom of the ring(s). Examples of heteroaryls include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzindolyl, 1,3-benzodioxolyl, benzofuranyl, benzo[di]azoyl, benzo[d]thiazoyl, benzothiadiazolyl, benzo[b][1,4]dioxepinyl, benzo[b][1,4]oxazinyl, 1,4-benzodioxanyll, benzonaphthofuranyll, benzoxazolyl, benzodioxynyl, benzoxazolyl, benzopyranoyll, benzofuranyl, benzo[d]furanyll, benzothiazoyll, benzothienyl(benzothiophenyl), benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridinyl, carbazoyll, cinnolinyl, cyclopentapyrimidinyl, 6,7-dihydro-5H-cyclopenta[4,5]thieno[2,3-d]pyrimidinyl, 5,6-dihydrobenzo[h]quinazolinyl, 5,6-dihydrobenzo[h]cinnolinyl, 6,7-dihydro-5H-benzo[6,7]cyclohepta[1,2-c]pyridazinyl, dibenzofuranyll, dibenzothiophenyl, furanyll, furazanyll, furanoyll, furo[3,2-c]pyridinyl, 5,6,7,8,9,10-hexahydrocyclooctadpyrimidinyl, 5,6,7,8,9,10-hexahydrocyclooctadpyridazinyl, 5,6,7,8,9,10-hexahydrocyclooctadpyridinyl, isothiazoyll, imidazoyll, indazoyll, indolyl, indazoyll, isoindolyl, indolinyl, isoindolinyll, isoquinolyl, indolizinyll, isoxazolyl, 5,8-methano-5,6,7,8-tetrahydroquinazolinyl, naphthyridinyl, 1,6-naphthyridinonyll, oxadiazoyll, 2-oxoazepinyl, oxazolyl, oxiranyll, 5,6,6a,7,8,9,10,10a-
octahydrobenzo[h]quinazolinyl, 1-phenyl-1H-pyrrolyl, phenazinyl, phenothiazinyl, phenoazinyl, phthalazinyl, pyridazinyl, pyrrolyl, pyridinyl, pyrazinyl, pyrrolo[3,4-d]pyrimidinyl, pyridinyl, pyrido[2,3-d]pyrimidinyl, pyrido[3,4-d]pyrimidinyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrrolyl, quinazolinyl, quinoxalinyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, 5,6,7,8-tetrahydroquinazolinyl, 5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidinyl, 6,7,8,9-tetrahydro-5H-cyclohepta[4,5]thieno[2,3-d]pyrimidinyl, 5,6,7,8-tetrahydroprido[4,5-c]pyridazinyl, thiazolyl, thiadiazolyl, thiapyranyl, tetrazolyl, tetrazolyl, thiazinyl, thieno[2,3-d]pyrimidinyl, thieno[3,2-d]pyrimidinyl, thieno[2,3-c]pyridinyl, and thiophenyl (i.e. thienyl). Unless stated otherwise specifically in the specification, a heteroaryl moiety is optionally substituted by one or more substituents which are independently: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroaryllalkyl, hydroxy, halo, cyano, nitro, o xo, thi oxo, trimethylsilyl, -OR, -SR, -OC(O)R', -N(R')2, -C(O)R', -C(O)OR', -OC(O)N(R')2, -C(O)N(R')2, -N(R')C(O)OR', -N(R')C(O)R', -N(R')C(O)N(R')2, N(R')C(NR')N(R')2, -N(R')S(O)R' (where t is 1 or 2), -S(O)R'2 (where t is 1 or 2), or PO3 (R')2, where each R' is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroaryllalkyl.

[00369] Substituted heteroaryl also includes ring systems substituted with one or more oxide (-O-) substituents, such as, for example, pyridinyl N-oxides.

[00370] "Heteroaryllalkyl" refers to a moiety having an aryl moiety, as described herein, connected to an alkylene moiety, as described herein, wherein the connection to the remainder of the molecule is through the alkylene group.

[00371] "Heterocycloalkyl" refers to a stable 3- to 18-membered non-aromatic ring radical that comprises two to twelve carbon atoms and from one to six heteroatoms selected from nitrogen, oxygen and sulfur. Whenever it appears herein, a numerical range such as "3 to 18" refers to each integer in the given range - e.g., "3 to 18 ring atoms" means that the heterocycloalkyl group may consist of 3 ring atoms, 4 ring atoms, etc., up to and including 18 ring atoms. Unless stated otherwise specifically in the specification, the heterocycloalkyl radical is a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which may include fused or bridged ring systems. The heteroatoms in the heterocycloalkyl radical may be optionally oxidized. One or more nitrogen
atoms, if present, are optionally quaternized. The heterocycloalkyl radical is partially or fully saturated. The heterocycloalkyl may be attached to the rest of the molecule through any atom of the ring(s). Examples of such heterocycloalkyl radicals include, but are not limited to, dioxolanyl, thieryl[1,3]dithianyl, decahydroisoquinolyl, imidazolinyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl, thiazolidinyl, tetrahydrofuryl, thianyl, tetrahydropropyryl, thiomorpholinyl, thiomorpholinyl, 1-oxo-thiomorpholinyl, and 1,1-dioxothiomorpholinyl. Unless stated otherwise specifically in the specification, a heterocycloalkyl moiety is optionally substituted by one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, nitro, oxo, thioxo, trimethylsilylanyl, -OR, -SR, -OC(O)R, -N(R')2, -C(O)R, -C(O)OR, -OC(O)N(R')2, -C(O)N(R')2, -N(R')C(O)OR, -N(R')C(O)R, -N(R')C(O)N(R')2, N(R')C(NR')N(R')2, -N(R')S(O)R (where t is 1 or 2), -S(O)R (where t is 1 or 2), or PO(R')2, where each R' is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[00372] "Heterocycloalkyl" also includes bicyclic ring systems wherein one non-aromatic ring, usually with 3 to 7 ring atoms, contains at least 2 carbon atoms in addition to 1-3 heteroatoms independently selected from oxygen, sulfur, and nitrogen, as well as combinations comprising at least one of the foregoing heteroatoms; and the other ring, usually with 3 to 7 ring atoms, optionally contains 1-3 heteroatoms independently selected from oxygen, sulfur, and nitrogen and is not aromatic.

[00373] "Nitro" refers to the -NO2 radical.

[00374] "Oxa" refers to the -O- radical.

[00375] "Oxo" refers to the =O radical.

[00376] "Isomers" are different compounds that have the same molecular formula. "Stereoisomers" are isomers that differ only in the way the atoms are arranged in space - i.e., having a different stereochemical configuration. "Enantiomers" are a pair of stereoisomers that
are non-superimposable mirror images of each other. A 1:1 mixture of a pair of enantiomers is a "racemic" mixture. The term "(±)" is used to designate a racemic mixture where appropriate. "Diastereoisomers" are stereoisomers that have at least two asymmetric atoms, but which are not mirror-images of each other. The absolute stereochemistry is specified according to the Cahn-Ingold-Prelog R-S system. When a compound is a pure enantiomer the stereochemistry at each chiral carbon can be specified by either (R) or (S). Resolved compounds whose absolute configuration is unknown can be designated (+) or (-) depending on the direction (dextro- or levorotatory) which they rotate plane polarized light at the wavelength of the sodium D line. Certain of the compounds described herein contain one or more asymmetric centers and can thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that can be defined, in terms of absolute stereochemistry, as (R) or (S). The present chemical entities, pharmaceutical compositions and methods are meant to include all such possible isomers, including racemic mixtures, optically pure forms and intermediate mixtures. Optically active (R)- and (S)-isomers can be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers.

"Enantiomeric purity" as used herein refers to the relative amounts, expressed as a percentage, of the presence of a specific enantiomer relative to the other enantiomer. For example, if a compound, which may potentially have an (R)- or an (S)-isomeric configuration, is present as a racemic mixture, the enantiomeric purity is about 50% with respect to either the (R)- or (S)-isomer. If that compound has one isomeric form predominant over the other, for example, 80% (S)-isomer and 20% (R)-isomer, the enantiomeric purity of the compound with respect to the (S)-isomeric form is 80%. The enantiomeric purity of a compound can be determined in a number of ways known in the art, including but not limited to chromatography using a chiral support, polarimetric measurement of the rotation of polarized light, nuclear magnetic resonance spectroscopy using chiral shift reagents which include but are not limited to lanthanide containing chiral complexes or Pirkle’s reagents, or derivatization of a compounds using a chiral compound such as Mosher’s acid followed by chromatography or nuclear magnetic resonance spectroscopy.
In preferred embodiments, the enantiomerically enriched composition has a higher potency with respect to therapeutic utility per unit mass than does the racemic mixture of that composition. Enantiomers can be isolated from mixtures by methods known to those skilled in the art, including chiral high pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts; or preferred enantiomers can be prepared by asymmetric syntheses. See, for example, Jacques, et al., Enantiomers, Racemates and Resolutions (Wiley Interscience, New York, 1981); E. L. Eliel, Stereochemistry of Carbon Compounds (McGraw-Hill, NY, 1962); and E. L. Eliel and S. H. Wilen, Stereochemistry of Organic Compounds (Wiley-Interscience, New York, 1994).

The terms "enantiomerically enriched" and "non-racemic," as used herein, refer to compositions in which the percent by weight of one enantiomer is greater than the amount of that one enantiomer in a control mixture of the racemic composition (e.g., greater than 1:1 by weight). For example, an enantiomerically enriched preparation of the (S)-enantiomer, means a preparation of the compound having greater than 50% by weight of the (S)-enantiomer relative to the (R)-enantiomer, such as at least 75% by weight, or such as at least 80% by weight. In some embodiments, the enrichment can be significantly greater than 80% by weight, providing a "substantially enantiomerically enriched" or a "substantially non-racemic" preparation, which refers to preparations of compositions which have at least 85% by weight of one enantiomer relative to other enantiomer, such as at least 90% by weight, or such as at least 95% by weight. The terms “enantiomerically pure” or "substantially enantiomerically pure" refers to a composition that comprises at least 98% of a single enantiomer and less than 2% of the opposite enantiomer.

"Moiety" refers to a specific segment or functional group of a molecule. Chemical moieties are often recognized chemical entities embedded in or appended to a molecule.

"Tautomers" are structurally distinct isomers that interconvert by tautomerization. "Tautomerization" is a form of isomerization and includes prototropic or proton-shift tautomerization, which is considered a subset of acid-base chemistry. "Prototropic tautomerization" or "proton-shift tautomerization" involves the migration of a proton accompanied by changes in bond order, often the interchange of a single bond with an adjacent double bond. Where tautomerization is possible (e.g. in solution), a chemical equilibrium of
tautomers can be reached. An example of tautomerization is keto-enol tautomerization. A specific example of keto-enol tautomerization is the interconversion of pentane-2,4-dione and 4-hydroxypent-3-en-2-one tautomers. Another example of tautomerization is phenol-keto tautomerization. A specific example of phenol-keto tautomerization is the interconversion of pyridin-4-ol and pyridin-4(1H)-one tautomers.

[00382] A "leaving group or atom" is any group or atom that will, under selected reaction conditions, cleave from the starting material, thus promoting reaction at a specified site. Examples of such groups, unless otherwise specified, include halogen atoms and mesyloxy, p-nitrobenzensulphonyloxy and tosyloxy groups.

[00383] "Protecting group" is intended to mean a group that selectively blocks one or more reactive sites in a multifunctional compound such that a chemical reaction can be carried out selectively on another unprotected reactive site and the group can then be readily removed after the selective reaction is complete. A variety of protecting groups are disclosed, for example, in T. H. Greene and P. G. M. Wuts, Protective Groups in Organic Synthesis, Third Edition, John Wiley & Sons, New York (1999).

[00384] "Solvate" refers to a compound in physical association with one or more molecules of a pharmaceutically acceptable solvent.

[00385] "Substituted" means that the referenced group may have attached one or more additional groups, radicals or moieties individually and independently selected from, for example, acyl, alkyl, alkylaryl, cycloalkyl, aralkyl, aryl, carbohydrate, carbonate, heteroaryl, heterocycloalkyl, hydroxy, alkoxy, aryloxy, mercapto, alkylthio, arylthio, cyano, halo, carbonyl, ester, thiocarbonyl, isocyanato, thiocyanato, isothiocyanato, nitro, oxo, perhaloalkyl, perfluoroalkyl, phosphate, silyl, sulfinyl, sulfonil, sulfonamidyl, sulfoxyl, sulfonate, urea, and amino, including mono- and di-substituted amino groups, and protected derivatives thereof. The substituents themselves may be substituted, for example, a cycloalkyl substituent may itself have a halide substituent at one or more of its ring carbons. The term "optionally substituted" means optional substitution with the specified groups, radicals or moieties.
"Sulfanyl" refers to groups that include -S-(optionally substituted alkyl), -S-(optionally substituted aryl), -S-(optionally substituted heteroaryl) and -S-(optionally substituted heterocycloalkyl).

"Sulfinyl" refers to groups that include -S(O)-H, -S(O)-(optionally substituted alkyl), -S(O)-(optionally substituted amino), -S(O)-(optionally substituted aryl), -S(O)-(optionally substituted heteroaryl) and -S(O)-(optionally substituted heterocycloalkyl).

"Sulfonyl" refers to groups that include -S(O)₂-H, -S(O)₂-(optionally substituted alkyl), -S(O)₂-(optionally substituted amino), -S(O)₂-(optionally substituted aryl), -S(O)₂-(optionally substituted heteroaryl), and -S(O)₂-(optionally substituted heterocycloalkyl).

"Sulfonamidyl" or "sulfonamido" refers to a -S(=O)₂-NRR radical, where each R is selected independently from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon). The R groups in -NRR of the -S(=O)₂-NRR radical may be taken together with the nitrogen to which it is attached to form a 4-, 5-, 6- or 7-membered ring. A sulfonamido group is optionally substituted by one or more of the substituents described for alkyl, cycloalkyl, aryl, heteroaryl, respectively.

"Sulfoxyl" refers to a -S(=O)OH radical.

"Sulfonate" refers to a -S(=O)₂-OR radical, where R is selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon). A sulfonate group is optionally substituted on R by one or more of the substituents described for alkyl, cycloalkyl, aryl, heteroaryl, respectively.

Compounds of the invention also include crystalline and amorphous forms of those compounds, including, for example, polymorphs, pseudopolymorphs, solvates, hydrates, unsolvated polymorphs (including anhydrates), conformational polymorphs, and amorphous forms of the compounds, as well as mixtures thereof. "Crystalline form" and "polymorph" are intended to include all crystalline and amorphous forms of the compound, including, for example, polymorphs, pseudopolymorphs, solvates, hydrates, unsolvated polymorphs (including
anhydrates), conformational polymorphs, and amorphous forms, as well as mixtures thereof, unless a particular crystalline or amorphous form is referred to.

Co-administration of compounds

[00393] An embodiment of the invention is a composition, such as a pharmaceutical composition, comprising a combination of a PI3K inhibitor, a BTK inhibitor, and/or a JAK-2 inhibitor. Another embodiment is a kit containing a BTK inhibitor, and/or a JAK-2 inhibitor formulated into separate pharmaceutical compositions, which are formulated for co-administration.

[00394] Another embodiment of the invention is a method of treating a disease or condition in a subject, in particular a hyperproliferative disorder like leukemia, lymphoma or a solid tumor cancer in a subject, comprising co-administering to the subject in need thereof a therapeutically effective amount of a combination of a PI3K inhibitor, a BTK inhibitor, and/or a JAK-2 inhibitor.

The pharmaceutical composition comprising the combination, and the kit, are both for use in treating such disease or condition.

[00395] In an exemplary embodiment, the solid tumor cancer is selected from the group consisting of breast, lung, colorectal, thyroid, bone sarcoma, and stomach cancers.

[00396] In an exemplary embodiment, the leukemia is selected from the group consisting of acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML), acute lymphoblastic leukemia (ALL), B cell chronic lymphocytic leukemia (B-CLL), and chronic lymphoid leukemia (CLL).

[00397] In an exemplary embodiment, the lymphoma is selected from the group consisting of Burkitt’s lymphoma, mantle cell lymphoma, follicular lymphoma, indolent B-cell non-Hodgkin’s lymphoma, histiocytic lymphoma, activated B-cell like diffuse large B cell lymphoma (DLBCL-ABC), germinal center B-cell like diffuse large B cell lymphoma (DLBCL-GCB), and diffuse large B cell lymphoma (DLBCL).

[00398] In a preferred embodiment, the PI3K inhibitor is a PI3K-γ inhibitor.

[00399] In another preferred embodiment, the PI3K inhibitor is a PI3K-δ inhibitor.
In another preferred embodiment, the PI3K inhibitor is a PI3K-γ,δ inhibitor.

In another preferred embodiment, the PI3K inhibitor is a selective PI3K inhibitor.

In a particularly preferred embodiment, the PI3K inhibitor is a PI3K-δ inhibitor. This PI3K-δ inhibitor is more preferably a compound of Formula VIII, even more preferably the compound of Formula IX.

The BTK inhibitor is preferably a compound of Formula XVII, even more preferably the compound of Formula XVIII.

In one specific embodiment, the PI3K inhibitor is a PI3K-δ inhibitor and the BTK inhibitor is a compound of Formula XVII, even more preferably the compound of Formula XVIII. In a specifically preferred embodiment, the PI3K inhibitor is the compound of Formula IX and the BTK inhibitor is the compound of Formula XVIII. One or both of said inhibitors may also be in the form of a pharmaceutically acceptable salt.

The combination may be administered by any route known in the art. In an embodiment, the combination of the the PI3K inhibitor, which is preferably selected from the group consisting of a PI3K-γ inhibitor, a PI3K-δ inhibitor, and a PI3K-γ,δ inhibitor with the BTK inhibitor is administered by oral, intravenous, intramuscular, intraperitoneal, subcutaneous or transdermal means. In one embodiment, the administration is by injection.

In an exemplary embodiment, the PI3K inhibitor, which is preferably selected from the group consisting of a PI3K-γ inhibitor, a PI3K-δ inhibitor, and a PI3K-γ,δ inhibitor, is in the form of a pharmaceutically acceptable salt, solvate, hydrate, complex, derivative, prodrug (such as an ester or phosphate ester), or cocrystal.

In an embodiment, the BTK inhibitor is in the form of a pharmaceutically acceptable salt, solvate, hydrate, complex, derivative, prodrug (such as an ester or phosphate ester), or cocrystal.

In an embodiment, the JAK-2 inhibitor is in the form of a pharmaceutically acceptable salt, solvate, hydrate, complex, derivative, prodrug (such as an ester or phosphate ester), or cocrystal.
[00409] In an embodiment, the PI3K inhibitor, which is preferably selected from the group consisting of a PI3K-γ inhibitor, a PI3K-δ inhibitor, and a PI3K-γ,δ inhibitor, is administered to the subject before administration of the BTK inhibitor.

[00410] In an embodiment, the PI3K inhibitor, which is preferably selected from the group consisting of a PI3K-γ inhibitor, a PI3K-δ inhibitor, and a PI3K-γ,δ inhibitor, is administered concurrently with the administration of the BTK inhibitor.

[00411] In an embodiment, the PI3K inhibitor, which is preferably selected from the group consisting of a PI3K-γ inhibitor, a PI3K-δ inhibitor, and a PI3K-γ,δ inhibitor, is administered to the subject after administration of the BTK inhibitor.

[00412] In an embodiment, the JAK-2 inhibitor is administered to the subject before administration of the BTK inhibitor.

[00413] In an embodiment, the JAK-2 inhibitor is administered concurrently with the administration of the BTK inhibitor.

[00414] In an embodiment, the JAK-2 inhibitor is administered to the subject after administration of the BTK inhibitor.

[00415] In an embodiment, the BTK inhibitor, JAK-2 inhibitor, and PI3K inhibitor, which is preferably selected from the group consisting of a PI3K-γ inhibitor, a PI3K-δ inhibitor, and a PI3K-γ,δ inhibitor, are administered concurrently.

[00416] In an embodiment, the subject is a mammal. In an embodiment, the subject is a human. In an embodiment, the subject is a mammal, such as a canine, feline or equine.

PI3K Inhibitors

[00417] The PI3K inhibitor may be any PI3K inhibitor known in the art. In particular, it is one of the PI3K inhibitors described in more detail in the following paragraphs. Preferably, it is a PI3K inhibitor selected from the group consisting of PI3K-γ inhibitor, PI3K-δ inhibitor, and PI3K-γ,δ inhibitor. In one specific embodiment, it is a PI3K-δ inhibitor. In a preferred embodiment, it is a compound of Formula IX or a pharmaceutically acceptable salt thereof.
In an exemplary embodiment, the PI3K inhibitor, which may preferably be selected from the group consisting of a PI3K-γ inhibitor, a PI3K-δ inhibitor, and a PI3K-γ,δ inhibitor, is a compound selected from the structures disclosed in U.S. Patent Nos. 8,193,182 and 8,569,323, and U.S. Patent Application Publication Nos. 2012/0184568 A1, 2013/0344061 A1, and 2013/0267521 A1, the disclosures of which are incorporated by reference herein. In an exemplary embodiment, the the PI3K inhibitor, is a compound of Formula (I):

![Formula (I)]

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal or prodrug thereof, wherein:

- Cy is aryl or heteroaryl substituted by 0 or 1 occurrences of \( R^1 \) and 0, 1, 2, or 3 occurrences of \( R^2 \);
- \( W^b_3 \) is \( CR^8 \), \( CHR^8 \), or N;
- \( R^8 \) is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfonamido, halo, cyano, hydroxyl or nitro;
- B is hydrogen, alkyl, amino, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of which is substituted with 0, 1, 2, 3, or 4 occurrences of \( R^2 \);
- each \( R^2 \) is independently alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, aroylalkyl, heteroarylalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxy carbonyl, sulfonamido, halo, cyano, hydroxyl, nitro, phosphate, urea, or carbonate;
- X is \(-(CH(R^9))_z\);-
- Y is \(-N(R^9)-C(=O)-\), \(-C(=O)-N(R^9)-\), \(-C(=O)-N(R^9)-(CHR^9)-\), \(-N(R^9)-S(=O)-\), \(-S(=O)-N(R^9)-\), \(-S(=O)-N(R^9)-\), \(-N(R^9)-C(=O)-N(R^9)-\), or \(-N(R^9)-S(=O)-\);-
- \( z \) is an integer of 1, 2, 3, or 4;
R² is alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, fluoroalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfinyl, sulfonyl, sulfoxide, sulfone, sulfonamido, halo, cyano, aryl, heteroaryl, hydroxyl, or nitro;

each R⁵ is independently alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, fluoroalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfonamido, halo, cyano, hydroxyl, or nitro;

each R⁷ is independently hydrogen, alkyl, cycloalkyl, heterocyclyl, or heteroalkyl; or two adjacent occurrences of R⁷ together with the atoms to which they are attached form a 4- to 7-membered ring;

W₉ is heterocyclyl, aryl, cycloalkyl, or heteroaryl, each of which is substituted with one or more R¹⁰, R¹¹, R¹² or R¹³, and

R¹⁰, R¹¹, R¹² and R¹³ are each independently hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, heterocyclyloxy, amido, amino, acyl, acyloxy, alkoxy carbonyl, sulfonamido, halo, cyano, hydroxyl, nitro, phosphate, urea, carbonate or NR'R" wherein R' and R" are taken together with nitrogen to form a cyclic moiety.

[00419] In an embodiment, the PI3K inhibitor, PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor is a compound of Formula (I-1):

![Formula (I-1)](formula)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof,

wherein:

B is a moiety of Formula (II):
$W_i$ is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl;
$q$ is an integer of 0, 1, 2, 3, or 4;
$X$ is a bond or $-(\text{CH}(R^q)^z)$, and $z$ is an integer of 1, 2, 3 or 4;
$Y$ is a bond, $-\text{N}(R^q)^z$, $-\text{O}$, $-\text{S}$, $-\text{S}^{(=\text{O})}$, $-\text{S}(^{(=\text{O})})$, $-\text{C}(^{(=\text{O})})$, $-\text{C}(^{(=\text{O})}(\text{CHR}^z)_z)$, $-\text{N}(R^q)^z$-$\text{C}(^{(=\text{O})}$,
$-\text{N}(R^q)^z$-$\text{C}(^{(=\text{O})}$-$\text{NH}$ or $-\text{N}(R^q)^z$-$\text{C}(^{(=\text{O})}$-$z$;
$z$ is an integer of 1, 2, 3, or 4;
$W_d$ is:
$X_1, X_2$ and $X_3$ are each independently $C, CR^{13}$ or $N$; and $X_4, X_5$ and $X_6$ are each independently $N, NH, CR^{13}, S$ or $O$;

$R^1$ is hydrogen, alkyl, alkenyl, alkynyl, alkoxy, amido, alkoxy carbonyl, sulfonamido, halo, cyano, or nitro;
R² is alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, heteroarylalkyl, alkoxy, amino, halo, cyano, hydroxy or nitro; R.sup.3 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, alkoxy, amido, amino, alkoxy carbonyl sulfonamido, halo, cyano, hydroxy or nitro; and each instance of R⁹ is independently hydrogen, alkyl, or heterocycloalkyl.

[00420] In an embodiment, the PI3K inhibitor, PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor is a compound of Formula (III) or Formula (IV):
or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

[00421] In an embodiment, the PI3K inhibitor, PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor is (S)-3-((9H-purin-6-yl)amino)-8-chloro-2-phenylisoquinolin-1(2H)-one or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

[00422] In an embodiment, the PI3K inhibitor, PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor is (S)-3-amino-N-(1-(5-chloro-4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)ethyl)pyrazine-2-carboxamide or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

[00423] In an embodiment, the PI3K inhibitor or PI3K-δ inhibitor is a compound selected from the structures disclosed in U.S. Patent Nos. 8,193,199 and 8,586,739, the disclosure of which is incorporated by reference herein. In an embodiment, the PI3K inhibitor or PI3K-δ inhibitor is a compound of Formula (V):

![Formula (V)]

or any pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, wherein:

X₁ is C(R⁹) or N;
X₂ is C(R₁₀) or N;
Y is N(R¹¹), O or S;
Z is CR¹² or N;
n is 0, 1, 2 or 3;
R¹ is a direct-bonded or oxygen -linked saturated, partially saturated or unsaturated 5-, 6- or 7-membered monocyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, but
containing no more than one 0 or S, wherein the available carbon atoms of the ring are
substituted by 0, 1 or 2, wherein the ring is additionally substituted by 0, 1, 2 or 3 substituents independently
selected from halo, nitro, cyano, (C_{1-4})alkyl, O(C_{1-4})alkyl, O(C_{1-4})haloalkyl, NH(C_{1-4}), N((C_{1-4})alkyl)alkyl and (C_{1-4})haloalkyl;

R^2 is selected from halo, (C_{1-4})haloalkyl, cyano, nitro, —C(═O)R^*, —C(═O)OR^*, —
C(═O)NR^*R^*, —C(═O)NR^*R^*R^*, —OR^*, —OC(═O)R^*, —OC(═O)NR^*R^*, —
OC(═O)N(R^*)S(═O)R^*, —O(C_{2-6})alkylNR^*R^*, —O(C_{2-6})alkylOR^*, —SR^*, OS(═O)R^*, —
S(═O)_2 R^*, —S(═O)_2 NR^*R^*, —S(═O)_2 N(R^*)C(═O)R^*, —S(═O)_2 N(R^*)C(═O)OR^*, —
S(═O)_2 N(R^*)C(═O)NR^*R^*, —NR^*R^*, —N(R^*)C(═O)OR^*, —N(R^*)C(═O)OR^*, —
N(R^*)C(═O)NR^*R^*, —N(R^*)C(═O)NR^*R^*, —N(R^*)S(═O)_2 R^*, —N(R^*)S(═O)_2 NR^*R^*, —
NR^*(C_{2-6})alkylNR^*R^* and —NR^*(C_{2-6})alkylOR^*; or R^2 is selected from (C_{1-4})alkyl, phenyl, benzyl, heteroaryl, heterocycle, —((C_{1-3})alkyl)heteroaryl, —((C_{1-3})alkyl)heterocycle, —
O((C_{1-3})alkyl)heteroaryl, —O((C_{1-3})alkyl)heterocycle, —NR^*((C_{1-3})alkyl)heteroaryl, —
NR^*((C_{1-3})alkyl)heterocycle, —(C_{1-4})alkyl)phenyl, —O((C_{1-4})alkyl)phenyl and —NR^*((C_{1-4})
alkyl)phenyl all of which are substituted by 0, 1, 2 or 3 substituents selected from (C_{1-4})alkyl, O((C_{1-4})alkyl), Br, Cl, F, I and (C_{1-4})alkyl;

R^1 is selected from H, halo, (C_{1-4})haloalkyl, cyano, nitro, —C(═O)R^*, —C(═O)OR^*, —
C(═O)NR^*R^*, —C(═O)NR^*R^*R^*, —OR^*, —OC(═O)R^*, —OC(═O)NR^*R^*, —
OC(═O)N(R^*)S(═O)R^*, —O(C_{2-6})alkylNR^*R^*, —O(C_{2-6})alkylOR^*, —SR^*, —S(═O)R^*, —
S(═O)_2 R^*, —S(═O)_2 NR^*R^*, —S(═O)_2 N(R^*)C(═O)R^*, —S(═O)_2 N(R^*)C(═O)OR^*, —
S(═O)_2 N(R^*)C(═O)NR^*R^*, —NR^*R^*, —N(R^*)C(═O)OR^*, —N(R^*)C(═O)OR^*, —
N(R^*)C(═O)NR^*R^*, —N(R^*)C(═O)NR^*R^*, —N(R^*)S(═O)_2 R^*, —N(R^*)S(═O)_2 NR^*R^*, —
NR^*(C_{2-6})alkylOR^*, (C_{1-6})alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the
(C_{1-4})alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or
3 substituents selected from (C_{1-6})haloalkyl, O((C_{1-6})alkyl), Br, Cl, F, I and (C_{1-6})alkyl;

R^2 is, independently, in each instance, halo, nitro, cyano, (C_{1-4})alkyl, O((C_{1-4})alkyl, O((C_{1-4})haloalkyl, NH(C_{1-4})alkyl, N((C_{1-4})alkyl)(C_{1-4})alkyl or (C_{1-4})haloalkyl;

R^1 is, independently, in each instance, H, halo, (C_{1-4})alkyl, (C_{1-4})haloalkyl, or (C_{1-4})alkyl
substituted by 1, 2 or 3 substituents selected from halo, cyano, OH, O((C_{1-4})alkyl, (C_{1-4})alkyl,
(C_{1-3})haloalkyl, O((C_{1-4})alkyl, NH_2, NH(C_{1-4})alkyl, N((C_{1-4})alkyl)(C_{1-4})alkyl; or both R^2 groups
together form a C₃₋₆ spiroalkyl substituted by 0, 1 or 2 spiroalkyl substituents selected from halo, cyano, OH, O(C₁₋₄)alkyl, (C₁₋₄)alkyl, (C₁₋₃)haloalkyl, O(C₁₋₄)alkyl, NH₂, NH(C₁₋₄)alkyl, N((C₁₋₄)alkyl)(C₁₋₄)alkyl;

R₃ is selected from H, halo, (C₁₋₆)alkyl, (C₁₋₄)haloalkyl, cyano, nitro, −C(=O)R′, −C(=O)OR′, −C(=O)NR′R″, −C(=O)NR′R″, −S(=O)₂R′, −S(=O)₂N(R′)C(=O)OR′, −S(=O)₂N(R′)C(=O)NR′R″;

R₃ is selected from H, halo, (C₁₋₆)alkyl, (C₁₋₄)haloalkyl, cyano, nitro, −C(=O)R′, −C(=O)OR′, −C(=O)NR′R″, −C(=O)NR′R″, −S(=O)₂R′, −S(=O)₂N(R′)C(=O)OR′, −S(=O)₂N(R′)C(=O)NR′R″;

R₃ is selected from H, halo, (C₁₋₆)haloalkyl, Br, Cl, F, I, OR′, NR′R″, (C₁₋₆)alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the (C₁₋₆)alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1 or 2 spiroalkyl substituents selected from (C₁₋₆)haloalkyl, O(C₁₋₆)alkyl, Br, Cl, F, I and (C₁₋₆)alkyl;

R₃ is selected from H, halo, (C₁₋₄)haloalkyl, cyano, nitro, −C(=O)R′, −C(=O)OR′, −C(=O)NR′R″, −C(=O)NR′R″, −OC(=O)R′, −OC(=O)OR′, −OC(=O)NR′R″, −OC(=O)NR′R″, −S(=O)₂R′, −S(=O)₂N(R′)C(=O)OR′, −S(=O)₂N(R′)C(=O)NR′R″, −S(=O)₂N(R′)C(=O)OR′, −S(=O)₂N(R′)C(=O)NR′R″, −N(R′)C(=O)NR′R″, −N(R′)C(=O)OR′, −N(R′)C(=O)NR′R″, −N(R′)C(=O)OR′, −N(R′)C(=O)NR′R″, −N(R′)C(=O)OR′, −N(R′)C(=O)NR′R″, −NR′C(=O)NR′R″; or R₃ is saturated, partially-saturated or unsaturated 5-, 6- or 7-membered monocyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is
substituted by 0, 1, 2, 3 or 4 substituents selected from halo, (C\textsubscript{1-4})haloalkyl, cyano, nitro, —C(=O)R', —C(=O)OR', —C(=O)NR' R', —C(=NR'R')NR'R', —OR', —OC(=O)R', —OC(=O)NR'R', —OC(=O)N(R')S(=O)\textsubscript{2} R', —O(C\textsubscript{2-6})alkylNR'R', —O(C\textsubscript{2-6})alkylOR', —SR', —S(=O)R', —S(=O)\textsubscript{2} R', —S(=O)\textsubscript{2} NR'R', —S(=O)\textsubscript{2} N(R')C(=O)R', —S(=O)\textsubscript{2} N(R')C(=O)NR'R', —N(R')C(=O)OR', —N(R')C(=O)N(R')NR'R', —N(R')C(=O)NR'R', —N(R')N(=O)R' R', —N(=O)R' R';

R'\textsuperscript{10} is H, (C\textsubscript{1-3})alkyl, (C\textsubscript{1-3})haloalkyl, cyano, nitro, CO\textsubscript{2} R'', C(=O)NR'R'', —C(=NR'R')NR'R'', —S(=O)\textsubscript{2} N(R')C(=O)R', —S(=O)\textsubscript{2} N(R')C(=O)OR', —S(=O)\textsubscript{2} N(R')C(=O)NR'R', —S(=O)\textsubscript{2} OR', —S(=O)\textsubscript{2} OR' or S(=O)\textsubscript{2} NR'R';

R'\textsuperscript{1} is H or (C\textsubscript{1-4})alkyl;

R'\textsuperscript{2} is independently, at each instance, H or R'\textsuperscript{b}; and

R'\textsuperscript{3} is independently, at each instance, phenyl, benzyl or (C\textsubscript{1-6})alkyl, the phenyl, benzyl and (C\textsubscript{1-6})alkyl being substituted by 0, 1, 2 or 3 substituents selected from halo, (C\textsubscript{1-4})alkyl, (C\textsubscript{1-3})haloalkyl, —O(C\textsubscript{1-4})alkyl, —NH\textsubscript{2}, —NHC\textsubscript{1-4}alkyl, —N((C\textsubscript{1-4})alkyl)(C\textsubscript{1-4})alkyl.

In another embodiment, the the PI3K inhibitor or PI3K-δ inhibitor is a compound of Formula (VI):

![Formula VI](image)

or any pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, wherein:

X'\textsuperscript{1} is C(R'\textsuperscript{9}) or N;

X'\textsuperscript{2} is C(R'\textsuperscript{10}) or N;

Y is N(R'\textsuperscript{1}), O or S;
Z is CR₈ or N;
R¹ is a direct-bonded or oxygen-linked saturated, partially-saturated or unsaturated 5-, 6- or 7-
membered monocyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, but
containing no more than one O or S, wherein the available carbon atoms of the ring are
substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0 or 1 R₂
substituents, and the ring is additionally substituted by 0, 1, 2 or 3 substituents independently
selected from halo, nitro, cyano, (C₁₋₆)alkyl, O(C₁₋₆)alkyl, O(C₁₋₆)haloalkyl, (NH₂₋₆)alkyl,
N(C₁₋₆ alkyl)(C₁₋₆)alkyl and (C₁₋₆)haloalkyl;
R² is selected from halo, (C₁₋₆)haloalkyl, cyano, nitro, —C(=O)R², —C(=O)OR², —
C(=O)NR'R², —C(=NR')NR'R², —OR², —OC(=O)R², —OC(=O)NR'R², —
OC(=O)N(R')S(O)₂R², —O(C₂₋₆)alkylnR'R², —O(C₂₋₆)alkyloR², —S(O)₂R², —
S(=O)₂SR², —S(=O)₂N(R')C(=O)R², —S(=O)₂N(R')C(=O)OR², —
S(=O)₂N(R')C(=O)NR'R², —N(R')C(=O)OR², —N(R')C(=O)OR², —
N(R')C(=O)NR'R², —N(R')C(=O)NR'R², —N(R')S(O)₂R², —N(R')S(O)₂NR'R², —
NR'(C₂₋₆)alkylNR'R² and —NR'(C₂₋₆)alkyloR²; or R² is selected from (C₁₋₆)alkyl, phenyl,
benzyl, heteroaryl, heterocycle, —((C₁₋₆)alkyl)heteroaryl, —((C₁₋₆)alkyl)heterocycle, —
O((C₁₋₆)alkyl)heteroaryl, —O((C₁₋₆)alkyl)heterocycle, —NR'((C₁₋₆)alkyl)heteroaryl,
—NR'((C₁₋₆)alkyl)heterocycle, —((C₁₋₆)alkyl)phenyl, —O((C₁₋₆)alkyl)phenyl and —NR'(C₁₋₆
alkyl)phenyl all of which are substituted by 0, 1, 2 or 3 substituents selected from (C₁₋₆)
haloalkyl, O(C₁₋₆)alkyl, Br, Cl, F, I and (C₁₋₆)alkyl;
R³ is selected from H, halo, (C₁₋₆)haloalkyl, cyano, nitro, —C(=O)R³, —C(=O)OR³,
C(=O)NR'R³C(=NR')NR'R³, —OR³, —OC(=O)R³, —OC(=O)NR'R³, —
OC(=O)N(R')S(O)₂R³, —O(C₂₋₆)alkylnR'R³, —O(C₂₋₆)alkyloR³, —SR³, —S(=O)₂R³, —
S(=O)₂R³, —S(=O)₂N(R')C(=O)R³, —S(=O)₂N(R')C(=O)OR³, —
S(=O)₂N(R')C(=O)NR'R³, —N(R')C(=O)OR³, —N(R')C(=O)OR³, —
N(R')C(=O)NR'R³, —N(R')C(=O)NR'R³, —N(R')S(O)₂R³, —N(R')S(O)₂NR'R³, —
NR'(C₂₋₆)alkyloR³, (C₁₋₆)alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the (C₁₋₆)
alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3
substituents selected from (C₁₋₆)haloalkyl, O(C₁₋₆)alkyl, Br, Cl, F, I and (C₁₋₆)alkyl;
R⁴ is, independently, in each instance, H, halo, (C₁₋₆)alkyl, (C₁₋₆)haloalkyl, or (C₁₋₆)alkyl
substituted by 1, 2 or 3 substituents selected from halo, cyano, OH, O(C₁₋₆)alkyl, (C₁₋₆)alkyl,
(C₁⁺₃)haloalkyl, O(C₁⁻₄)alkyl, NH₂, (NHC₁⁻₄)alkyl, N(C₁⁻₄)alkyl)C₁⁻₄)alkyl; or both R⁵ groups together form a C₃₋₆-spiroalkyl substituted by 0, 1, 2 or 3 substituents selected from halo, cyano, OH, O(C₁⁻₄)alkyl, (C₁⁻₄)alkyl, (C₁⁻₃)haloalkyl, O(C₁⁻₄)alkyl, NH₂, (NHC₁⁻₄)alkyl, N((C₁⁻₄)alkyl)(C₁⁻₄)alkyl;

R² is selected from H, halo, (C₁⁻₆)alkyl, (C₁⁻₄)haloalkyl, cyano, nitro, —C(=O)R², —C(=O)OR²,
—C(=O)NR'R'', —C(=NR')NR'R'', —S(=O)₂R², —S(=O)₂NR'R'', —S(=O)₂N(R')C(=O)OR'', —S(=O)₂N(R')C(=O)NR'R'';

R³ is selected from H, halo, (C₁⁻₆)alkyl, (C₁⁻₄)haloalkyl, cyano, nitro, —C(=O)R³, —C(=O)OR³,
—C(=O)NR'R'', —C(=NR')NR'R'', —S(=O)₂R², —S(=O)₂NR'R'', —S(=O)₂N(R')C(=O)OR'',
—S(=O)₂N(R')C(=O)NR'R'';

R⁴ is selected from H, (C₁⁻₆)haloalkyl, Br, Cl, F, I, OR⁴, NR'R'', (C₁⁻₆)alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the (C₁⁻₆)alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from (C₁⁻₆)haloalkyl, O(C₁⁻₄)alkyl, Br, Cl, F, I and (C₁⁻₆)alkyl;

R⁵ is selected from H, halo, (C₁⁻₆)haloalkyl, cyano, nitro, —C(=O)R⁵, —C(=O)OR⁵,
—C(=O)NR'R'', —C(=NR')NR'R'', —OR'', —OC(=O)R⁵, OC(=O)NR'R'',
—OC(=O)N(R')S(=O)₂R'', —O(C₂₋₆)alkylNR'R'', —O(C₂₋₆)alkylOR'', —SR'', —S(=O)₂R'', —S(=O)₂N(R')C(=O)R'', —S(=O)₂N(R')C(=O)OR'',
—S(=O)₂N(R')C(=O)NR'R'', —NR''R'', —N(R')C(=O)OR'', —N(R')C(=O)NR'R'';

NR'R''(C₂₋₆)alkylNR'R'', —NR'R''(C₂₋₆)alkylOR'', (C₁⁻₆)alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the (C₁⁻₆)alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from halo, (C₁⁻₆)haloalkyl, cyano, nitro, —C(=O)R''', —C(=O)OR''', —C(=O)NR'R''', —C(=NR')NR'R''', —OR'', —OC(=O)R'',
—OC(=O)N(R')S(=O)₂R''', —O(C₂₋₆)alkylOR'', —SR'', —S(=O)₂R''', —S(=O)₂N(R')C(=O)R''', —S(=O)₂N(R')C(=O)OR''',
—S(=O)₂N(R')C(=O)NR'R''', NR''R''', —N(R')C(=O)OR''', —N(R')C(=O)NR'R'''.
atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0, 1, 2, 3 or 4 substituents selected from halo, (C<sub>1-4</sub>)haloalkyl, cyano, nitro, —C(=O)R<sup>1</sup>, —C(=O)OR<sup>1</sup>, —C(=O)NR<sup>1</sup>R<sup>2</sup>, —C(=NR<sup>1</sup>)NR<sup>1</sup>R<sup>2</sup>, —OR<sup>1</sup>, —OC(=O)R<sup>1</sup>, —OC(=O)NR<sup>1</sup>R<sup>2</sup>, —OC(=O)N(R<sup>1</sup>)S(=O)R<sup>1</sup>, —O(C<sub>2-6</sub>)alkylOR<sup>1</sup>, —SR<sup>1</sup>, —S(=O)R<sup>1</sup>, —S(=O)<sub>2</sub>NR<sup>1</sup>R<sup>2</sup>, —S(=O)<sub>2</sub>N(R<sup>1</sup>)C(=O)R<sup>1</sup>, —S(=O)<sub>2</sub>N(=O)<sub>2</sub>(R<sup>1</sup>)C(=O)OR<sup>1</sup>, —S(=O)<sub>2</sub>N(R<sup>1</sup>)C(=O)NR<sup>1</sup>R<sup>2</sup>, —NR<sup>1</sup>R<sup>2</sup>, —N(R<sup>1</sup>)C(=O)R<sup>1</sup>, —N(R<sup>1</sup>)C(=O)OR<sup>1</sup>, —N(R<sup>1</sup>)C(=O)NR<sup>1</sup>R<sup>2</sup>, —N(R<sup>1</sup>)N(R<sup>2</sup>)NR<sup>1</sup>R<sup>2</sup>, —N(R<sup>1</sup>)S(=O)<sub>2</sub>R<sup>1</sup>, —N(R<sup>1</sup>)S(=O)<sub>2</sub>NR<sup>1</sup>R<sup>2</sup>, —NR<sup>1</sup>(C<sub>2-6</sub>)alkylNR<sup>1</sup>R<sup>2</sup> and —NR<sup>1</sup>(C<sub>2-6</sub>)alkylOR<sup>1</sup>; 
R<sup>10</sup> is H, (C<sub>1-3</sub>)alkyl, (C<sub>1-3</sub>)haloalkyl, cyano, nitro, CO<sub>2</sub>R<sup>1</sup>, C(=O)NR<sup>1</sup>R<sup>2</sup>, —C(=NR<sup>1</sup>)NR<sup>1</sup>R<sup>2</sup>, —S(=O)<sub>2</sub>N(R<sup>1</sup>)C(=O)OR<sup>1</sup>, —S(=O)<sub>2</sub>N(=O)<sub>2</sub>(R<sup>1</sup>)C(=O)NR<sup>1</sup>R<sup>2</sup>, —S(=O)<sub>2</sub>R<sup>1</sup>, S(=O)<sub>2</sub>R<sup>1</sup> or S(=O)<sub>2</sub>NR<sup>1</sup>R<sup>2</sup>; —R<sup>11</sup> is H or (C<sub>1-4</sub>)alkyl; 
R<sup>1</sup> is independently, at each instance, H or R<sup>1</sup>; and 
R<sup>1</sup> is independently, at each instance, phenyl, benzyl or (C<sub>1-6</sub>)alkyl, the phenyl, benzyl and (C<sub>1-6</sub>)alkyl being substituted by 0, 1, 2 or 3 substituents selected from halo, (C<sub>1-4</sub>)alkyl, (C<sub>1-3</sub>)haloalkyl, —O(C<sub>1-4</sub>)alkyl, —NH<sub>2</sub>, —NH(C<sub>1-4</sub>)alkyl, —N(C<sub>1-4</sub>)alkyl(C<sub>1-4</sub>)alkyl.

[00425] In another embodiment, the the PI3K inhibitor or PI3K-δ inhibitor is a compound of Formula (VII):

![Formula (VII)](image)

or any pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, wherein: 
X<sup>1</sup> is C(R<sup>9</sup>) or N; 
X<sup>2</sup> is C(R<sup>10</sup>) or N;
Y is N(R^{1}), O or S;
Z is CR^{3} or N;
R^{1} is a direct-bonded or oxygen-linked saturated, partially-saturated or unsaturated 5-, 6- or 7-
membered monocyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, but
containing no more than one O or S, wherein the available carbon atoms of the ring are
substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0 or 1 R^{2}
substituents, and the ring is additionally substituted by 0, 1, 2 or 3 substituents independently
selected from halo, nitro, cyano, (C_{1-4})alkyl, O(C_{1-4})alkyl, O(C_{1-4})haloalkyl, NH(C_{1-4})alkyl,
N(C_{1-4})alkyl(C_{1-4})alkyl and (C_{1-4})haloalkyl;
R^{2} is selected from halo, (C_{1-4})haloalkyl, cyano, nitro, —C(=O)R^{2}, —C(=O)OR^{2}, —
C(=O)NR^{2}R^{2}, —C(=NR^{2})NR^{2}R^{2}, —OR^{2}, —OC(=O)R^{2}, —OC(=O)NR^{2}R^{2}, —
OC(=O)N(R^{3})S(=O)_{2}R^{2}, —OC(=O)alkylNR^{2}R^{2}, —O(C_{1-4})alkylOR^{2}, —SR^{2}, —S(=O)R^{2}, —
S(=O)_{2}R^{2}, —S(=O)_{2}NR^{2}R^{2}, —S(=O)_{2}N(R^{3})C(=O)R^{2}, —S(=O)_{2}N(R^{3})C(=O)OR^{2}, —
S(=O)_{2}N(R^{3})C(=O)NR^{2}R^{2}, NR^{2}R^{2}, —N(R^{3})C(=O)R^{2}, —N(R^{3})C(=O)OR^{2}, —
N(R^{3})C(=O)NR^{2}R^{2}, —N(R^{3})C(=O)NR^{2}R^{2}, —N(R^{3})S(=O)_{2}R^{2}, —N(R^{3})S(=O)_{2}NR^{2}R^{2}, —
N(R^{3})alkylNR^{2}R^{2} and —NR^{3}(C_{1-4})alkylOR^{2}; or R^{2} is selected from (C_{1-6})alkyl, phenyl,
benzyl, heteroaryl, heterocycle, —(C_{1-4} alkyl)heteroaryl, —(C_{1-3} alkyl)alkylheterocycle, —O(C_{1-3}
alcohol)heteroaryl, —O((C_{1-3} alkyl)heteroaryl, —NR^{3}(C_{1-3} alkyl)heteroaryl, —NR^{3}(C_{1-3})alkylheterocycle, —(C_{1-3} alkyl)phenyl, —O(C_{1-3})alkylphenyl and —NR^{3}(C_{1-3})alkylphenyl
all of which are substituted by 0, 1, 2 or 3 substituents selected from (C_{1-4} haloalkyl, O(C_{1-4})
alkyl, Br, Cl, F, I and (C_{1-4})alkyl;
R^{1} is selected from H, halo, (C_{1-4} haloalkyl, cyano, nitro, —C(=O)R^{2}, —C(=O)OR^{2}, —
C(=O)NR^{2}R^{2}, —C(=NR^{2})NR^{2}R^{2}, —OR^{2}, —OC(=O)R^{2}, —OC(=O)NR^{2}R^{2}, —
OC(=O)N(R^{3})S(=O)_{2}R^{2}, —OC(=O)alkylNR^{2}R^{2}, —OC(=O)alkylOR^{2}, —SR^{2}, —S(=O)R^{2}, —
S(=O)_{2}R^{2}, —S(=O)_{2}NR^{2}R^{2}, —S(=O)_{2}N(R^{3})C(=O)R^{2}, —S(=O)_{2}N(R^{3})C(=O)OR^{2}, —
S(=O)_{2}N(R^{3})C(=O)NR^{2}R^{2}, NR^{2}R^{2}, —N(R^{3})C(=O)R^{2}, —N(R^{3})C(=O)OR^{2}, —
N(R^{3})C(=O)NR^{2}R^{2}, —N(R^{3})C(=O)NR^{2}R^{2}, —N(R^{3})S(=O)_{2}R^{2}, —N(R^{3})S(=O)_{2}NR^{2}R^{2}, —
NR^{3}(C_{1-4})alkylNR^{2}R^{2} and —NR^{3}(C_{1-4})alkylOR^{2}; wherein the (C_{1-4})alkyl, phenyl, benzyl, heteroaryl and
heterocycle, wherein the (C_{1-4})alkyl, phenyl, benzyl, heteroaryl and heterocycle are
additionally substituted by 0, 1, 2 or 3 substituents selected from (C_{1-6})haloalkyl, O(C_{1-6})
alkyl, Br, Cl, F, I and (C_{1-6})alkyl;
$R^2$ is, independently, in each instance, H, halo, $(C_{1-4})$alkyl, $(C_{1-4})$haloalkyl, or $(C_{1-4})$alkyl substituted by 1, 2 or 3 substituents selected from halo, cyano, OH, O$(C_{1-4})$alkyl, $(C_{1-4})$alkyl, $(C_{1-4})$haloalkyl, O$(C_{1-4})$alkyl, NH$_2$, NH$_2$(C$_{1-4}$)alkyl, N$(C_{1-4})$alkyl)C$_{1-4}$alkyl; or both $R^2$ groups together form a C$_{3-6}$spiroalkyl substituted by 0, 1, 2 or 3 substituents selected from halo, cyano, OH, O$(C_{1-4})$alkyl, $(C_{1-4})$alkyl, $(C_{1-4})$haloalkyl, O$(C_{1-4})$alkyl, NH$_2$, NH$_2$(C$_{1-4}$)alkyl, N$(C_{1-4})$alkyl)C$_{1-4}$alkyl;

$R^3$ is selected from H, halo, $(C_{1-4})$alkyl, $(C_{1-4})$haloalkyl, cyano, nitro, $-C(=O)R^2$, $-C(=O)OR^2$, $-C(=O)NR^2R^3$, $-C(=O)NR^2R^3$, $-S(=O)R^4S(=O)R^5$, $-S(=O)_2NR^6R^7$, $-S(=O)_2NR^6R^7$;

$R^7$ is selected from H, halo, $(C_{1-6})$alkyl, $(C_{1-4})$haloalkyl, cyano, nitro, $-C(=O)R^2$, $-C(=O)OR^2$, $-C(=O)NR^2R^3$, $-C(=O)NR^2R^3$, $-S(=O)R^4S(=O)R^5$, $-S(=O)_2NR^6R^7$, $-S(=O)_2NR^6R^7$;

$R^8$ is selected from H, (C$_{1-6}$)haloalkyl, Br, Cl, F, I, OR, NR$^8$R$^9$, (C$_{1-6}$)alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the (C$_{1-6}$)alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from (C$_{1-6}$)haloalkyl, O(C$_{1-6}$)alkyl, Br, Cl, F, I and (C$_{1-6}$)alkyl;

$R^9$ is selected from H, halo, (C$_{1-4}$)haloalkyl, cyano, nitro, $-C(=O)R^2$, $-C(=O)OR^2$, $-C(=O)NR^2R^3$, $-C(=O)NR^2R^3$, $-OC(=O)R^4$, $-OC(=O)NR^5R^6$, $-OC(=O)NR^5R^6$, $-OC(=O)NR^5R^6$;

$R^{10}$ is selected from H, halo, (C$_{1-4}$)haloalkyl, cyano, nitro, $-C(=O)R^2$, $-C(=O)OR^2$, $-C(=O)NR^2R^3$, $-C(=O)NR^2R^3$, $-OC(=O)NR^5R^8$, $-OC(=O)NR^5R^8$, $-OC(=O)NR^5R^8$;
unsaturated 5-, 6- or 7-membered monocyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thiolo groups, wherein the ring is substituted by 0, 1, 2, 3 or 4 substituents selected from halo, (C\(_{1-6}\))haloalkyl, cyano, nitro, —C(=O)R\(^a\), —C(=O)OR\(^a\), —C(=O)NR\(^a\)R\(^b\), —C(=NR\(^a\))NR\(^a\)R\(^b\), —OR\(^b\), —OC(=O)R\(^b\), —OC(=O)NR\(^a\)R\(^b\), —OC(=O)N(R\(^a\))S(=O)\(_2\)R\(^b\), —OC(=O)alkylNR\(^a\)R\(^b\), —OC(=O)alkylOR\(^a\), —SR\(^b\), —S(=O)\(_2\)R\(^b\), —S(=O)\(_2\)NR\(^a\)R\(^b\), —S(=O)\(_2\)N(R\(^a\))C(=O)R\(^b\), —S(=O)\(_2\)N(R\(^a\))C(=O)alkyl, —S(=O)\(_2\)N(R\(^a\))C(=O)alkylNR\(^a\)R\(^b\), —S(=O)\(_2\)N(R\(^a\))C(=O)alkylOR\(^a\), —R\(^1\) is H, (C\(_{1-3}\))alkyl, (C\(_{1-3}\))haloalkyl, cyano, nitro, CO\(_2\)R\(^b\), C(=O)NR\(^a\)R\(^b\), —C(=NR\(^a\))NR\(^a\)R\(^b\), —S(=O)\(_2\)N(R\(^a\))C(=O)alkyl, —S(=O)\(_2\)N(R\(^a\))C(=O)alkylOR\(^a\), —S(=O)\(_2\)N(R\(^a\))C(=O)alkylNR\(^a\)R\(^b\), —S(=O)\(_2\)N(R\(^a\))C(=O)alkylOR\(^a\), —S(=O)\(_2\)N(R\(^a\))C(=O)alkylNR\(^a\)R\(^b\), —S(=O)\(_2\)N(R\(^a\))C(=O)alkylOR\(^a\), —R\(^1\) is H or (C\(_{1-6}\))alkyl;

R\(^2\) is independently, at each instance, H or R\(^b\); and

R\(^3\) is independently, at each instance, phenyl, benzyl or (C\(_{1-6}\))alkyl, the phenyl, benzyl and (C\(_{1-6}\))alkyl being substituted by 0, 1, 2 or 3 substituents selected from halo, (C\(_{1-6}\))alkyl, (C\(_{1-6}\))haloalkyl, —O(C\(_{1-6}\))alkyl, —NH\(_2\), —NH(C\(_{1-6}\))alkyl, —N(C\(_{1-6}\))alkyl(C\(_{1-6}\))alkyl.

[00426] In another embodiment, the the PI3K inhibitor or PI3K-δ inhibitor is a compound of Formula (VIII):

![Formula (VIII)](image-url)
or any pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, wherein:
X is C(R') or N;
X' is C(R') or N;
Y is N(R'), O or S;
Z is CR' or N;
R' is a direct-bonded or oxygen-linked saturated, partially-saturated or unsaturated 5-, 6- or 7-membered monocyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0 or 1 R^2 substituents, and the ring is additionally substituted by 0, 1, 2 or 3 substituents independently selected from halo, nitro, cyano, (C_{1-4})alkyl, O(C_{1-4})alkyl, O(C_{1-4})hlmocalkyl, NH(C_{1-4})alkyl, N(C_{1-4})alkyl(C_{1-4})alkyl and (C_{1-4})haloalkyl;
R^2 is selected from halo, (C_{1-4})haloalkyl, cyano, nitro, —C(═O)R', —C(═O)OR', —
C(═O)NR'R'—C(═NR')NR'R', —OR', —OC(═O)R', —OC(═O)NR'R', —
OC(═O)N(R')S(═O)R', —OC_{2-6} alkyilor', —SR', —S(═O)R', —S(═O)R', —
S(═O)_{2}NR'R', —S(═O)_{2}N(R')C(═O)R', —S(═O)_{2}N(R')C(═O)OR', —
S(═O)_{2}N(R')C(═O)NR'R', —NR'R', —N(R')C(═O)OR', —N(R')C(═O)OR', —
N(R')C(═O)NR'R', —N(R')C(═O)NR'R', —N(R')S(═O)_{2}R', —N(R')S(═O)_{2}NR'R', —
NR'(C_{2-6})alkylNR'R' and —NR'(C_{2-6})alkylOR'; or R^2 is selected from (C_{1-4})alkyl, phenyl, benzyl, heteroaryl, heterocycle, —(C_{1-3}) alkylheteroaryl, —(C_{1-3}) alkylheterocycle, —O(C_{1-3} alkylheteroaryl, —O(C_{1-13} alkylheterocycle, —NR'(C_{1-3})alkylheteroaryl, —NR'(C_{1-3} alkylheterocycle, —(C_{1-3}) alkylphenyl, —O(C_{1-3}) alkylphenyl and —NR'(C_{1-3}) alkylphenyl all of which are substituted by 0, 1, 2 or 3 substituents selected from (C_{1-4}) haloalkyl, O(C_{1-4})alkyl, Br, Cl, F, I and (C_{1-4})alkyl;
R^3 is selected from H, halo, (C_{1-6})haloalkyl, cyano, nitro, —C(═O)R', —C(═O)OR', —
C(═O)NR'R'—C(═NR')NR'R', —OR', —OC(═O)R', —OC(═O)NR'R', —
OC(═O)N(R')S(═O)R', —OC_{2-6} alkyilor', —SR', —S(═O)R', —S(═O)R', —
S(═O)_{2}NR'R', —S(═O)_{2}N(R')C(═O)R', —S(═O)_{2}N(R')C(═O)OR', —
S(═O)_{2}N(R')C(═O)NR'R', —NR'R', —N(R')C(═O)OR', —N(R')C(═O)OR', —
N(R')C(═O)NR'R', —N(R')C(═O)NR'R', —N(R')S(═O)_{2}R', —N(R')S(═O)_{2}NR'R', —
NR', —NR'(C_{2-6})alkylOR', (C_{1-6})alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein
the (C$_{1-6}$ alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from (C$_{1-6}$)haloalkyl, OC$_{1-6}$ alkyl, Br, Cl, F, I and (C$_{1-6}$)alkyl; R$^5$ is, independently, in each instance, H, halo, (C$_{1-6}$)alkyl, (C$_{1-6}$)haloalkyl, or (C$_{1-6}$)alkyl substituted by 1, 2 or 3 substituents selected from halo, cyano, OH, O(C$_{1-4}$)alkyl, (C$_{1-4}$)alkyl, (C$_{1-6}$)haloalkyl, O(C$_{1-4}$)alkyl, NH$_2$, NH(C$_{1-4}$)alkyl, N(C$_{1-4}$)alkyl(C$_{1-4}$)alkyl; or both R$^5$ groups together form a (C$_{3-6}$)spiroalkyl substituted by 0, 1, 2 or 3 substituents selected from halo, cyano, OH, O(C$_{1-4}$)alkyl, (C$_{1-4}$)alkyl, (C$_{1-6}$)haloalkyl, O(C$_{1-4}$)alkyl, NH$_2$, NH(C$_{1-4}$)alkyl, N(C$_{1-4}$)alkyl(C$_{1-4}$)alkyl; R$^6$ is selected from H, halo, (C$_{1-4}$)alkyl, (C$_{1-6}$)haloalkyl, cyano, nitro, —C(=O)R$^6$, —C(=O)OR$^6$, —C(=O)NR$^6$R$^6$, —C(=NR$^6$)NR$^6$R$^6$, —S(=O)R$^6$, —S(=O)$_2$R$^6$, —S(=O)$_2$NR$^6$R$^6$, —S(=O)$_2$N(R$^6$)C(=O)OR$^6$, —S(=O)$_2$N(R$^6$)C(=O)NR$^6$R$^6$; R$^7$ is selected from H, halo, (C$_{1-4}$)alkyl, (C$_{1-6}$)haloalkyl, cyano, nitro, —C(=O)R$^7$, —C(=O)OR$^7$, —C(=O)NR$^7$R$^7$, —C(=NR$^7$)NR$^7$R$^7$, —S(=O)R$^7$, —S(=O)$_2$R$^7$, —S(=O)$_2$NR$^7$R$^7$, —S(=O)$_2$N(R$^7$)C(=O)OR$^7$, —S(=O)$_2$N(R$^7$)C(=O)NR$^7$R$^7$; R$^8$ is selected from H, (C$_{1-6}$)haloalkyl, Br, Cl, F, I, OR$^8$, NR$^8$R$^8$, (C$_{1-6}$)alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the (C$_{1-6}$)alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from (C$_{1-6}$)haloalkyl, O(C$_{1-6}$)alkyl, Br, Cl, F, I and (C$_{1-6}$)alkyl; R$^9$ is selected from H, halo, (C$_{1-4}$)haloalkyl, cyano, nitro, —C(=O)R$^9$, —C(=O)OR$^9$, —C(=O)NR$^9$R$^9$, —C(=NR$^9$)NR$^9$R$^9$, —OR$^9$, —OC(=O)R$^9$, —OC(=O)NR$^9$R$^9$, —OC(=O)NR$^9$R$^9$, —OC$_{2-6}$alkylNR$^9$R$^9$, —OC$_{2-6}$alkylOR$^9$, —SR$^9$, —S(=O)R$^9$, —S(=O)$_2$R$^9$, —S(=O)$_2$NR$^9$R$^9$, —S(=O)$_2$N(R$^9$)C(=O)OR$^9$, —S(=O)$_2$N(R$^9$)C(=O)OR$^9$, —S(=O)$_2$N(R$^9$)C(=O)OR$^9$, —N(R$^9$)C(=O)NR$^9$R$^9$, —N(R$^9$)C(=O)NR$^9$R$^9$, —N(R$^9$)C(=O)NR$^9$R$^9$, —N(R$^9$)S(=O)$_2$R$^9$, —N(R$^9$)S(=O)$_2$NR$^9$R$^9$, —NR$^9$R$_2$, —NR$^9$R$_2$, —NR$^9$R$_2$, —NR$^9$R$_2$, —NR$^9$R$_2$, —NR$^9$R$_2$, —NR$^9$R$_2$, —NR$^9$R$_2$, —NR$^9$R$_2$.
N(R')C(=O)NR'R', —N(R')C(=NR')NR'R', —N(R')S(=O)₂R', —N(R')S(=O)₂NR'R', —NR'(C₆₋₉)alkylNR'R', —NR'(C₆₋₉)alkylOR'; or R' is a saturated, partially-saturated or unsaturated 5-, 6- or 7-membered monocyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0, 1, 2, 3 or 4 substituents selected from halo, (C₁₋₄)haloalkyl, cyano, nitro, —C(O)R', —C(=O)OR', —C(=O)NR'R', —C(=NR')NR'R', —OR', —OC(=O)R', —OC(=O)NR'R', —OC(=O)N(R')S(=O)₂R', —O(C₂₋₆)alkylNR'R', —O(C₂₋₆)alkylOR', —SR', —S(=O)R', —S(=O)₂R', —S(=O)₂NR'R', —S(=O)₂N(R')C(=O)R', —S(=O)₂N(R')C(=O)OR', —S(=O)₂N(R')C(=O)NR'R', —S(=O)₂N(R')C(=O)NR'R', —S(=O)₂N(R')C(=O)NR'R', —N(R')S(=O)₂R', —N(R')S(=O)₂NR'R', —NR'(C₂₋₆)alkylNR'R' and —NR'(C₂₋₆)alkylOR'; R¹₀ is H, (C₆₋₉) alkyl, (C₁₋₄)haloalkyl, cyano, nitro, CO₂R', C(=O)NR'R', —C(=NR')NR'R', —S(=O)₂N(R')C(=O)OR', —S(=O)₂N(R')C(=O)NR'R', —S(=O)₂N(R')C(=O)NR'R', —S(=O)₂N(R')C(=O)NR'R', —S(=O)₂N(R')C(=O)NR'R', —S(=O)₂N(R')C(=O)NR'R'; R¹¹ is H or (C₁₋₄)alkyl; R' is independently, at each instance, H or R²; and R² is independently, at each instance, phenyl, benzyl or (C₁₋₆)alkyl, the phenyl, benzyl and (C₁₋₆)alkyl being substituted by 0, 1, 2 or 3 substituents selected from halo, (C₁₋₄)alkyl, (C₁₋₆)haloalkyl, —O(C₁₋₄)alkyl, —NH₂, —NH(C₁₋₄)alkyl, —N(C₁₋₄)alkyl(C₁₋₄)alkyl.

[00427] In another embodiment, in conjunction with any of the above or below embodiments, X¹ is C(R⁹) and X² is N.

[00428] In another embodiment, in conjunction with any of the above or below embodiments, X¹ is C(R⁹) and X² is C(R¹₀).

[00429] In another embodiment, in conjunction with any of the above or below embodiments, R' is phenyl substituted by 0 or 1 R² substituents, and the phenyl is additionally substituted by 0, 1, 2 or 3 substituents independently selected from halo, nitro, cyano, (C₁₋₄)alkyl, O(C₁₋₄)alkyl, O(C₁₋₄)haloalkyl, NH(C₁₋₄)alkyl, N(C₁₋₄)alkyl(C₁₋₄)alkyl and (C₁₋₄)haloalkyl.
[00430] In another embodiment, in conjunction with any of the above or below embodiments, 
R' is phenyl.

[00431] In another embodiment, in conjunction with any of the above or below embodiments, 
R' is phenyl substituted by R^2, and the phenyl is additionally substituted by 0, 1, 2 or 3 
substituents independently selected from halo, nitro, cyano, (C_{1-4})alkyl, O(C_{1-4})alkyl, O(C_{1-4})haloalkyl, 
NH(C_{1-4})alkyl, N(C_{1-4})alkyl(C_{1-4})alkyl and C_{1-4} haloalkyl.

[00432] In another embodiment, in conjunction with any of the above or below embodiments, 
R' is selected from 2-methylphenyl, 2-chlorophenyl, 2-trifluoromethylphenyl, 2-fluorophenyl 
and 2-methoxyphenyl.

[00433] In another embodiment, in conjunction with any of the above or below embodiments, 
R' is phenoxy.

[00434] In one specific embodiment, R'^1 is a directly-bonded or an oxygen-linked saturated, 
partially-saturated or unsaturated 5-, 6- or 7-membered monocyclic ring containing 1, 2, 3 or 4 
atoms selected from N, O and S, but containing no more than one O or S, wherein the available 
carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is 
substituted by 0 or 1 R^2 substituents, and the ring is additionally substituted by 0, 1, 2 or 3 
substituents independently selected from halo, nitro, cyano, (C_{1-4})alkyl, O(C_{1-4})alkyl, O(C_{1-4})haloalkyl, 
NH(C_{1-4})alkyl, N(C_{1-4})alkyl(C_{1-4})alkyl and (C_{1-4})haloalkyl.

[00435] In another specific embodiment, R'^1 is an unsaturated 5- or 6-membered monocyclic 
ring containing 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O 
or S, wherein the ring is substituted by 0 or 1 R^2 substituents, and the ring is additionally 
substituted by 0, 1, 2 or 3 substituents independently selected from halo, nitro, cyano, (C_{1-4})alkyl, 
O(C_{1-4})alkyl, O(C_{1-4})haloalkyl, NH(C_{1-4})alkyl, N(C_{1-4})alkyl(C_{1-4})alkyl and (C_{1-4})haloalkyl.

[00436] In another embodiment, in conjunction with any of the above or below embodiments, 
R'^1 is an unsaturated 5- or 6-membered monocyclic ring containing 1, 2, 3 or 4 atoms selected 
from N, O and S, but containing no more than one O or S, wherein the ring is substituted by 0 or 
1 R^2 substituents, and the ring is additionally substituted by 1, 2 or 3 substituents independently
selected from halo, nitro, cyano, (C\textsubscript{1-4})alkyl, (OC\textsubscript{1-4})alkyl, O(C\textsubscript{1-4})haloalkyl, NH(C\textsubscript{1-4})alkyl, N(C\textsubscript{1-4})alkyl(C\textsubscript{1-4})alkyl and (C\textsubscript{1-4})haloalkyl.

[00437] In another embodiment, in conjunction with any of the above or below embodiments, R' is an unsaturated 5- or 6-membered monocyclic ring containing 1, 2, 3 or 4 atoms selected from N, O and S.

[00438] In another embodiment, in conjunction with any of the above or below embodiments, R' is selected from pyridyl and pyrimidinyl.

[00439] In a further specific embodiment, R' is selected from halo, C\textsubscript{1-4} haloalkyl, cyano, nitro, —C(O)R', —C(=O)OR', —C(=O)NR'R', —C(NR')NR'R', —OR', —OC(=O)R', —OC(=O)NR'R', —OC\textsubscript{1-4}alkylNR'R', —OC\textsubscript{1-4}alkylOR', —S=O, —S(=O)R', —S(=O)NR'R', —S(=O)N(R')C(=O)R', —S(=O)N(R')C(=O)OR', —S(=O)\textsubscript{2}N(R')(C(=O)NR'R', —NR'R', —N(R')C(=O)R', —N(R')C(=O)OR', —N(R')C(=O)NR'R', —N(R')C(=O)NR'R', —N(R')S(=O)\textsubscript{2}R', —N(R')S(=O)\textsubscript{2}NR'R', —NR'R', C\textsubscript{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C\textsubscript{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from C\textsubscript{1-6}haloalkyl, OC\textsubscript{1-6}alkyl, Br, Cl, F, I and C\textsubscript{1-6}alkyl.

[00440] In a preferred embodiment, X'\textsubscript{1} is C(R')\textsubscript{9} N. In a further preferred embodiment, X'\textsubscript{1} is C(R')\textsubscript{9} and X'\textsubscript{2} is N. In a further embodiment, X'\textsubscript{1} is C(R')\textsubscript{9} and X'\textsubscript{2} is C(R')\textsubscript{10}.

[00441] In another embodiment, in conjunction with any of the above or below embodiments, R' is selected from F, Cl, C\textsubscript{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C\textsubscript{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from C\textsubscript{1-6}haloalkyl, OC\textsubscript{1-6}alkyl, Br, Cl, F, I and C\textsubscript{1-6}alkyl.

[00442] In another embodiment, in conjunction with any of the above or below embodiments, R' is, independently, in each instance, H, halo, (C\textsubscript{1-6})alkyl, (C\textsubscript{1-4})haloalkyl, or (C\textsubscript{1-6})alkyl substituted by 1, 2 or 3 substituents selected from halo, cyano, OH, O(C\textsubscript{1-4})alkyl, (C\textsubscript{1-4})alkyl, (C\textsubscript{1-4})haloalkyl, O(C\textsubscript{1-4})alkyl, NH\textsubscript{2}, NH(C\textsubscript{1-4})alkyl, N(C\textsubscript{1-4})alkyl(C\textsubscript{1-4})alkyl; or both R' groups together form a C\textsubscript{3,6}spiroalkyl substituted by 0, 1, 2 or 3 substituents selected from halo, cyano, OH,
O(C\(_{1-4}\))alkyl, (C\(_{1-4}\))alkyl, (C\(_{1-3}\))haloalkyl, O(C\(_{1-4}\))alkyl, NH\(_2\), NH(C\(_{1-4}\))alkyl, N(C\(_{1-4}\))alkyl(C\(_{1-4}\)), haloalkyl.

[00443] In a preferred embodiment, R\(^5\) is H.

[00444] In a preferred embodiment, one R\(^2\) is S-methyl, the other is H.

[00445] In a preferred embodiment, at least one R\(^5\) is halo, C\(_{1-4}\) alkyl, C\(_{1-4}\) haloalkyl, or C\(_{1-6}\) alkyl substituted by 1, 2 or 3 substituents selected from halo, cyano, OH, OC\(_{1-4}\) alkyl, C\(_{1-4}\) alkyl, C\(_{1-4}\) haloalkyl, OC\(_{1-4}\) alkyl, NH\(_2\), NH(C\(_{1-4}\))alkyl, N(C\(_{1-4}\))alkyl(C\(_{1-4}\)) alkyl.

[00446] In a preferred embodiment, R\(^6\) is H.

[00447] In a preferred embodiment, R\(^6\) is F, Cl, cyano or nitro.

[00448] In a preferred embodiment, R\(^7\) is H.

[00449] In a preferred embodiment, R\(^7\) is F, Cl, cyano or nitro.

[00450] In a preferred embodiment, R\(^8\) is selected from H, CF\(_3\), C\(_{1-3}\) alkyl, Br, Cl and F.

[00451] In a preferred embodiment, R\(^8\) is selected from H.

[00452] In a preferred embodiment, R\(^8\) is selected from CF\(_3\), C\(_{1-3}\) alkyl, Br, Cl and F.

[00453] In a preferred embodiment, R\(^9\) is H.

[00454] In a preferred embodiment, R\(^9\) is selected from halo, C\(_{1-4}\) haloalkyl, cyano, nitro, — C(=O)R\(^\ast\), —C(=O)OR\(^\ast\), —C(=O)NR\(^\ast\)R\(^\ast\), —C(=NR\(^\ast\))NR\(^\ast\)R\(^\ast\), —OR\(^\ast\), —OC(=O)R\(^\ast\), —OC(=O)NR\(^\ast\)R\(^\ast\), —OC(=O)alkylNR\(^\ast\)R\(^\ast\), —OC\(_{2-6}\) alkylOR\(^\ast\), —SR\(^\ast\), —S(=O)R\(^\ast\), —S(=O)\(_2\)R\(^\ast\), —S(=O)\(_2\)NR\(^\ast\)R\(^\ast\), —S(=O)\(_2\)N(R\(^\ast\))C(=O)R\(^\ast\), —S(=O)\(_2\)N(R\(^\ast\))C(=O)OR\(^\ast\), —S(=O)\(_2\)N(R\(^\ast\))C(=O)NR\(^\ast\)R\(^\ast\), —NR\(^\ast\)R\(^\ast\), —N(R\(^\ast\))C(=O)R\(^\ast\), —N(R\(^\ast\))C(=O)OR\(^\ast\), —N(R\(^\ast\))C(=O)NR\(^\ast\)R\(^\ast\), —NR\(^\ast\)C\(_{2-6}\) alkylNR\(^\ast\)R\(^\ast\), —NR\(^\ast\)C\(_{2-6}\) alkylOR\(^\ast\), C\(_{1-4}\) alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C\(_{1-4}\) alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from halo, C\(_{1-4}\) haloalkyl, cyano, nitro, —C(=O)R\(^\ast\), —C(=O)OR\(^\ast\), —C(=O)NR\(^\ast\)R\(^\ast\), —C(=NR\(^\ast\))NR\(^\ast\)R\(^\ast\), —OR\(^\ast\), —OC(=O)R\(^\ast\), —OC(=O)NR\(^\ast\)R\(^\ast\), —
In a preferred embodiment, the PI3K inhibitor or PI3K-δ inhibitor is a compound of Formula (IX):

[R09] is a saturated, partially-saturated or unsaturated 5-, 6- or 7-membered monocyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0, 1, 2, 3 or 4 substituents selected from halo, C₁₋₄ haloalkyl, cyano, nitro, —C(=O)Rₙ, —C(=O)ORₙ, —C(=O)NRₙR', —OC₂₋₆ alkylOR', —SR', —S(=O)R', —S(=O)₂R', —S(=O)₂NR'R', —N'R'C(=O)OR', —N'R'C(=O)NR'R', —N'R'C(=O)NR'R', —N(R')S(=O)₂R', —N(R')S(=O)(C₂₋₆ alkyl)R', —NR'(C₂₋₆ alkyl)OR'.

In another embodiment, in conjunction with any of the above or below embodiments, R¹ is H.

In one specific embodiment, R¹ is cyano, nitro, CO₂R', C(=O)NR'R', —C(=O)NR'R', —S(=O)₂N(R')C(=O)R', —S(=O)₂N(R')C(=O)OR', —S(=O)₂N(R')C(=O)NR'R', —N(R')S(=O)₂R', —N(R')S(=O)(C₂₋₆ alkyl)R', —NR'(C₂₋₆ alkyl)OR'.

In another specific embodiment, R¹ is H.

In a preferred embodiment, the PI3K inhibitor or PI3K-δ inhibitor is a compound of Formula (IX):
or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

[00460] In an embodiment, the PI3K inhibitor or PI3K-δ inhibitor is \((S)-N-(1-(7\text{-fluoro}-2-(pyridin-2-yl)quinolin-3-yl)ethyl)-9H\text{-purin-6-amine}\) or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

[00461] In an embodiment, the PI3K inhibitor or PI3K-δ inhibitor is a compound of Formula (X):

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

[00462] In an embodiment, the PI3K inhibitor or PI3K-δ inhibitor is \((S)-N-(1-(6\text{-fluoro}-3-(pyridin-2-yl)quinazalin-2-yl)ethyl)-9H\text{-purin-6-amine}\) or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.
[00463] In an embodiment, the PI3K inhibitor or PI3K-δ inhibitor is a compound of Formula (XI):

\[
\text{Formula (XI)}
\]

, which is \((S)-N-(1-(7\text{-fluoro}-2\text{-}(\text{pyridin}-2\text{-yl})\text{quinolin}-3\text{-yl})\text{ethyl})\cdot9\text{H-purin-6-amine},\) or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

[00464] In an embodiment, the PI3K inhibitor or PI3K-δ inhibitor is \((S)-N-(1-(2\cdot(3,5\text{-difluorophenyl})\text{-8-fluoroquinolin}-3\text{-yl})\text{ethyl})\cdot9\text{H-purin-6-amine} or a pharmaceutically-acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

[00465] In an embodiment, the PI3K inhibitor is PI3K-δ inhibitor which is a compound of Formula (XII):

\[
\text{Formula (XII)}
\]
or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

[00466] In an embodiment, the PI3K inhibitor or PI3K-δ inhibitor is (S)-3-(1-((9H-purin-6-yl)amino)ethyl)-2-(pyridin-2-yl)quinoline-8-carbonitrile or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

[00467] In an embodiment, the PI3K inhibitor or PI3K-δ inhibitor is a compound of Formula (XIII):

![Formula (XIII)](image)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

[00468] In an embodiment, the PI3K inhibitor or PI3K-δ inhibitor is (S)-N-(1-(5,7-difluoro-2-(pyridin-2-yl)quinolin-3-yl)ethyl)-9H-purin-6-amine or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

[00469] In an embodiment, the PI3K inhibitor or PI3K-δ inhibitor is a compound selected from the structures disclosed in U.S. Patent Nos. 7,932,260 and 8,207,153, the disclosure of which is incorporated by reference herein. In an embodiment, the PI3K inhibitor or PI3K-δ inhibitor is a compound of Formula (XIV):
wherein
X and Y, independently, are N or CH;
Z is N—R^7 or O;
R^1 are the same and are hydrogen, halo, or C\textsubscript{1-3} alkyl;
R^2 and R^3, independently, are hydrogen, halo, or C\textsubscript{1-3} alkyl;
R^4 is hydrogen, halo, OR^e, CN, C\textsubscript{2-6} alkynyl, C(═O)R^7, C(═O)NR^aR^b, C\textsubscript{3-6} heterocycloalkyl, C\textsubscript{1-3} alkylenec\textsubscript{3-6} heterocycloalkyl, O(C\textsubscript{1-3})alkyleneOR^e, O(C\textsubscript{1-3})alkyleneNR^aR^b, O(C\textsubscript{1-3})alkyleneC\equiv CH, or O(C\textsubscript{1-3})alkyleneC(═O)OR^e;
R^5 is (C\textsubscript{1-3})alkyl, CH\textsubscript{2} CF\textsubscript{3}, phenyl, CH\textsubscript{2} C\equiv CH, (C\textsubscript{1-3})alkyleneOR^e, (C\textsubscript{1-4})alkyleneNR^aR^b, or C\textsubscript{1-4} alkylenenHC(═O)OR^e;
R^6 is hydrogen, halo, or NR^aR^b;
R^7 is hydrogen or R^5 and R^7 are taken together with the atoms to which they are attached to form a five- or six-membered saturated ring;
R^8 is C\textsubscript{1-3} alkyl, halo, CF\textsubscript{3}, or CH\textsubscript{2} C\textsubscript{3-6} heterocycloalkyl;
n is 0, 1, or 2;
R^9 is hydrogen, (C\textsubscript{1-4})alkyl, or CH\textsubscript{2} C\textsubscript{6} H\textsubscript{5};
R^b is hydrogen or C\textsubscript{1-3} alkyl; and
R^c is hydrogen, C\textsubscript{1-3} alkyl, or halo,
wherein when the \( R^1 \) groups are different from hydrogen, \( R^2 \) and \( R^4 \) are the same; or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

[00470] In a preferred embodiment, the PI3K inhibitor or PI3K-\( \delta \) inhibitor is an enantiomer of Formula (XIV), as shown in Formula (XV):

![Diagram of Formula (XV)]

wherein \( X, Y, Z, R^1 \) through \( R^8, R^2, R^3, R^4, R^6, \) and \( n \) are as defined above for Formula (XIV).

[00471] In various embodiments exhibiting increased potency relative to other compounds, \( R^8 \) is \( \text{C}_{1-3} \) alkyl, F, Cl, or CF\(_3\). Alternatively, in such embodiments, \( n \) is 0 (such that there is no \( R^8 \) substituent).

[00472] In other embodiments exhibiting such increased potency, \( X \) and \( Y \), independently, are N or CH. In further embodiment exhibiting increased potency, \( X \) is N and \( Y \) is CH. Alternatively, \( X \) and \( Y \) may also both be CH. In further embodiments exhibiting increased potency, \( R^6 \) is hydrogen, halo, or NH\(_2\).

[00473] Unexpectedly, potency against PI3K-\( \delta \) is conserved when \( R^1 \) is the same. In structural formulae (XIV) and (XV), \( R^2 \) and \( R^4 \) may differ provided that \( R^1 \) is H. When \( R^1 \) is H, free rotation is unexpectedly permitted about the bond connecting the phenyl ring substituent to the quinazoline ring, and the compounds advantageously do not exhibit atropisomerism (i.e.,
multiple diastereomer formation is avoided). Alternatively, \( R^2 \) and \( R^4 \) can be the same such that the compounds advantageously do not exhibit atropisomerism.

[00474] As used with respect to Formula (XIV) and Formula (XV), the term “alkyl” is defined as straight chained and branched hydrocarbon groups containing the indicated number of carbon atoms, e.g., methyl, ethyl, and straight chain and branched propyl and butyl groups. The terms “\((C_{\text{1-3}})\)alkylene” and “\((C_{\text{1-4}})\)alkylene” are defined as hydrocarbon groups containing the indicated number of carbon atoms and one less hydrogen than the corresponding alkyl group. The term “\((C_{\text{2-6}})\)alkynyl” is defined as a hydrocarbon group containing the indicated number of carbon atoms and a carbon-carbon triple bond. The term “\((C_{\text{3-6}})\)cycloalkyl” is defined as a cyclic hydrocarbon group containing the indicated number of carbon atoms. The term “\((C_{\text{2-6}})\)heterocycloalkyl” is defined similarly as cycloalkyl except the ring contains one or two heteroatoms selected from the group consisting of O, NR\(^+\), and S. The term “halo” is defined as fluoro, bromo, chloro, and iodo.

[00475] In preferred embodiments of Formula (I), \( Z \) is \( N—R^7 \), and the bicyclic ring system containing \( X \) and \( Y \) is:

\[
\text{or}
\]

[00476] In other preferred embodiments, \( R^1 \) is hydrogen, fluoro, chloro, methyl, or

\[
\text{and } \text{R}^2 \text{ is hydrogen, methyl, chloro, or fluoro; } \text{R}^3 \text{ is hydrogen or fluoro; } \text{R}^6 \text{ is NH}_2, \text{hydrogen, or fluoro; } \text{R}^7 \text{ is hydrogen or R}^5 \text{ and R}^7 \text{ are taken together to form}
\]
R is methyl, trifluoromethyl, chloro, or fluoro; R is hydrogen, fluoro, chloro, OH, OCH3, OCH2C≡CH, O(CH2)2N(CH3)2, C(=O)CH3, C≡CH, CN, C(=O)NH2, OCH2C(=O)NH2, O(CH2)2OCH3, O(CH2)2N(CH3)2, C(═O)CH3, C≡CH, CN, C(═O)NH2, OCH2C(═O)NH2, O(CH2)2OCH3, O(CH2)2N(CH3)2,

and R is methyl, ethyl, propyl, phenyl, CH2OH, CH2OCH2C6H5, CH2CF3, CH2OC(CH3)3, CH2C≡CH, (CH2)2N(C2H5)2, (CH2)3NH2, (CH2)4NH2, (CH2)5NH(=O)OCH2C6H5, or (CH2)4NHC(=O)OCH2C6H5; R is hydrogen, methyl, fluoro, or bromo; and n is 0 or 1. Preferably, R is hydrogen.

In a preferred embodiment, the PI3K inhibitor or PI3K-δ inhibitor idelalisib, also known as GS-1101 or CAL-101. In a preferred embodiment, the PI3K inhibitor or PI3K-δ inhibitor is the compound of Formula (XVI):
which is (S)-2-(1-((9H-purin-6-yl)amino)propyl)-5-fluoro-3-phenylquinazolin-4(3H)-one (other names: 4(3H)-quinazolinone, 5-fluoro-3-phenyl-2-[(1S)-1-(9H-purin-6-ylamino)propyl], and 5-fluoro-3-phenyl-2-[(1S)-1-[(7H-purin-6-yl)amino]propyl]quinazolin-4(3H)-one) or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

[00479] In a preferred embodiment, the PI3K inhibitor or PI3K-δ inhibitor is (S)-2-(1-((9H-purin-6-yl)amino)propyl)-5-fluoro-3-phenylquinazolin-4(3H)-one or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

[00480] In an embodiment, the PI3K inhibitor or PI3K-δ inhibitor is 4(3H)-quinazolinone, 5-fluoro-3-phenyl-2-[(1S)-1-(9H-purin-6-ylamino)propyl]-5-fluoro-3-phenyl-2-[(1S)-1-[(7H-purin-6-yl)amino]propyl]quinazolin-4(3H)-one or or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

[00481] Other PI3K inhibitors suitable for use in the described combination with a BTK inhibitor also include, but are not limited to, those described in, for example, U.S. Patent No. 8,193,182 and U.S. Published Application Nos. 2013/0267521; 2013/0053362; 2013/0029984; 2013/0029982; 2012/0184568; and 2012/0059000, the disclosures of each of which are incorporated by reference in their entireties.

BTK Inhibitors

[00482] The BTK inhibitor may be any BTK inhibitor known in the art. In particular, it is one of the BTK inhibitors described in more detail in the following paragraphs. Preferably, it is a...
compound of Formula XVII or a pharmaceutically acceptable salt thereof. In one specific embodiment, it is a compound of Formula XVIII or a pharmaceutically acceptable salt thereof.

[00483] In an embodiment, the BTK inhibitor is a compound of Formula (XVII):

```
\[
\begin{align*}
X & = \text{CH, N, O or S;} \\
Y & = \text{C}(R_1), \text{N, O or S;} \\
Z & = \text{CH, N or bond;} \\
A & = \text{CH or N;} \\
B_1 & = \text{N or C}(R_4); \\
B_2 & = \text{N or C}(R_5); \\
B_3 & = \text{N or C}(R_6); \\
B_4 & = \text{N or C}(R_7); \\
R_1 & = \text{R}_{11} \text{C}(=O), \text{R}_{12} \text{S}(=O), \text{R}_{13} \text{S}(=O)_{12} \text{or (C}_{1-6}) \text{alkyl optionally substituted with R}_{14}; \\
R_2 & = \text{H, (C}_{1-3}) \text{alkyl or (C}_{3-7}) \text{cycloalkyl;} \\
R_3 & = \text{H, (C}_{1-6}) \text{alkyl or (C}_{3-7}) \text{cycloalkyl); or} \\
R_2 \text{ and } R_3 \text{ form, together with the N and C atom they are attached to, a (C}_{3-7}) \text{heterocycloalkyl} \\
\text{optionally substituted with one or more fluorine, hydroxyl, (C}_{1-3}) \text{alkyl, (C}_{1-3}) \text{alkoxy or oxo;} \\
\end{align*}
\]
```

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, wherein:

- X is CH, N, O or S;
- Y is C(R₆), N, O or S;
- Z is CH, N or bond;
- A is CH or N;
- B₁ is N or C(R₄);
- B₂ is N or C(R₅);
- B₃ is N or C(R₆);
- B₄ is N or C(R₇);
- R₁ is R₁₁ C(=O), R₁₂ S(=O), R₁₃ S(=O)₂ or (C₁⁻₆) alkyl optionally substituted with R₁₄;
- R₂ is H, (C₁⁻₃) alkyl or (C₃⁻₇) cycloalkyl;
- R₃ is H, (C₁⁻₆) alkyl or (C₃⁻₇) cycloalkyl; or
- R₂ and R₃ form, together with the N and C atom they are attached to, a (C₃⁻₇) heterocycloalkyl optionally substituted with one or more fluorine, hydroxyl, (C₁⁻₃) alkyl, (C₁⁻₃) alkoxy or oxo;
R\textsubscript{4} is H or (C\textsubscript{1-3})alkyl;
R\textsubscript{5} is H, halogen, cyano, (C\textsubscript{1-4})alkyl, (C\textsubscript{1-3})alkoxy, (C\textsubscript{3-6})cycloalkyl, any alkyl group of which is optionally substituted with one or more halogen; or R\textsubscript{5} is (C\textsubscript{6-10})aryl or (C\textsubscript{2-6})heterocycloalkyl;
R\textsubscript{6} is H or (C\textsubscript{1-3})alkyl; or
R\textsubscript{5} and R\textsubscript{6} together may form a (C\textsubscript{3-7})cycloalkenyl or (C\textsubscript{2-6})heterocycloalkenyl, each optionally substituted with (C\textsubscript{1-3})alkyl or one or more halogens;
R\textsubscript{7} is H, halogen, CF\textsubscript{3}, (C\textsubscript{1-3})alkyl or (C\textsubscript{1-3})alkoxy;
R\textsubscript{8} is H, halogen, CF\textsubscript{3}, (C\textsubscript{1-3})alkyl or (C\textsubscript{1-3})alkoxy; or
R\textsubscript{7} and R\textsubscript{8} together with the carbon atoms they are attached to, form (C\textsubscript{6-10})aryl or (C\textsubscript{1-5})heteroaryl;
R\textsubscript{9} is H, halogen, (C\textsubscript{1-3})alkyl or (C\textsubscript{1-3})alkoxy;
R\textsubscript{10} is H, halogen, (C\textsubscript{1-3})alkyl or (C\textsubscript{1-3})alkoxy;
R\textsubscript{11} is independently selected from the group consisting of (C\textsubscript{1-6})alkyl, (C\textsubscript{2-6})alkenyl and (C\textsubscript{2-6})alkynyl, where each alkyl, alkenyl or alkylnyl is optionally substituted with one or more substituents selected from the group consisting of hydroxyl, (C\textsubscript{1-4})alkyl, (C\textsubscript{3-7})cycloalkyl, [(C\textsubscript{1-4})alkyl]amino, di[(C\textsubscript{1-4})alkyl]amino, (C\textsubscript{1-3})alkoxy, (C\textsubscript{3-7})cycloalkoxy, (C\textsubscript{6-10})aryl and (C\textsubscript{3-7})heterocycloalkyl; or R\textsubscript{11} is (C\textsubscript{1-3})alkyl-C(O)-S-(C\textsubscript{1-3})alkyl; or
R\textsubscript{11} is (C\textsubscript{1-5})heteroaryl optionally substituted with one or more substituents selected from the group consisting of halogen or cyano;
R\textsubscript{12} and R\textsubscript{13} are independently selected from the group consisting of (C\textsubscript{2-6})alkenyl or (C\textsubscript{2-6})alkynyl, both optionally substituted with one or more substituents selected from the group consisting of hydroxyl, (C\textsubscript{1-4})alkyl, (C\textsubscript{3-7})cycloalkyl, [(C\textsubscript{1-4})alkyl]amino, di[(C\textsubscript{1-4})alkyl]amino, (C\textsubscript{1-3})alkoxy, (C\textsubscript{3-7})cycloalkoxy, (C\textsubscript{6-10})aryl and (C\textsubscript{3-7})heterocycloalkyl; or a (C\textsubscript{1-5})heteroaryl optionally substituted with one or more substituents selected from the group consisting of halogen and cyano; and
R\textsubscript{14} is independently selected from the group consisting of halogen, cyano, (C\textsubscript{2-6})alkenyl and (C\textsubscript{2-6})alkynyl, both optionally substituted with one or more substituents selected from the group consisting of hydroxyl, (C\textsubscript{1-4})alkyl, (C\textsubscript{3-7})cycloalkyl, (C\textsubscript{1-4})alkylamino, di[(C\textsubscript{1-4})alkyl]amino, (C\textsubscript{1-3})alkoxy, (C\textsubscript{3-7})cycloalkoxy, (C\textsubscript{6-10})aryl, (C\textsubscript{1-5})heteroaryl and (C\textsubscript{3-7})heterocycloalkyl; with the proviso that:
0 to 2 atoms of X, Y, Z can simultaneously be a heteroatom;
when one atom selected from X, Y is O or S, then Z is a bond and the other atom selected from X, Y can not be O or S;
when Z is C or N then Y is C(R_o) or N and X is C or N;
0 to 2 atoms of B_1, B_2, B_3 and B_4 are N;
with the terms used having the following meanings:
(C_{1-2})alkyl means an alkyl group having 1 to 2 carbon atoms, being methyl or ethyl,
(C_{1-3})alkyl means a branched or unbranched alkyl group having 1-3 carbon atoms, being methyl, ethyl, propyl or isopropyl;
(C_{1-4})alkyl means a branched or unbranched alkyl group having 1-4 carbon atoms, being methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl and tert-butyl, (C_{1-3})alkyl groups being preferred;
(C_{1-5})alkyl means a branched or unbranched alkyl group having 1-5 carbon atoms, for example methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl and isopentyl, (C_{1-4})alkyl groups being preferred. (C_{1-6})Alkyl means a branched or unbranched alkyl group having 1-6 carbon atoms, for example methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, n-pentyl and n-hexyl. (C_{1-5})alkyl groups are preferred, (C_{1-4})alkyl being most preferred;
(C_{1-2})alkoxy means an alkoxy group having 1-2 carbon atoms, the alkyl moiety having the same meaning as previously defined;
(C_{1-3})alkoxy means an alkoxy group having 1-3 carbon atoms, the alkyl moiety having the same meaning as previously defined. (C_{1-2})alkoxy groups are preferred;
(C_{1-4})alkoxy means an alkoxy group having 1-4 carbon atoms, the alkyl moiety having the same meaning as previously defined. (C_{1-3})alkoxy groups are preferred, (C_{1-2})alkoxy groups being most preferred;
(C_{2-4})alkenyl means a branched or unbranched alkenyl group having 2-4 carbon atoms, such as ethenyl, 2-propenyl, isobutenyl or 2-butenyl;
(C_{2-6})alkenyl means a branched or unbranched alkenyl group having 2-6 carbon atoms, such as ethenyl, 2-butenyl, and n-pentenyl, (C_{2-4})alkenyl groups being most preferred;
(C_{2-4})alkynyl means a branched or unbranched alkynyl group having 2-4 carbon atoms, such as ethynyl, 2-propynyl or 2-butylnyl;
(C_{2-6})alkynyl means a branched or unbranched alkynyl group having 2-6 carbon atoms, such as ethynyl, propynyl, n-butynyl, n-pentynyl, isopentynyl, isohexynyl or n-hexynyl. (C_{2-6})alkynyl groups are preferred; (C_{3-6})cycloalkyl means a cycloalkyl group having 3-6 carbon atoms, being cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl;

(C_{3-7})cycloalkyl means a cycloalkyl group having 3-7 carbon atoms, being cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl;

(C_{2-6})heterocycloalkyl means a heterocycloalkyl group having 2-6 carbon atoms, preferably 3-5 carbon atoms, and one or two heteroatoms selected from N, O and/or S, which may be attached via a heteroatom if feasible, or a carbon atom; preferred heteroatoms are N or O; also preferred are piperidine, morpholine, pyrrolidine and piperazine; with the most preferred (C_{2-6})heterocycloalkyl being pyrrolidine; the heterocycloalkyl group may be attached via a heteroatom if feasible;

(C_{3-7})heterocycloalkyl means a heterocycloalkyl group having 3-7 carbon atoms, preferably 3-5 carbon atoms, and one or two heteroatoms selected from N, O and/or S. Preferred heteroatoms are N or O; preferred (C_{3-7}) heterocycloalkyl groups are azetidinyl, pyrrolidinyl, piperidinyl, homopiperidinyl or morpholinyl; more preferred (C_{3-7}) heterocycloalkyl groups are piperidine, morpholine and pyrrolidine; and the heterocycloalkyl group may be attached via a heteroatom if feasible;

(C_{3-7})cycloalkoxy means a cycloalkyl group having 3-7 carbon atoms, with the same meaning as previously defined, attached via a ring carbon atom to an exocyclic oxygen atom;

(C_{6-10})aryl means an aromatic hydrocarbon group having 6-10 carbon atoms, such as phenyl, naphthyl, tetrahydronaphthyl or indenyl; the preferred (C_{6-10}) aryl group is phenyl;

(C_{1-5})heteroaryl means a substituted or unsubstituted aromatic group having 1-5 carbon atoms and 1-4 heteroatoms selected from N, O and/or S; the (C_{1-5})heteroaryl may optionally be substituted; preferred (C_{1-5})heteroaryl groups are tetrazolyl, imidazolyl, thiadiazolyl, pyridyl, pyrimidyl, triazinyl, thienyl or furyl, a more preferred (C_{1-5})heteroaryl is pyrimidyl;

(C_{1-9})heteroaryl means a substituted or unsubstituted aromatic group having 1-9 carbon atoms and 1-4 heteroatoms selected from N, O and/or S; the (C_{1-9})heteroaryl may optionally be substituted; preferred (C_{1-9})heteroaryl groups are quinoline, isoquinoline and indole;
[(C<sub>1-4</sub>)alkyl]amino means an amino group, monosubstituted with an alkyl group containing 1-4 carbon atoms having the same meaning as previously defined; preferred [(C<sub>1-4</sub>)alkyl]amino group is methylamino;

di[(C<sub>1-4</sub>)alkyl]amino means an amino group, disubstituted with alkyl group(s), each containing 1-4 carbon atoms and having the same meaning as previously defined; preferred di[(C<sub>1</sub>-<sub>4</sub>)alkyl]amino group is dimethylamino;

halogen means means fluorine, chlorine, bromine or iodine;

(C<sub>1-3</sub>)alkyl-C(O)-S-(C<sub>1-3</sub>)alkyl means an alkyl-carbonyl-thio-alkyl group, each of the alkyl groups having 1 to 3 carbon atoms with the same meaning as previously defined;

(C<sub>3-7</sub>)cycloalkenyl means a cycloalkenyl group having 3-7 carbon atoms, preferably 5-7 carbon atoms; preferred (C<sub>3-7</sub>)cycloalkenyl groups are cyclopentenyl or cyclohexenyl; cyclohexenyl groups are most preferred;

(C<sub>2-6</sub>)heterocycloalkenyl means a heterocycloalkenyl group having 2-6 carbon atoms, preferably 3-5 carbon atoms; and 1 heteroatom selected from N, O and/or S; preferred (C<sub>2</sub>-<sub>6</sub>)heterocycloalkenyl groups are oxycyclohexenyl and azacyclohexenyl group.

In the above definitions with multifunctional groups, the attachment point is at the last group. When, in the definition of a substituent, is indicated that "all of the alkyl groups" of said substituent are optionally substituted, this also includes the alkyl moiety of an alkoxy group.

A circle in a ring of Formula (XVII) indicates that the ring is aromatic.

Depending on the ring formed, the nitrogen, if present in X or Y, may carry a hydrogen.

[00484] In a preferred embodiment, the BTK inhibitor is a compound of Formula (XVII) or a pharmaceutically acceptable salt thereof, wherein:

X is CH or S;
Y is C(R<sub>6</sub>);
Z is CH or bond;
A is CH;
B<sub>1</sub> is N or C(R<sub>7</sub>);
B<sub>2</sub> is N or C(R<sub>8</sub>);
B<sub>3</sub> is N or CH;
B<sub>4</sub> is N or CH;
R₁ is R₁₁C(=O),
R₂ is (C₁₋₃)alkyl;
R₃ is (C₁₋₃)alkyl;
R₂ and R₃ form a (C₃₋₇)heterocycloalkyl ring selected from the group consisting of azetidinyl, pyrrolidinyl, piperidinyl, and morpholinyl, optionally substituted with one or more fluorine, hydroxyl, (C₁₋₃)alkyl, or (C₁₋₃)alkoxy;
R₄ is H;
R₅ is H, halogen, cyano, (C₁₋₄)alkyl, (C₁₋₃)alkoxy, (C₃₋₆)cycloalkyl, or any alkyl group of which is optionally substituted with one or more halogen;
R₆ is H or (C₁₋₃)alkyl;
R₇ is H, halogen or (C₁₋₃)alkoxy;
R₈ is H or (C₁₋₃)alkyl; or
R₅ and R₆ form, together with the carbon atom they are attached to a (C₆₋₁₀)aryl or (C₁₋₉)heteroaryl;
R₅ and R₆ together may form a (C₃₋₇)cycloalkenyl or (C₂₋₆)heterocycloalkenyl, each optionally substituted with (C₁₋₃)alkyl or one or more halogen;
R₅ is independently selected from the group consisting of (C₂₋₆)alkenyl and (C₂₋₆)alkynyl, where each alkenyl or alkynyl is optionally substituted with one or more substituents selected from the group consisting of hydroxyl, (C₁₋₄)alkyl, (C₃₋₇)cycloalkyl, [(C₁₋₄)alkyl]amino, di[(C₁₋₄)alkyl]amino, (C₁₋₃)alkoxy, (C₃₋₇)cycloalkoxy, (C₆₋₁₀)aryl and (C₃₋₇)heterocycloalkyl;
with the proviso that 0 to 2 atoms of B₁, B₂, B₃ and B₄ are N.

[00485] In an embodiment of Formula (XVII), B₁ is C(R₇); B₂ is C(R₈); B₃ is C(R₉); B₄ is C(R₁₀); R₇, R₈, and R₁₀ are each H; and R₉ is hydrogen or methyl.

[00486] In an embodiment of Formula (XVII), the ring containing X, Y and Z is selected from the group consisting of pyridyl, pyrimidyl, pyrazidyl, triazinyl, thiazolyl, oxazolyl and isoxazolyl.

[00487] In an embodiment of Formula (XVII), the ring containing X, Y and Z is selected from the group consisting of pyridyl, pyrimidyl and pyrazidyl.
In an embodiment of Formula (XVII), the ring containing X, Y and Z is selected from the group consisting of pyridyl and pyrimidyl.

In an embodiment of Formula (XVII), the ring containing X, Y and Z is pyridyl.

In an embodiment of Formula (XVII), R₅ is selected from hydrogen, fluorine, methyl, methoxy and trifluoromethyl.

In an embodiment of Formula (XVII), R₅ is hydrogen.

In an embodiment of Formula (XVII), R₂ and R₃ together form a heterocycloalkyl ring selected from the group consisting of azetidinyl, pyrrolidinyl, piperidinyl, homopiperidinyl and morpholinyl, optionally substituted with one or more of fluoro, hydroxy, (C₁₋₃)alkyl and (C₁₋₃)alkoxy.

In an embodiment of Formula (XVII), R₂ and R₃ together form a heterocycloalkyl ring selected from the group consisting of azetidinyl, pyrrolidinyl and piperidinyl.

In an embodiment of Formula (XVII), R₂ and R₃ together form a pyrrolidinyl ring.

In an embodiment of Formula (XVII), R₁ is independently selected from the group consisting of (C₁₋₆)alkyl, (C₂₋₆)alkenyl or (C₂₋₆)alkynyl, each optionally substituted with one or more substituents selected from the group consisting of hydroxy, (C₁₋₄)alkyl, (C₁₋₃)cycloalkyl, [(C₁₋₄)alkyl]amino, di[(C₁₋₄)alkyl] amino, (C₁₋₃)alkoxy, (C₁₋₃)cycloalkoxy, (C₁₋₁₀)aryl and (C₁₋₃)heterocycloalkyl.

In an embodiment of Formula (XVII), B₁, B₂, B₃ and B₄ are CH; X is N; Y and Z are CH; R₃ is CH₃; A is N; R₂, R₃ and R₄ are H; and R₁ is CO-CH₃.

In an embodiment of Formula (XVII), B₁, B₂, B₃ and B₄ are CH; X and Y are N; Z is CH; R₃ is CH₃; A is N; R₂, R₃ and R₄ are H; and R₁ is CO-CH₃.

In an embodiment of Formula (XVII), B₁, B₂, B₃ and B₄ are CH; X and Y are N; Z is CH; R₁ is CH₃; A is CH; R₂ and R₃ together form a piperidinyl ring; R₄ is H; and R₅ is CO-ethenyl.
In an embodiment of Formula (XVII), B₁, B₂, B₃ and B₄ are CH; X, Y and Z are CH; R₅ is H; A is CH; R₂ and R₃ together form a pyrrolidinyl ring; R₄ is H; and R₁ is CO-propynyl.

In an embodiment of Formula (XVII), B₁, B₂, B₃ and B₄ are CH; X, Y and Z are CH; R₅ is CH₃; A is CH; R₂ and R₃ together form a piperidinyl ring; R₄ is H; and R₁ is CO-propynyl.

In an embodiment of Formula (XVII), B₁, B₂, B₃ and B₄ are CH; X and Y are N; Z is CH; R₃ is H; A is CH; R₂ and R₃ together form a morpholinyl ring; R₄ is H; and R₁ is CO-ethenyl.

In an embodiment of Formula (XVII), B₁, B₂, B₃ and B₄ are CH; X and Y are N; Z is CH; R₃ is CH₃; A is CH; R₂ and R₃ together form a morpholinyl ring; R₄ is H; and R₁ is CO-propynyl.

In a preferred embodiment, the BTK inhibitor is a compound of Formula (XVIII):

\[
\text{\begin{align*}
\text{Formula (XVIII)}
\end{align*}}
\]

which is (S)-4-(8-amino-3-(1-(but-2ynylo)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide, or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. The preparation of this compound is described in International Patent Application Publication No. WO 2013/010868, the disclosure of which is incorporated herein by reference. In brief, Formula (XVIII) and related compounds, such as those according to Formula (XVII), may be prepared as follows.
(S)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide was made from (S)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide and 2-butynoic acid as follows. To a solution of (S)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide (19.7 mg, 0.049 mmol), triethylamine (20 mg, 0.197 mmol, 0.027 mL) 2-butynoic acid (4.12 mg, 0.049 mmol) in dichloromethane (2 mL) was added HATU (18.75 mg, 0.049 mmol). The mixture was stirred for 30 min at room temperature. The mixture was washed with water dried over magnesium sulfate and concentrated in vacuo. The residue was purified by preparative HPLC. Fractions containing product were collected and reduced to dryness to afford the title compound (10.5 mg, 18.0%).

(S)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide was prepared from the following intermediary compounds.

(a). (3-Chloropyrazin-2-yl)ethanamine hydrochloride was prepared as follows. To a solution of 3-chloropyrazine-2-carbonitrile (160 g, 1.147 mol) in acetic acid (1.5 L) was added Raney Nickel (50% slurry in water, 70 g, 409 mmol). The resulting mixture was stirred under 4 bar hydrogen at room temperature overnight. Raney Nickel was removed by filtration over decaflate and the filtrate was concentrated under reduced pressure and co-evaporated with toluene. The remaining brown solid was dissolved in ethyl acetate at 50°C and cooled on an ice-bath. 2M hydrogen chloride solution in diethyl ether (1.14 L) was added in 30 min. The mixture was allowed to stir at room temperature overnight. The crystals were collected by filtration, washed with diethyl ether and dried under reduced pressure at 40°C. The product brown solid obtained was dissolved in methanol at 60°C. The mixture was filtered and partially concentrated, cooled to room temperature and diethyl ether (1000 ml) was added. The mixture was allowed to stir at room temperature overnight. The solids formed were collected by filtration, washed with diethyl ether and dried under reduced pressure at 40°C to give 153.5 g of (3-chloropyrazin-2-yl)ethanamine hydrochloride as a brown solid (74.4%, content 77%).

(b). (S)-benzyl 2-((3-chloropyrazin-2-yl)methylcarbamoyl)pyrrolidine-1-carboxylate was prepared as follows. To a solution of (3-chloropyrazin-2-yl)methanamine HCl (9.57 g, 21.26 mmol, 40% wt) and Z-Pro-OH (5.3 g, 21.26 mmol) in dichloromethane (250 mL) was added triethylamine (11.85 mL, 85 mmol) and the reaction mixture was cooled to 0°C. After 15
min stirring at 0°C, HATU (8.49 g, 22.33 mmol) was added. The mixture was stirred for 1 hour at 0°C and then overnight at room temperature. The mixture was washed with 0.1 M HCl-solution, 5% NaHCO3, water and brine, dried over sodium sulfate and concentrated in vacuo. The product was purified using silica gel chromatography (heptane/ethyl acetate = 1/4 v/v%) to give 5 g of (S)-benzyl 2-((3-chloropyrazin-2-yl)methylcarbamoyl)pyrrolidine-1-carboxylate (82.3%).

[00508] (c) (S)-Benzy1 2-(8-chloroimidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate was prepared as follows. (S)-Benzy1 2-((3-chloropyrazin-2-yl)methylcarbamoyl)pyrrolidine-1-carboxylate (20.94 mmol, 7.85 g) was dissolved in acetonitrile (75 ml), 1.3-dimethyl-2-imidazolidinone (62.8 mmol, 6.9 ml, 7.17 g) was added and the reaction mixture was cooled to 0°C before POCl3 (84 mmol, 7.81 ml, 12.84 g) was added drop wise while the temperature remained around 5°C. The reaction mixture was refluxed at 60-65°C overnight. The reaction mixture was poured carefully in ammonium hydroxide 25% in water (250 ml)/crushed ice (500 ml) to give a yellow suspension (pH -8-9) which was stirred for 15 min until no ice was present in the suspension. Ethyl acetate was added, layers were separated and the aqueous layer was extracted with ethyl acetate (3x). The organic layers were combined and washed with brine, dried over sodium sulfate, filtered and evaporated to give 7.5 g crude product. The crude product was purified using silica gel chromatography (heptane/ethyl acetate = 1/4 v/v%) to give 6.6 g of (S)-benzyl 2-(8-chloroimidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate (88%).

[00509] (d) (S)-Benzy1 2-(1-bromo-8-chloroimidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate was prepared as follows. N-Bromosuccinimide (24.69 mmol, 4.4 g) was added to a stirred solution of (S)-benzyl 2-(8-chloroimidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate (24.94 mmol, 8.9 g) in DMF (145 mL). The reaction was stirred 3 h at rt. The mixture was poured (slowly) in a stirred mixture of water (145 mL), ethyl acetate (145 mL) and brine (145 mL). The mixture was then transferred into a separating funnel and extracted. The water layer was extracted with 2x145 mL ethyl acetate. The combined organic layers were washed with 3x300 mL water, 300 mL brine, dried over sodium sulfate, filtered and evaporated. The product was purified using silica gel chromatography (ethyl acetate/heptane = 3/1 v/v%) to give 8.95 g of (S)-benzyl 2-(1-bromo-8-chloroimidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate (82.3%).
(e). (S)-Benzyl 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate was prepared as follows. (S)-Benzyl 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate (20.54 mmol, 8.95 g) was suspended in 2-propanol (113 ml) in a pressure vessel. 2-propanol (50 ml) was cooled to -78°C in a pre-weighed flask (with stopper and stirring bar) and ammonia gas (646 mmol, 11 g) was lead through for 15 minutes. The resulting solution was added to the suspension in the pressure vessel. The vessel was closed and stirred at room temperature and a slight increase in pressure was observed. Then the suspension was heated to 110 °C which resulted in an increased pressure to 4.5 bar. The clear solution was stirred at 1 10 °C, 4.5 bar overnight. After 18h the pressure remained 4 bar. The reaction mixture was concentrated in vacuum, the residue was suspended in ethyl acetate and subsequent washed with water. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with water, saturated sodium chloride solution, dried over sodium sulfate and concentrated to give 7.35 g of (S)-benzyl 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate (86%).

(S)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide was prepared as follows.

(S)-benzyl 2-(8-amino-1-(4-(pyridin-2ylcarbamoyl)phenyl)imidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate was prepared as follows. (S)-benzyl 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate (0.237 mmol, 98.5 mg) and 4-(pyridin-2-ylaminocarbonyl)benzeneboronic acid (0.260 mmol, 63.0 mg) were suspended in a mixture of 2N aqueous potassium carbonate solution (2.37 mmol, 1.18 mL) and dioxane (2.96 mL). Nitrogen was bubbled through the mixture, followed by the addition of 1,1’-bis(diphenylphosphino)ferrocene palladium (ii) chloride (0.059 mmol, 47.8 mg). The reaction mixture was heated for 20 minutes at 140°C in the microwave. Water was added to the reaction mixture, followed by an extraction with ethyl acetate (2x). The combined organic layer was washed with brine, dried over magnesium sulfate and evaporated. The product was purified using silicagel and dichloromethane/methanol = 9/1 v/v% as eluent to afford 97.1 mg of (S)-benzyl 2-(8-amino-1-(4-(pyridin-2ylcarbamoyl)phenyl)imidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate (77%).
(b). (S)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide was prepared as follows. To (S)-benzyl 2-(8-amino-1-(4-(pyridin-2-ylcarbamoyl)phenyl)imidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate (0.146 mmol, 78 mg) was added a 33% hydrobromic acid/acetic acid solution (1.26 mmol, 2 ml) and the mixture was left at room temperature for 1 hour. The mixture was diluted with water and extracted with dichloromethane. The aqueous phase was neutralized using 2N sodium hydroxide solution, and then extracted with dichloromethane. The organic layer was dried over magnesium sulfate, filtered and evaporated to give 34 mg of (S)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide (58%).

In an embodiment, the BTK inhibitor is (S)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide or pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. In other embodiments, the BTK inhibitors include, but are not limited to, those compounds described in International Patent Application Publication No. WO 2013/010868, the disclosures of each of which are specifically incorporated by reference herein.

In a preferred embodiment, the BTK inhibitor is a compound of Formula (XVIII-A):
or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. The preparation of this compound is described in International Patent Application Publication No. WO 2013/010868, the disclosure of which is incorporated herein by reference.

[00516] In a preferred embodiment, the BTK inhibitor is a compound of Formula (XVIII-B):

![Formula (XVIII-B)](image)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. The preparation of this compound is described in International Patent Application Publication No. WO 2013/010868, the disclosure of which is incorporated herein by reference.

[00517] In a preferred embodiment, the BTK inhibitor is a compound of Formula (XVIII-C):
or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. The preparation of this compound is described in International Patent Application Publication No. WO 2013/010868, the disclosure of which is incorporated herein by reference.

[00518] In a preferred embodiment, the BTK inhibitor is a compound of Formula (XVIII-D):
or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. The preparation of this compound is described in International Patent Application Publication No. WO 2013/010868, the disclosure of which is incorporated herein by reference.

[00519] In a preferred embodiment, the BTK inhibitor is a compound of Formula (XVIII-E):

![Formula (XVIII-E)](image)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. The preparation of this compound is described in International Patent Application Publication No. WO 2013/010868, the disclosure of which is incorporated herein by reference.

[00520] In other embodiments, the BTK inhibitors include, but are not limited to, those compounds described in International Patent Application Publication No. WO 2013/010868, the disclosures of each of which are specifically incorporated by reference herein.

[00521] In an embodiment, the BTK inhibitor is a compound of Formula (XIX) or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug of a compound of Formula (XIX):
In Formula (XIX) the substituents are defined as:

- \( X \) is CH, N, O or S;
- \( Y \) is C(R\(_6\)), N, O or S;
- \( Z \) is CH, N or bond;
- \( A \) is CH or N;
- \( B_1 \) is N or C(R\(_7\));
- \( B_2 \) is N or C(R\(_8\));
- \( B_3 \) is N or C(R\(_9\));
- \( B_4 \) is N or C(R\(_{10}\));
- \( R_1 \) is R\(_{11}\)C(O), R\(_{12}\)S(O), R\(_{13}\)SO\(_2\) or (C\(_{1-6}\))alkyl optionally substituted with R\(_{14}\);
- \( R_2 \) is H, (C\(_{1-3}\))alkyl or (C\(_{3-7}\))cycloalkyl;
- \( R_3 \) is H, (C\(_{1-6}\))alkyl or (C\(_{3-7}\))cycloalkyl; or
- \( R_2 \) and \( R_4 \) form, together with the N and C atom they are attached to, a (C\(_{3-7}\))heterocycloalkyl optionally substituted with one or more fluorine, hydroxyl, (C\(_{1-3}\))alkyl, (C\(_{1-3}\))alkoxy or oxo;
- \( R_4 \) is H or (C\(_{1-3}\))alkyl;
- \( R_5 \) is H, halogen, cyano, (C\(_{1-4}\))alkyl, (C\(_{1-3}\))alkoxy, (C\(_{3-6}\))cycloalkyl; all alkyl groups of R5 are optionally substituted with one or more halogen; or \( R_5 \) is (C\(_{6-10}\))aryl or (C\(_{2-6}\))heterocycloalkyl;
$R_6$ is H or $(C_{1-3})$alkyl; or $R_5$ and $R_6$ together may form a $(C_{3-7})$cycloalkenyl, or $(C_{2-6})$heterocycloalkenyl; each optionally substituted with $(C_{1-3})$alkyl, or one or more halogen;

$R_7$ is H, halogen, CF$_3$, $(C_{1-3})$alkyl or $(C_{1-3})$alkoxy;

$R_8$ is H, halogen, CF$_3$, $(C_{1-3})$alkyl or $(C_{1-3})$alkoxy; or

$R_7$ and $R_8$ together with the carbon atoms they are attached to, form $(C_{6-10})$aryl or $(C_{1-3})$heteroaryl;

$R_9$ is H, halogen, $(C_{1-3})$alkyl or $(C_{1-3})$alkoxy;

$R_{10}$ is H, halogen, $(C_{1-3})$alkyl or $(C_{1-3})$alkoxy;

$R_{11}$ is independently selected from a group consisting of $(C_{1-6})$alkyl, $(C_{2-6})$alkenyl and $(C_{2-6})$alkynyl each alkyl, alkenyl or alkynyl optionally substituted with one or more groups selected from hydroxyl, $(C_{1-4})$alkyl, $(C_{3-7})$cycloalkyl, $(C_{1-4})$alkylamino, $di[(C_{1-4})$alkylamino, $(C_{1-3})$alkoxy, $(C_{1-3})$cycloalkoxy, $(C_{6-10})$aryl or $(C_{3-7})$heterocycloalkyl, or

$R_{14}$ is $(C_{1-3})$alkyl-C(O)-S-(C$_{1-3}$)alkyl; or

$R_{15}$ is $(C_{1-5})$heteroaryl optionally substituted with one or more groups selected from halogen or cyano.

$R_{16}$ and $R_{17}$ are independently selected from a group consisting of $(C_{2-6})$alkenyl or $(C_{2-6})$alkynyl both optionally substituted with one or more groups selected from hydroxyl, $(C_{1-4})$alkyl, $(C_{1-3})$cycloalkyl, $(C_{1-4})$alkylamino, $di[(C_{1-4})$alkylamino, $(C_{1-3})$alkoxy, $(C_{3-7})$cycloalkoxy, $(C_{6-10})$aryl, or $(C_{3-7})$heterocycloalkyl; or

$(C_{1-5})$heteroaryl optionally substituted with one or more groups selected from halogen or cyano;

$R_{14}$ is independently selected from a group consisting of halogen, cyano or $(C_{2-6})$alkenyl or $(C_{2-6})$alkynyl both optionally substituted with one or more groups selected from hydroxyl, $(C_{1-4})$alkyl, $(C_{3-7})$cycloalkyl, $di[(C_{1-4})$alkylamino, $(C_{1-4})$alkylamino, $(C_{1-3})$alkoxy, $(C_{3-7})$cycloalkoxy, $(C_{6-10})$aryl, or $(C_{3-7})$heteroaryl or $(C_{3-7})$heterocycloalkyl;

with the proviso that
- 0 to 2 atoms of X, Y, Z can simultaneously be a heteroatom;
- when one atom selected from X, Y is O or S, then Z is a bond and the other atom selected from X, Y can not be O or S;
- when Z is C or N then Y is C($R_8$) or N and X is C or N;
- 0 to 2 atoms of $B_1$, $B_2$, $B_3$ and $B_4$ are N;

with the terms used having the following meanings:
alkyl means a branched or unbranched alkyl group having 1-3 carbon atoms, being methyl, ethyl, propyl or isopropyl;

alkyl means a branched or unbranched alkyl group having 1-4 carbon atoms, being methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl and tert-butyl, (C<sub>1,3</sub>)alkyl groups being preferred;

alkyl means a branched or unbranched alkyl group having 1-6 carbon atoms, for example methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, n-pentyl and n-hexyl. (C<sub>1,5</sub>)alkyl groups are preferred, (C<sub>1,4</sub>)alkyl being most preferred;

alkoxy means an alkoxy group having 1-2 carbon atoms, the alkyl moiety having the same meaning as previously defined;

alkoxy means an alkoxy group having 1-3 carbon atoms, the alkyl moiety having the same meaning as previously defined, with (C<sub>1,3</sub>)alkoxy groups preferred;

alkenyl means an alkenyl group having 2-3 carbon atoms, such as ethenyl or 2-propenyl;

alkenyl means a branched or unbranched alkenyl group having 2-4 carbon atoms, such as ethenyl, 2-propenyl, isobuteny1 or 2-butenyl;

alkenyl means a branched or unbranched alkenyl group having 2-6 carbon atoms, such as ethenyl, 2-butenyl, and n-pentenyl, with (C<sub>2,4</sub>)alkenyl groups preferred, and (C<sub>2,6</sub>)alkenyl groups even more preferred;

alkynyl means a branched or unbranched alkynyl group having 2-4 carbon atoms, such as ethynyl, 2-propynyl or 2-butylnyl;

alkynyl means an alkynyl group having 2-3 carbon atoms, such as ethynyl or 2-propynyl;

alkynyl means a branched or unbranched alkynyl group having 2-6 carbon atoms, such as ethynyl, propynyl, n-butynyl, n-pentynyl, isopentynyl, isohexynyl or n-hexynyl, with (C<sub>2,4</sub>)alkynyl groups preferred, and (C<sub>2,6</sub>)alkynyl groups more preferred;

cycloalkyl means a cycloalkyl group having 3-6 carbon atoms, being cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl;

cycloalkyl means a cycloalkyl group having 3-7 carbon atoms, being cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl;

cycloalkyl means a heterocycloalkyl group having 2-6 carbon atoms, preferably 3-5 carbon atoms, and one or two heteroatoms selected from N, O and/or S, which may be attached via a heteroatom if feasible, or a carbon atom; preferred heteroatoms are N or O;
preferred groups are piperidine, morpholine, pyrrolidine and piperazine; a most preferred \((C_2-6)\)heterocycloalkyl is pyrrolidine; and the heterocycloalkyl group may be attached via a heteroatom if feasible;

\((C_{3-7})\)heterocycloalkyl means a heterocycloalkyl group having 3-7 carbon atoms, preferably 3-5 carbon atoms, and one or two heteroatoms selected from N, O and/or S; preferred heteroatoms are N or O; preferred \((C_{3-7})\)heterocycloalkyl groups are azetidinyl, pyrrolidinyl, piperidinyl, homopiperidinyl or morpholinyl; more preferred \((C_{3-7})\)heterocycloalkyl groups are piperidine, morpholine and pyrrolidine; even more preferred are piperidine and pyrrolidine; and the heterocycloalkyl group may be attached via a heteroatom if feasible;

\((C_{3-7})\)cycloalkoxy means a cycloalkyl group having 3-7 carbon atoms, with the same meaning as previously defined, attached via a ring carbon atom to an exocyclic oxygen atom;

\((C_{6-10})\)aryl means an aromatic hydrocarbon group having 6-10 carbon atoms, such as phenyl, naphthyl, tetrahydronaphthyl or indenyl; the preferred \((C_{6-10})\)aryl group is phenyl;

\((C_{1-5})\)heteroaryl means a substituted or unsubstituted aromatic group having 1-5 carbon atoms and 1-4 heteroatoms selected from N, O and/or S, wherein the \((C_{1-5})\)heteroaryl may optionally be substituted.; preferred \((C_{1-5})\)heteroaryl groups are tetrazolyl, imidazolyl, thiadiazolyl, pyridyl, pyrimidyl, triazinyl, thienyl or furyl, and the more preferred \((C_{1-5})\)heteroaryl is pyrimidyl;

\([(C_{1-4})\text{alkyl}]{\text{amino}}\) means an amino group, monosubstituted with an alkyl group containing 1-4 carbon atoms having the same meaning as previously defined; the preferred \([(C_{1-4})\text{alkyl}]{\text{amino}}\) group is methylamino;

\([\text{di}[(C_{1-4})\text{alkyl}]{\text{amino}}\) means an amino group, disubstituted with alkyl group(s), each containing 1-4 carbon atoms and having the same meaning as previously defined; the preferred \([\text{di}[(C_{1-4})\text{alkyl}]{\text{amino}}\) group is dimethylamino;

halogen means means fluorine, chlorine, bromine or iodine;

\((C_{1-3})\text{alkyl-C(O)-S-(C}_{1-3})\text{alkyl}\) means an alkyl-carbonyl-thio-alkyl group, each of the alkyl groups having 1 to 3 carbon atoms with the same meaning as previously defined;

\((C_{3-7})\)cycloalkenyl means a cycloalkenyl group having 3-7 carbon atoms, preferably 5-7 carbon atoms; preferred \((C_{3-7})\)cycloalkenyl groups are cyclopentenyl or cyclohexenyl; and cyclohexenyl groups are most preferred;
(C\textsubscript{2-6}) heterocycloalkenyl means a heterocycloalkenyl group having 2-6 carbon atoms, preferably 3-5 carbon atoms; and 1 heteroatom selected from N, O and/or S; the preferred (C\textsubscript{2-6}) heterocycloalkenyl groups are oxycyclohexenyl and azacyclohexenyl groups.

In the above definitions with multifunctional groups, the attachment point is at the last group. When, in the definition of a substituent, is indicated that "all of the alkyl groups" of said substituent are optionally substituted, this also includes the alkyl moiety of an alkoxy group.

A circle in a ring of Formula (XIX) indicates that the ring is aromatic. Depending on the ring formed, the nitrogen, if present in X or Y, may carry a hydrogen.

[00522] In one aspect the invention provides a compound according to Formula (XIX) wherein B\textsubscript{1} is C(R\textsubscript{7}); B\textsubscript{2} is C(R\textsubscript{8}); B\textsubscript{3} is C(R\textsubscript{9}) and B\textsubscript{4} is C(R\textsubscript{10}).

[00523] In other embodiments, the BTK inhibitors include, but are not limited to, those compounds described in International Patent Application Publication No. WO 2013/010869, the disclosures of each of which are specifically incorporated by reference herein.

[00524] In an embodiment, the BTK inhibitor is a compound of Formula (XX):

![Formula (XX)](image)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, wherein:

L\textsubscript{a} is CH\textsubscript{2}, O, NH or S;

Ar is a substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl;
Y is an optionally substituted group selected from the group consisting of alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl; Z is C(=O), OC(=O), NRC(=O), C(=S), S(=O)$_x$, OS(=O)$_x$, or NRS(=O)$_x$, where x is 1 or 2; $R^7$ and $R^8$ are each independently H; or $R^7$ and $R^8$ taken together form a bond; $R^6$ is H; and $R$ is H or (C$_1$-$_6$)alkyl.

[00525] In an embodiment, the BTK inhibitor is ibrutinib or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. In an embodiment, the BTK inhibitor is (R)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one. In an embodiment, the BTK inhibitor is 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]piperidin-1-yl]prop-2-en-1-one. In another embodiment, the BTK inhibitor is (S)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one. In an embodiment, which has the structure of Formula (XX-A), or an enantiomer thereof, or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

![Formula (XX-A)]

[00526] In an embodiment, the BTK inhibitor is a compound of Formula (XXI):
or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof,
wherein:
$L_a$ is CH$_2$, O, NH or S;
$Ar$ is a substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl;
$Y$ is an optionally substituted group selected from the group consisting of alkyl, heteroalkyl,
cycloalkyl, heterocycloalkyl, aryl and heteroaryl;
$Z$ is C(=O), OC(=O), NRC(=O), C(=S), S(=O)\_x$ or NRS(=O)\_x, where x is 1 or 2;
$R^7$ and $R^8$ are each H; or $R^7$ and $R^8$ taken together form a bond;
$R^6$ is H; and
$R$ is H or (C$_1$-6)alkyl.

[00527] In an embodiment, the BTK inhibitor is a compound of Formula (XXII):
or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, wherein:

L is CH₂, O, NH or S;

Ar is a substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl;

Y is an optionally substituted group selected from the group consisting of alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl;

Z is C(=O), OC(=O), NRC(=O), C(=S), S(=O)ₓ, OS(=O)ₓ or NRS(=O)ₓ, where x is 1 or 2;

R⁷ and R⁸ are each H; or R⁷ and R⁸ taken together form a bond;

R⁶ is H; and

R is H or (C₁₋₆)alkyl.

[00528] In an embodiment, the BTK inhibitor is a compound of Formula (XXIII):
or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof,
wherein:

- \( L_a \) is \( \text{CH}_2, \text{O}, \text{NH} \) or \( \text{S} \);
- \( \text{Ar} \) is a substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl;
- \( Y \) is an optionally substituted group selected from the group consisting of alkyl, heteroalkyl,
cycloalkyl, heterocycloalkyl, aryl and heteroaryl;
- \( Z \) is \( \text{C(=O)}, \text{OC(=O)}, \text{NRC(=O)}, \text{C(=S)}, \text{S(=O)}_x, \text{OS(=O)}_x \) or \( \text{NRS(=O)}_x \), where \( x \) is 1 or 2;
- \( R^7 \) and \( R^8 \) are each \( \text{H} \); or \( R^7 \) and \( R^8 \) taken together form a bond;
- \( R^x \) is \( \text{H} \); and
- \( R \) is \( \text{H} \) or \( (\text{C}_{1-6}) \)alkyl.

[00529] In an embodiment, the BTK inhibitor is a compound disclosed in U.S. Patent No. 7,459,554, the disclosure of which is specifically incorporated herein by reference. In an embodiment, the BTK inhibitor is a compound of Formula (XXIV):
or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, wherein:

Q\(^1\) is aryl\(^1\), heteroaryl\(^1\), cycloalkyl, heterocyclyl, cycloalkenyl, or heterocycloalkenyl, any of which is optionally substituted by one to five independent G\(^1\) substituents;

R\(^1\) is alkyl, cycloalkyl, bicycloalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, heterocyclyl, or heterobicycloalkyl, any of which is optionally substituted by one or more independent G\(^1\) substituents;

G\(^1\) and G\(^{11}\) are each independently halo, oxo, -CF\(_3\), -OCF\(_3\), -OR\(^2\), -NR\(^2\)R\(^2\), -C(O)R\(^2\), -CONR\(^2\)R\(^2\), -NO\(_2\), -CN, -S(O)\(_2\)R\(^3\), -SO\(_2\)NR\(^2\)R\(^3\), NR\(^2\)(C=O)R\(^3\), NR\(^2\)(C=O)OR\(^3\), NR\(^2\)(C=O)NR\(^2\)R\(^3\), NR\(^2\)(C=O)S(O)\(_3\), -(C=NR)R\(^2\), -(C=O)SR\(_2\), -NR\(^2\)(C=NR\(^3\))OR\(_2\), -NR\(^2\)(C=NR\(^3\))SR\(_3\), -O(C=O)OR\(_2\), -O(C=O)NR\(^2\)R\(_3\), -O(C=O)SR\(_2\), -S(C=O)OR\(_2\), -S(C=O)NR\(^2\)R\(_3\), -(C\(_{2-10}\))alkyl, -(C\(_{2-10}\))alkenyl, -(C\(_{2-10}\))alkynyl, -(C\(_{1-10}\))alkoxy(C\(_{1-10}\))alkyl, -(C\(_{1-10}\))alkoxy(C\(_{2-10}\))alkenyl, -(C\(_{1-10}\))alkoxy(C\(_{1-10}\))alkynyl, -(C\(_{1-10}\))alkylthio(C\(_{1-10}\))alkenyl, -(C\(_{1-10}\))alkylthio(C\(_{2-10}\))alkenyl, -(C\(_{1-10}\))alkylthio(C\(_{1-10}\))alkynyl, -(C\(_{1-10}\))alkenyl, -(C\(_{2-10}\))alkyl, -(C\(_{3-8}\))alkenyl, -(C\(_{3-8}\))alkenyl(C\(_{1-10}\))alkenyl, -(C\(_{3-8}\))alkenyl(C\(_{2-10}\))alkenyl, -(C\(_{3-8}\))alkenyl(C\(_{1-10}\))alkynyl, -(C\(_{2-10}\))alkenyl, -(C\(_{2-10}\))alkyl, -(C\(_{3-8}\))alkenyl, -(C\(_{3-8}\))alkenyl(C\(_{2-10}\))alkenyl, -(C\(_{3-8}\))alkenyl (C\(_{1-10}\))alkeny1, -(C\(_{2-10}\))alkeny1, -(C\(_{2-10}\))alkeny1, -(C\(_{3-8}\))alkeny1, -(C\(_{3-8}\))alkeny1(C\(_{1-10}\))alkeny1, -(C\(_{3-8}\))alkeny1(C\(_{2-10}\))alkeny1, -(X\(_n\))-(Y\(_m\))R\(^4\), or aryl-(C\(_{0-10}\))alkyl, aryl-(C\(_{2-10}\))alkenyl, or aryl-(C\(_{2-10}\))alkynyl, any of which is optionally substituted with one or more independent halo, -CF\(_3\), -
OCF$_3$, -OR$_{2}$, -NR$_2$R$_3$ (R$_{333}$)$_2$, -C(O)R$_2$, -CONR$_2$R$_3$, -NO$_2$, -CN, -S(O)$_2$, -SO$_2$NR$_2$R$_3$, -NR$_2^2$ (C=O)R$_{333}$, -NR$_{2}^2$ (C=O)OR$_{333}$, -NR$_{2}^2$ (C=O)NR$_{2}^2$R$_{333}$, -NR$_{2}^2$ S(O)$_2$R$_{3}$, -S(O)NR$_{2}^2$R$_{3}$, -C(S)OR$_{2}^2$, -(C=O)SR$_{2}^2$, -NR$_{2}^2$ (C=NR$_{3}^3$)OR$_{2}^2$, -NR$_{2}^2$ (C=NR$_{3}^3$)SR$_{333}$a, -(O=C=O)OR$_{2}^2$, -(O=C=O)NR$_{2}^2$R$_{333}$, -(O=C=O)SR$_{2}^2$, -S(C=O)OR$_{2}^2$, or -S(C=O)NR$_{2}^2$R$_{333}$ substituents; or hetaryl-(C$_{0,10}$)alkyl, hetaryl-(C$_{2,10}$)alkenyl, or hetaryl-(C$_{2,10}$)alkynyl, any of which is optionally substituted with one or more independent halo, -CF$_3$, -OCF$_3$, -OR$_{2}^2$, -NR$_{2}^2$ (R$_{333}$)$_2$, -(C=O)R$_2$, -CO$_2$R$_{333}$, -CONR$_2$R$_{333}$, -NO$_2$, -CN, -(S=O)$_{3}^a$, -SO$_2$NR$_{2}^2$R$_{3}$, -NR$_{2}^2$ (C=O)R$_{333}$, -NR$_{2}^2$ (C=O)OR$_{333}$, -NR$_{2}^2$ (C=O)NR$_{2}^2$R$_{333}$, -NR$_{2}^2$ S(O)$_2$R$_{3}$, -(C=S)OR$_{2}^2$, -(C=O)SR$_{2}^2$, -NR$_{2}^2$ (C=NR$_{3}^3$)OR$_{2}^2$, -NR$_{2}^2$ (C=NR$_{3}^3$)SR$_{333}$a, -(O=C=O)OR$_{2}^2$, -(O=C=O)NR$_{2}^2$R$_{333}$, -(O=C=O)SR$_{2}^2$, -S(C=O)OR$_{2}^2$, or -S(C=O)NR$_{2}^2$R$_{333}$ substituents;

G$^{11}$ is halo, oxo, -CF$_3$, -OCF$_3$, -OR$_{2}$, -NR$_2$R$^1$ (R$_{3}^a$)$_2$, -(C=O)R$_2$, -CO$_2$R$_{2}$, -CONR$_2$R$^1$ (R$_{3}^a$)$_2$, -S(O)$_2$, -SO$^2$NR$_2$R$_3$, -NR$^2_1$ (C=O)R$_{333}$, -NR$^2_1$ (C=O)OR$_{333}$, -NR$^2_1$ (C=O)NR$^2_1$R$_{333}$, -NR$^2_1$ S(O)$_2$R$_{3}$, -(C=S)OR$_{2}$, -(C=O)SR$_{2}$, -NR$^2_1$ (C=NR$_{3}^3$)OR$_{2}^2$, -NR$^2_1$ (C=NR$_{3}^3$)SR$_{333}$a, -(O=C=O)OR$_{2}$, -(O=C=O)NR$^2_1$R$_{333}$, -(O=C=O)SR$_{2}$, -S(C=O)OR$_{2}$, -(O=C=O)SR$_{2}$, -S(C=O)OR$_{2}$, or -S(C=O)NR$_{2}^2$R$_{333}$ substituents;
2221

-CONR
2221

NR

3331

R

2221

3331

(C=O)OR
2221

, NR

2221

(C=O)SR

, -NR

2221

3331

NR

(C=NR
2221

)SR

2221

2221

(C=O)NR
3331

222a1

(C=NR
333a1

, -SO2 NR
R

)NR

R

, -P(O)OR

R

, NR

R

2221

3331

, -NR

, or -S(C=O)NR

R

3331

3331

(C=NR

, -O(C=O)NR
2221

2221

3331

3331

, NR

S(O)j5a R

2221

2221

, -O(C=O)OR
3331

3331

333a1

2221

2221

S(C=O)OR

2221

, -NO2 , -CN, -S(O)j5a R

R

3331

(C=O)R

,

2221

, -(C=S)OR
222a1

)OR

,-

,2221

, -O(C=O)SR

,-

substituents; or hetaryl-(C0 -1 0 )

alkyl, hetaryl-(C2 -1 0 )alkenyl, or hetaryl-(C2 -1 0 )alkynyl, any of which is optionally substituted
2221

2221

with one or more independent halo, -CF3 , -OCF3 , -OR
2221

-CO2 R
2221

NR

, -CONR

2221

3331

(C=O)OR
2221

2221

, -NR
3331

-NR

(C=NR
2221

-S(C=O)OR

R

, NR

2221

(C=O)SR

3331

, -NO2 , -CN, -S(O)j6a R

2221

2221

(C=O)NR
3331

222a1

(C=NR

)SR

333a1

R

3331

333a1

)NR

R

2221

, -P(O)OR

OR

3331

, NR

, -SO2 NR

2221

, -NR

(C=NR

3331

2221

, or -S(C=O)NR

R

3331

3331

333a1

(R

3331

R

3331

3331

, -O(C=O)NR

R

2221

S(O)j6a R

2221

2221

, -O(C=O)OR
2221

2221

, -NR

, NR

2221

)j6a , -C(O)R

2221

3331

(C=O)R

2221

, -(C=S)OR
222a1

)OR

,

,

,-

,
2221

, -O(C=O)SR

,

11

R

substituents; or G is taken

together with the carbon to which it is attached to form a double bond which is substituted
2

2a

3

3a

R ,R ,R ,R ,R

222

222

333

, R a, R , R

333a

21

2a1

31

3a1

,R ,R ,R ,R ,R

2221

222a1

,R

3331

,R

333a1

, and R

are

each independently equal to (C0 -1 0 )alkyl, (C2 -1 0 )alkenyl, (C2 -1 0 )alkynyl, (C1 -1 0 )alkoxy(C1 10

)alkyl, (C1 -1 0 )alkoxy(C2 -1 0 )alkenyl, (C1 -1 0 )alkoxy(C2 -1 0 )alkynyl, (C1 -1 0 )alkylthio(C1 -

10

)alkyl, (C1 -1 0 )alkylthio(C2 -1 0 )alkenyl, (C1 -1 0 )alkylthio(C2 -1 0 )alkynyl, cyclo(C3 -8 )alkyl,

cyclo(C3 -8 )alkenyl, cyclo(C3 -8 )alkyl(C1 -1 0 )alkyl, cyclo(C3 -8 )alkenyl(C1 -1 0 )alkyl, cyclo(C3 8

)alkyl(2 -1 0 )alkenyl, cyclo(C3 -8 )alkenyl(C2 -1 0 )alkenyl, cyclo(C3 -8 )alkyl(C2 -1 0 )alkynyl,

cyclo(C3 -8 )alkenyl(C2 -1 0 )alkynyl, heterocyclyl-(C0 -1 0 )alkyl, heterocyclyl-(C2 -1 0 )alkenyl, or
111

heterocyclyl-(C2 -1 0 )alkynyl, any of which is optionally substituted by one or more G

substituents; or aryl-(C0 -1 0 )alkyl, aryl-(C2 -1 0 )alkenyl, or aryl-(C2 -1 0 )alkynyl, hetaryl-(C0 10

)alkyl, hetaryl-(C2 -1 0 )alkenyl, or hetaryl-(C2 -1 0 )alkynyl, any of which is optionally
111

substituted by one or more G
222

333

333

222

NR R (R a)j1a or -NR
2221

or -NR
3331

R

3331

R

333a1

(R

2

3

3a

substituents; or in the case of -NR R (R )j1 or -

333

333

2221

R (R a)j2a or -NR
2221

)j5a or -NR

R

3331

333a1

(R

R

3331

(R

2

333a1

3

)j3a or -NR

)j6a , R and R or R

222

2221

333

R

3331

333a1

(R

and R 3 or R

2221

)j4a

and

taken together with the nitrogen atom to which they are attached form a 3-10 membered

saturated ring, unsaturated ring, heterocyclic saturated ring, or heterocyclic unsaturated ring,
111

wherein said ring is optionally substituted by one or more G

substituents;


X¹ and Y¹ are each independently -O-, -NR²-, -S(O)₇-,-NC(O)OR⁷-, -N(C(O)R⁷)-, 
-N(SO₂R⁷)-,-CH₂O-, -CH₂S-, -CH₂N(R⁷)-,-CH(NR⁷)-,-CH₂N(C(O)R⁷)-,-CH₂N(C(O)OR⁷)-, 
-CH₇N(SO₂R⁷)-,-CH(NHR⁷)-,-CH(NH(C(O)R⁷)-,-CH(NHSO₂R⁷)-,-CH(NH(C(O)OR⁷)-, 
-CH(O(C(O)R⁷)-,-CH=CH-, -C:ident.C-, -C(=NOR⁷)-, -C(O)-, - 
CH(OR⁷)-,-C(O)N(R⁷)-,-N(R⁷)C(O) -, -N(R⁷)S(O)-,-N(R⁷)S(O)_₂- -OC(O)N(R⁷)-, - 
N(R⁷)C(O)N(R⁷)-,-NR²C(O)O,- -S(O)N(R⁷)-,-SO₂N(R⁷)-,-C(O)-, -N(R⁷)P(OR⁸)-, - 
N(R⁷)P(OR⁸)-,-N(R⁷)P(OR⁸)-,-N(R⁷)O-,-N(R⁷)N(R⁷)-,-C(O)N(R⁷)C(O)-, - 
S(O)N(R⁷)C(O) -, -S(O)N(R⁷)C(O) -, -OS(O)N(R⁷) -, -OS(O)N(R⁷) -, -N(R⁷)S(O)-, - 
N(R⁷)S(O)_₂-, -N(R⁷)S(O)C(O)-,-N(R⁷)S(O)C(O)-,-SON(C(O)R⁷)-,-SO₂N(C(O)R⁷)-, - 
N(R⁷)SONR⁷-, -N(R⁷)SO₂N(R⁷)-,-C(O)O,-,-N(R⁷)P(OR⁸)-, -N(R⁷)P(OR⁸)-, - 
N(R⁷)P(OR⁸)-,-N(R⁷)P(OR⁸)-,-N(R⁷)P(OR⁸)-,-N(C(O)R⁷)P(OR⁸)-, - 
N(C(O)R⁷)P(O)(OR⁸)-,-N(C(O)R⁷)P(O)(OR⁸)-,-CH(R⁷)S(O) -, -CH(R⁷)S(O) -, - 
CH(R⁷)N(C(O)OR⁷)-,-CH(R⁷)N(C(O)R⁷)-,-CH(R⁷)N(SO₂R⁷)-,-CH(R⁷)O-, - 
CH(R⁷)O-, -CH(R⁷)S-, - 
CH(R⁷)N(R⁷)-,-CH(R⁷)N(C(O)R⁷)-,-CH(R⁷)N(C(O)OR⁷)-,-CH(R⁷)N(SO₂R⁷)-,- 
CH(R⁷)C(=NOR⁷)-,-CH(R⁷)C(O)-,-CH(R⁷)CH(OR⁷)-,-CH(R⁷)CH(OR⁷)-, - 
CH(R⁷)N(R⁷)C(O)-,-CH(R⁷)N(R⁷)S(O)-,-CH(R⁷)N(R⁷)S(O)₂-, -CH(R⁷)OC(O)N(R⁷)-, - 
CH(R⁷)N(R⁷)C(O)N(R⁷)-,-CH(R⁷)N(R⁷)C(O)O-, -CH(R⁷)S(O)N(R⁷)-,- 
CH(R⁷)S(O)N(R⁷)-,CH(R⁷)N(C(O)R⁷)-,-CH(R⁷)N(C(O)OR⁷)-,-CH(R⁷)N(SO₂R⁷)-,- 
CH(R⁷)N(R⁷)S(O)₂N(R⁷)-,-CH(R⁷)S(O)S(O)N(R⁷)-, -CH(R⁷)C(O)N(R⁷)C(O)-, - 
CH(R⁷)N(R⁷)C(O)N(R⁷)-, -CH(R⁷)C(O)N(R⁷)-, -CH(R⁷)OS(O)N(R⁷)-,- 
CH(R⁷)OS(O)S(O)₂N(R⁷)-, -CH(R⁷)N(R⁷)S(O)O-, -CH(R⁷)N(R⁷)S(O)₂-, -CH(R⁷)N(R⁷)S(O)C(O)-, - 
CH(R⁷)N(R⁷)S(O)C(O)-,-CH(R⁷)SON(C(O)R⁷)-,-CH(R⁷)SO₂N(C(O)R⁷)-, - 
CH(R⁷)N(R⁷)SON(R⁷)-,-CH(R⁷)N(R⁷)SO₂N(R⁷)-,-CH(R⁷)C(O)-, - 
CH(R⁷)N(R⁷)P(OR⁸)-,-CH(R⁷)N(R⁷)P(O)(OR⁸)-,-CH(R⁷)N(R⁷)P(O)(OR⁸)-O-, - 
CH(R⁷)N(R⁷)P(O)(OR⁸)-,-CH(R⁷)N(C(O)R⁷)P(OR⁸)-O-, -CH(R⁷)N(C(O)R⁷)P(OR⁸)-, - 
CH(R⁷)N(C(O)R⁷)P(O)(OR⁸)-O-, -CH(R⁷)N(C(O)R⁷)P(O)(OR⁸)-O-, - 
CH(R⁷)N(C(O)R⁷)P(O)(OR⁸)-O-, or -CH(R⁷)N(C(O)R⁷)P(O)(OR⁸)-; 

or X¹ and Y¹ are each independently represented by one of the following structural formulas:
$R^{10}$, taken together with the phosphinamide or phosphonamide, is a 5-, 6-, or 7-membered aryl, heteroaryl or heterocyclyl ring system;

$R^5$, $R^6$, and $G^{11}$ are each independently a ($C_{0-10}$)-alkyl, ($C_{1-10}$)-alkenyl, ($C_{1-10}$)-alkynyl, ($C_{1-10}$)-alkoxy($C_{1-10}$)-alkyl, ($C_{1-10}$)-alkoxy($C_{1-10}$)-alkenyl, ($C_{1-10}$)-alkoxy($C_{1-10}$)-alkynyl, ($C_{1-10}$)-alkylthio($C_{1-10}$)-alkyl, ($C_{1-10}$)-alkylthio($C_{1-10}$)-alkenyl, ($C_{1-10}$)-alkylthio($C_{1-10}$)-alkynyl, cyclo($C_{1-8}$)-alkyl, cyclo($C_{1-8}$)-alkenyl, cyclo($C_{1-8}$)-alkynyl($C_{1-10}$)-alkenyl, cyclo($C_{1-8}$)-alkynyl, cyclo($C_{1-8}$)-alkenyl($C_{1-10}$)-alkenyl, cyclo($C_{1-8}$)-alkynyl, cyclo($C_{1-8}$)-alkenyl($C_{1-10}$)-alkenyl, cyclo($C_{1-8}$)-alkynyl, cyclo($C_{1-8}$)-alkenyl($C_{1-10}$)-alkenyl, heterocyclyl($C_{1-10}$)-alkenyl, heterocyclyl($C_{1-10}$)-alkenyl, or heterocyclyl($C_{1-10}$)-alkenyl, any of which is optionally substituted with one or more independent halo, -CF$_3$, -OCF$_3$, -OR$_7$, -NR$_7$R$_7$, -(C=O)R$_7$, -CO$_2$R$_7$, -CONR$_7$R$_7$, -NO$_2$, -CN, -S(O)$_{5a}$, R$_7$, -SO$_2$NR$_7$R$_7$, NR$_7$(C=O)R$_7$, NR$_7$(C=O)NR$_7$R$_7$, NR$_7$S(O)$_{10a}$R$_7$, -(C=S)OR$_7$, -(C=O)SR$_7$, -NR$_7$(C=NR$_7$)OR$_7$, -NR$_7$(C=NR$_7$)SR$_7$, -O(C=O)OR$_7$, -O(C=O)NR$_7$R$_7$, -O(C=O)SR$_7$, -S(C=O)OR$_7$, -P(O)OR$_7$R$_7$, -O(C=O)NR$_7$R$_7$, or -S(C=O)NR$_7$R$_7$ substituents; or aryl($C_{0-10}$)-alkyl, aryl($C_{1-10}$)-alkenyl, or aryl($C_{1-10}$)-alkynyl, any of which is optionally substituted with one or more independent halo, -CF$_3$, -OCF$_3$, -OR$_7$, -NR$_7$R$_7$, -C(O)R$_7$, -CO$_2$R$_7$, -CONR$_7$R$_7$, -NO$_2$, -CN, -S(O)$_{5a}$, R$_7$, -SO$_2$NR$_7$R$_7$, NR$_7$(C=O)R$_7$, NR$_7$(C=O)NR$_7$R$_7$, NR$_7$S(O)$_{10a}$R$_7$, -(C=S)OR$_7$, -(C=O)SR$_7$, -NR$_7$(C=NR$_7$)OR$_7$, -NR$_7$(C=NR$_7$)SR$_7$, -(C=O)OR$_7$, -(C=O)NR$_7$R$_7$, -(C=O)SR$_7$, -NR$_7$(C=NR$_7$)NR$_7$R$_7$, -NR$_7$(C=NR$_7$)OR$_7$, -NR$_7$(C=NR$_7$)SR$_7$, -(C=O)OR$_7$, -
O(C=O)NR\textsuperscript{7} R\textsuperscript{8}, -O(C=O)SR\textsuperscript{7}, -S(C=O)OR\textsuperscript{7}, -P(O)OR\textsuperscript{7} R\textsuperscript{8}, or -S(C=O)NR\textsuperscript{7} R\textsuperscript{8} substituents; or heteraryl-(C\textsubscript{6-10})alkyl, heteraryl-(C\textsubscript{2-10})alkenyl, or heteraryl-(C\textsubscript{2-10})alkynyl, any of which is optionally substituted with one or more independent halo, -CF\textsubscript{3}, -OCF\textsubscript{3}, -OR\textsuperscript{7}, -NR\textsuperscript{7} R\textsuperscript{8}, -C(O)R\textsuperscript{7}, -CO\textsubscript{2} R\textsuperscript{7}, -CONR\textsuperscript{7} R\textsuperscript{8}, -NO\textsubscript{2}, -CN, -S(O)\textsubscript{2} R\textsuperscript{7}, -SO\textsubscript{2} NR\textsuperscript{7} R\textsuperscript{8}, NR\textsuperscript{7} (C=O)R\textsuperscript{7}, NR\textsuperscript{7} (C=O)OR\textsuperscript{7}, NR\textsuperscript{7} (C=O)NR\textsuperscript{7} R\textsuperscript{8}, NR\textsuperscript{7} S(O)\textsubscript{2} R\textsuperscript{7}, -(C=S)OR\textsuperscript{7}, -(C=O)SR\textsuperscript{7}, -NR\textsuperscript{7} (C=NR\textsuperscript{7})NR\textsuperscript{7} R\textsuperscript{8}, -NR\textsuperscript{7} (C=NR\textsuperscript{7})OR\textsuperscript{7}, -NR\textsuperscript{7} (C=NR\textsuperscript{7})SR\textsuperscript{7}, -O(C=O)OR\textsuperscript{7}, -O(C=O)NR\textsuperscript{7} R\textsuperscript{8}, -O(C=O)S\textsuperscript{2}R\textsuperscript{7}, -S(C=O)OR\textsuperscript{7}, -P(O)OR\textsuperscript{7} OR\textsuperscript{7}, or -S(C=O)NR\textsuperscript{7} R\textsuperscript{8} substituents; or R\textsuperscript{5} with R\textsuperscript{6} taken together with the respective carbon atom to which they are attached, form a 3-10 membered saturated or unsaturated ring, wherein said ring is optionally substituted with R\textsuperscript{69}; or R\textsuperscript{5} with R\textsuperscript{6} taken together with the respective carbon atom to which they are attached, form a 3-10 membered saturated or unsaturated heterocyclic ring, wherein said ring is optionally substituted with R\textsuperscript{69}; R\textsuperscript{7} and R\textsuperscript{8} are each independently H, acyl, alkyl, alkenyl, aryl, heteroaryl, heterocyclyl or cycloalkyl, any of which is optionally substituted by one or more G\textsuperscript{41} substituents; R\textsuperscript{7} is H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocyclyl, cycloalkenyl, or heterocycloalkenyl, any of which is optionally substituted by one or more G\textsuperscript{41} substituents; R\textsuperscript{69} is equal to halo, -OR\textsuperscript{7}, -SH, -NR\textsuperscript{7} R\textsuperscript{8}, -CO\textsubscript{2} R\textsuperscript{7}, -CONR\textsuperscript{7} R\textsuperscript{8}, -NO\textsubscript{2}, -CN, -S(O)\textsubscript{2} R\textsuperscript{7}, -SO\textsubscript{2} NR\textsuperscript{7} R\textsuperscript{8}, (C\textsubscript{1-10})alkyl, (C\textsubscript{2-10})alkenyl, (C\textsubscript{2-10})alkynyl, (C\textsubscript{1-10})alkoxy(C\textsubscript{1-10})alkyl, (C\textsubscript{1-10})alkoxy(C\textsubscript{2-10})alkenyl, (C\textsubscript{1-10})alkoxy(C\textsubscript{2-10})alkynyl, (C\textsubscript{1-10})alkylthio(C\textsubscript{1-10})alkyl, (C\textsubscript{1-10})alkylthio(C\textsubscript{2-10})alkenyl, (C\textsubscript{1-10})alkylthio(C\textsubscript{2-10})alkynyl, cyclo(C\textsubscript{3-8})alkyl, cyclo(C\textsubscript{3-8})alkenyl, cyclo(C\textsubscript{3-8})alkynyl, cyclo(C\textsubscript{3-8})alkenyl, cyclo(C\textsubscript{3-8})alkenyl(C\textsubscript{2-10})alkenyl, cyclo(C\textsubscript{3-8})alkenyl(C\textsubscript{2-10})alkynyl, cyclo(C\textsubscript{3-8})alkenyl(C\textsubscript{2-10})alkenyl, heterocyclyl-(C\textsubscript{0-10})alkyl, heterocyclyl-(C\textsubscript{2-10})alkenyl, or heterocyclyl-(C\textsubscript{2-10})alkynyl, any of which is optionally substituted with one or more independent halo, cyano, nitro, -OR\textsuperscript{7}, -SO\textsubscript{2} NR\textsuperscript{7} R\textsuperscript{8}, or -NR\textsuperscript{7} R\textsuperscript{8} substituents; or aryl-(C\textsubscript{2-10})alkyl, aryl-(C\textsubscript{2-10})alkenyl, or aryl-(C\textsubscript{2-10})alkynyl, any of which is optionally substituted with one or more independent halo, cyano, nitro, -OR\textsuperscript{7}, (C\textsubscript{1-10})alkyl, (C\textsubscript{2-10})alkenyl, (C\textsubscript{2-10})alkynyl, halo(C\textsubscript{1-10})alkyl, halo(C\textsubscript{1-10})alkenyl, halo(C\textsubscript{1-10})alkynyl, -COOH, (C\textsubscript{1-4})alkoxy carbonyl, -CONR\textsuperscript{7} R\textsuperscript{8}, -SO\textsubscript{2} NR\textsuperscript{7} R\textsuperscript{8}, or -NR\textsuperscript{7} R\textsuperscript{8} substituents; or hetaryl-(C\textsubscript{2-10})alkyl, hetaryl-(C\textsubscript{2-10})alkenyl, or hetaryl-(C\textsubscript{2-10})alkynyl, any of which is optionally substituted with one or more independent halo, cyano, nitro, -OR\textsuperscript{7}, (C\textsubscript{1-10})alkyl, (C\textsubscript{2-10})alkyl, -
alkenyl, (C₁₀₋₀)alkynyl, halo(C₁₋₀)alkenyl, halo(C₂₋₁₀)alkenyl, COOH, (C₁₋₀)alkoxycarbonyl, -CONR²⁺, -SO₂NR²⁺, or -NR²⁺ substituents; or mono(C₁₋₀ alkyl)amino(C₁₋₀ alkyl), di((C₁₋₀ alkyl)amino(C₁₋₀ alkyl), mono(aryl)amino(C₁₋₀ alkyl), di(aryl)amino(C₁₋₀ alkyl), or -N((C₁₋₀ alkyl)-(C₁₋₀ alkyl)aryl-aryl, any of which is optionally substituted with one or more independent halo, cyano, nitro, -OR⁷⁺, (C₁₋₀ alkyl), (C₂₋₁₀)alkenyl, (C₂₋₁₀)alkynyl, halo(C₁₋₀)alkenyl, halo(C₂₋₁₀)alkenyl, COOH, (C₁₋₀)alkoxycarbonyl, -CONR²⁺, -SO₂NR²⁺, or -NR²⁺ substituents; or in the case of -NR²⁺, R⁷⁺ and R⁸⁺ taken together with the nitrogen atom to which they are attached form a 3-10 membered saturated ring, unsaturated ring, heterocyclic saturated ring, or heterocyclic unsaturated ring, wherein said ring is optionally substituted with one or more independent halo, cyano, hydroxy, nitro, (C₁₋₀ alkoxo, -SO₂NR²⁺, or -NR²⁺ substituents; R⁷⁺, R⁷⁺, R⁷⁺, R⁸⁺, R⁷⁺, and R⁸⁺ are each independently (C₁₋₀ alkyl), (C₂₋₁₀)alkenyl, (C₁₋₀ alkynyl, (C₁₋₀ alkoxoy(C₁₋₀ alkyl), (C₁₋₀)alkoxoy(C₂₋₁₀)alkenyl, (C₁₋₀ alkoxoy(C₂₋₁₀)alkynyl, (C₁₋₀)alkylethio(C₁₋₀ alkyl), (C₁₋₀)alkylethio(C₂₋₁₀)alkenyl, (C₁₋₀)alkylethio(C₂₋₁₀)alkynyl, cyclo(C₃₋₈)alkyl, cyclo(C₃₋₈)alkenyl, cyclo(C₃₋₈)alkynyl, cyclo(C₃₋₈)alkenyl(C₁₋₁₀)alkyl, cyclo(C₃₋₈)alkenyl(C₂₋₁₀)alkenyl, cyclo(C₃₋₈)alkenyl(C₂₋₁₀)alkynyl, cyclo(C₃₋₈)alkenyl(C₂₋₁₀)alkenyl, heterocyclyl-alkenyl, heterocyclyl-alkenyl, heterocyclyl-alkynyl, heterocyclyl-alkylcarbonyl, (C₁₋₀ alkoxycarbonyl, (C₁₋₀)alkynylcarbonyl, (C₂₋₁₀)alkoxycarbonyl(C₁₋₁₀)alkyl, mono(C₁₋₀)alkylaminocarbonyl, di(C₁₋₀)alkylaminocarbonyl, mono(aryl)aminocarbonyl, di(aryl)aminocarbonyl, or (C₁₋₀)alkyl(aryl)aminocarbonyl, any of which is optionally substituted with one or more independent halo, cyano, hydroxy, nitro, (C₁₋₀)alkoxo, -SO₂N((C₁₋₀)alkyl)((C₁₋₀)alkyl), or -N((C₁₋₀)alkyl)((C₁₋₀)alkyl) substituents; or alkyl(C₁₋₀ alkyl), ary(C₁₋₀ alkyl), or aryl(C₂₋₁₀)alkenyl, any of which is optionally substituted with one or more independent halo, cyano, nitro, -O((C₀₋₄)alkyl), (C₁₋₀ alkyl, (C₂₋₁₀)alkenyl, (C₂₋₁₀)alkynyl, halo(C₁₋₀)alkenyl, halo(C₂₋₁₀)alkenyl, halo(C₂₋₁₀)alkynyl, COOH, (C₁₋₀ alkoxycarbonyl, -CON(C₁₋₀)alkyl)((C₁₋₀)alkyl), -SO₂N((C₀₋₄)alkyl)((C₁₋₀ alkyl)), or -N((C₀₋₄)alkyl)((C₁₋₀)alkyl) substituents; or hetaryl, hetaryl, heterocyclylalkenyl, any of which is optionally substituted with one or more independent halo, cyano, nitro, -O((C₀₋₄)alkyl), (C₁₋₀)alkyl, (C₂₋₁₀)alkenyl, (C₂₋₁₀)alkynyl,
halo(C$_{1-10}$)alkyl, halo(C$_{2-10}$)alkenyl, halo(C$_{2-10}$)alkynyl, -COOH, (C$_{1-4}$)alkoxycarbonyl, -CON((C$_{1-4}$)alkyl)((C$_{0-4}$)alkyl), -SO$_2$N((C$_{0-4}$)alkyl)((C$_{0-4}$)alkyl), or -N((C$_{0-4}$)alkyl)((C$_{0-4}$)alkyl) substituents; or mono((C$_{1-6}$)alkyl)amino(C$_{1-6}$)alkyl, di((C$_{1-6}$)alkyl)amino(C$_{1-6}$)alkyl, mono(aryl)amino(C$_{1-6}$)alkyl, di(aryl)amino(C$_{1-6}$)alkyl, or -N((C$_{1-6}$)alkyl)-(C$_{1-6}$)alkyl-aryl, any of which is optionally substituted with one or more independent halo, cyano, nitro, -O((C$_{0-4}$)alkyl), (C$_{1-10}$)alkyl, (C$_{2-10}$)alkenyl, (C$_{2-10}$)alkynyl, halo(C$_{1-10}$)alkyl, halo(C$_{2-10}$)alkenyl, halo(C$_{2-10}$)alkynyl, -COOH, (C$_{1-4}$)alkoxycarbonyl, -CON((C$_{1-4}$)alkyl)((C$_{0-4}$)alkyl), -SO$_2$N((C$_{0-4}$)alkyl)((C$_{0-4}$)alkyl), or -N((C$_{0-4}$)alkyl)((C$_{0-4}$)alkyl) substituents; and

n, m, j1, j1a, j2a, j3a, j4, j4a, j5a, j6a, j7, and j8 are each independently equal to 0, 1, or 2.

[00530] In an embodiment, the BTK inhibitor is a compound selected from the structures disclosed in U.S. Patent Nos. 8,450,335 and 8,609,679, and U.S. Patent Application Publication Nos. 2010/0029610 A1, 2012/0077832 A1, 2013/0065879 A1, 2013/0072469 A1, and 2013/0165462 A1, the disclosures of which are incorporated by reference herein. In an embodiment, the BTK inhibitor is a compound of Formula (XXV) or Formula (XXVI):
or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, wherein:
Ring A is an optionally substituted group selected from phenyl, a 3-7 membered saturated or partially unsaturated carbocyclic ring, an 8-10 membered bicyclic saturated, partially unsaturated or aryl ring, a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, an optionally substituted 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, an optionally substituted 7-10 membered bicyclic saturated or partially unsaturated heterocyclic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;
Ring B is an optionally substituted group selected from phenyl, a 3-7 membered saturated or partially unsaturated carbocyclic ring, an 8-10 membered bicyclic saturated, partially unsaturated or aryl ring, a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, an optionally substituted 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, an optionally substituted 7-10 membered bicyclic saturated or partially unsaturated heterocyclic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;
R' is a warhead group;
R' is hydrogen, halogen, —CN, —CF₃, C₁₋₄ aliphatic, C₁₋₄ haloaliphatic, —OR, —C(O)R, or —C(O)N(R)₂;
each R group is independently hydrogen or an optionally substituted group selected from C₁₋₄ aliphatic, phenyl, an optionally substituted 4-7 membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;
W¹ and W² are each independently a covalent bond or a bivalent C₁₋₃ alkylene chain wherein one methylene unit of W¹ or W² is optionally replaced by —NR² —, —N(R²)C(O) —, —
C(O)N(R₂)—, —N(R₂)SO₂—, —SO₂N(R₂)—, —O—, —C(O)—, —OC(O)—, —C(O)O—, —S—, —SO— or —SO₂—; R₂ is hydrogen, optionally substituted C₁₋₆ aliphatic, or —C(O)R, or:

R₂ and a substituent on Ring A are taken together with their intervening atoms to form a 4-6
membered saturated, partially unsaturated, or aromatic fused ring, or:

R₂ and R’ are taken together with their intervening atoms to form an optionally substituted 4-7
membered partially unsaturated or aromatic fused ring;

m and p are independently 0-4; and

R’ and R’ are independently selected from —R, halogen, —OR, —O(CH₂)₉ OR, —CN, —NO₂,
—SO₂R, —SO₂N(R)₂, —SOR, —C(O)R, —CO₂R, —C(O)N(R)₂, —NRC(O)R, —NRC(O)NR₂, —NRSO₂R, or —N(R)₂, wherein q is 1-4; or:

R’ and R’ when concurrently present on Ring B are taken together with their intervening atoms to
form a 5-7 membered saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms
independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with
a warhead group and 0-3 groups independently selected from oxo, halogen, —CN, or C₁₋₆
aliphatic; or

R’ and R’ when concurrently present on Ring A are taken together with their intervening atoms
to form a 5-7 membered saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms
independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with
a warhead group and 0-3 groups independently selected from oxo, halogen, —CN, or C₁₋₆
aliphatic.

[00531] In an embodiment, the BTK inhibitor is a compound of Formula (XXV) or Formula
(XXVI), wherein:

Ring A is an optionally substituted group selected from phenyl, a 3-7 membered saturated or
partially unsaturated carbocyclic ring, an 8-10 membered bicyclic saturated, partially unsaturated
or aryl ring, a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently
selected from nitrogen, oxygen, or sulfur, an optionally substituted 4-7 membered saturated or
partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from
nitrogen, oxygen, or sulfur, an optionally substituted 7-10 membered bicyclic saturated or
partially unsaturated heterocyclic ring having 1-5 heteroatoms independently selected from
nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

Ring B is an optionally substituted group selected from phenyl, a 3-7 membered saturated or partially unsaturated carbocyclic ring, an 8-10 membered bicyclic saturated, partially unsaturated or aryl ring, a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, an optionally substituted 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, an optionally substituted 7-10 membered bicyclic saturated or partially unsaturated heterocyclic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R¹ is -L-Y, wherein:

L is a covalent bond or a bivalent C₁₋₈ saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one, two, or three methylene units of L are optionally and independently replaced by cyclopropylene, —NR—, —N(R)C(O)—, —C(O)N(R)—, —N(R)SO₂—, —SO₂N(R)—, —O—, —C(O)—, —OC(O)—, —C(O)O—, —S—, —SO—, —SO₂—, —C(═S)—, —C(═NR)—, —N═N—, or —C(═N₂)—;

Y is hydrogen, C₁₋₆ aliphatic optionally substituted with oxo, halogen, or CN, or a 3-10 membered monocyclic or bicyclic, saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, and wherein said ring is substituted with at 1-4 groups independently selected from -Q-Z, oxo, NO₂, halogen, CN, or C₁₋₆ aliphatic, wherein:

Q is a covalent bond or a bivalent C₁₋₆ saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one or two methylene units of Q are optionally and independently replaced by —NR—, —S—, —O—, —C(O)—, —SO—, or —SO₂—; and

Z is hydrogen or C₁₋₆ aliphatic optionally substituted with oxo, halogen, or CN;

R² is hydrogen, halogen, —CN, —CF₃, C₁₋₄ aliphatic, C₁₋₄ haloaliphatic, —OR, —C(O)R, or —C(O)N(R)₂;
each R group is independently hydrogen or an optionally substituted group selected from C₁⁻₆ aliphatic, phenyl, an optionally substituted 4-7 membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

W¹ and W² are each independently a covalent bond or a bivalent C₁⁻₃ alkylene chain wherein one methylene unit of W¹ or W² is optionally replaced by —NR², —N(R')₂C(O)—, —C(O)N(R')—, —N(R')₂SO —, —SO₂N(R')—, —O—, —C(O)—, —OC(O)—, —C(O)O—, —S—, —SO— or —SO₂—;

R² is hydrogen, optionally substituted C₁⁻₆ aliphatic, or —C(O)R, or:

R² and a substituent on Ring A are taken together with their intervening atoms to form a 4-6 membered partially unsaturated or aromatic fused ring; or

R² and R³ are taken together with their intervening atoms to form a 4-6 membered saturated, partially unsaturated, or aromatic fused ring;

m and p are independently 0-4; and

R' and R'¹ are independently selected from —R, halogen, —OR, —O(CH₂)₉ OR, —CN, —NO₂, —SO₂R, —SO₂N(R)₂, —SOR, —C(O)R, —CO₂R, —C(O)N(R)₂, —NRC(O)R, —NRC(O)NR₂, —NRSO₂R, or —N(R)₂, wherein R is independently selected from the group consisting of hydrogen, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, heteroaryl, and heterocyclic; or:

R' and R'¹ when concurrently present on Ring B are taken together with their intervening atoms to form a 5-7 membered saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with a warhead group and 0-3 groups independently selected from oxo, halogen, —CN, or C₁⁻₆ aliphatic; or

R’ and R’¹ when concurrently present on Ring A are taken together with their intervening atoms to form a 5-7 membered saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms
independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 
a warhead group and 0-3 groups independently selected from oxo, halogen, —CN, or C₁₋₆ 
aliphatic.

As defined generally above, Ring A is an optionally substituted group selected from phenyl, a 3-
7 membered saturated or partially unsaturated carbocyclic ring, an 8-10 membered bicyclic 
saturated, partially unsaturated or aryl ring, a 5-6 membered monocyclic heteroaryl ring having 
1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 4-7 membered 
saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently 
selected from nitrogen, oxygen, or sulfur, an optionally substituted 7-10 membered bicyclic 
saturated or partially unsaturated heterocyclic ring having 1-5 heteroatoms independently 
selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaryl ring having 
1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In certain 
embodiments, Ring A is an optionally substituted phenyl group. In some embodiments, Ring A 
is an optionally substituted naphthyl ring or a bicyclic 8-10 membered heteroaryl ring having 1-4 
heteroatoms independently selected from nitrogen, oxygen, or sulfur. In certain other 
embodiments, Ring A is an optionally substituted 3-7 membered carbocyclic ring. In yet other 
embodiments, Ring A is an optionally substituted 4-7 membered heterocyclic ring having 1-3 
heteroatoms independently selected from nitrogen, oxygen, or sulfur.

In certain embodiments, Ring A in Formula (XXV) or Formula (XXVI) is substituted as 
defined herein. In some embodiments, Ring A is substituted with one, two, or three groups 
independently selected from halogen, R″, or —(CH₂)₀₋₄ OR″, or —O(CH₂)₀₋₄ R″, wherein each R″ 
is independently selected from the group consisting of cycloalkyl, alkenyl, cycloalkenyl, alkynyl, 
aryl, heteroaryl, and heterocyclyl. Exemplary substituents on Ring A include Br, I, Cl, methyl, 
—CF₃, —C=CH, —OCH₂phenyl, —OCH₂(fluorophenyl), or —OCH₂pyridyl.

In an embodiment, the BTK inhibitor is a compound of Formula (XXVII), also known 
as CC-292 (Celgene):
which is N-(3-((5-fluoro-2-((4-(2-methoxyethoxy)phenyl)amino)pyrimidin-4-yl)amino)phenyl)acrylamide, or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, in an exemplary embodiment is a hydrochloride salt or a besylate salt thereof. The preparation of this compound is described in U.S. Patent Application Publication No. 2010/0029610 A1 at Example 20. The preparation of the besylate salt of this compound is described in U.S. Patent Application Publication No. 2012/0077832 A1. In an embodiment, the BTK inhibitor is a compound selected from the structures disclosed in U.S. Patent Application Publication No. 2010/0029610 A1 or No. 2012/0077832 A1, the disclosures of which are incorporated by reference herein.

[0054] In a preferred embodiment, the BTK inhibitor is (N-(3-(5-fluoro-2-(4-(2-methoxyethoxy)phenyl)amino)pyrimidin-4-yl)amino)phenyl)acrylamide, or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, or a besylate salt thereof. The preparation of this compound is described in U.S. Patent Application Publication No. 2010/0029610 A1 at Example 20. The preparation of its besylate salt is described in U.S. Patent Application Publication No. 2012/0077832 A1.

[0055] In an exemplary embodiment, the BTK inhibitor is a compound of Formula (XXVIII):
or a pharmaceutically acceptable salt, hydrate, solvate, cocrystal, or prodrug thereof, wherein

$L$ represents (1) –O–, (2) –S–, (3) –SO–, (4) –SO$_2$–, (5) –NH–, (6) –C(O)–, (7) –CH$_2$O–, (8) –O–CH$_2$–, (9) –CH$_2$–, or (10) –CH(OH)–;

$R^1$ represents (1) a halogen atom, (2) a C$_{1-4}$ alkyl group, (3) a C$_{1-4}$ alkoxy group, (4) a C$_{1-4}$ haloalkyl group, or (5) a C$_{1-4}$ haloalkoxy group;

$\text{ring1}$ represents a 4- to 7-membered cyclic group, which may be substituted by from one to five substituents each independently selected from the group consisting of (1) halogen atoms, (2) C$_{1-4}$ alkyl groups, (3) C$_{1-4}$ alkoxy groups, (4) nitrile, (5) C$_{1-4}$ haloalkyl groups, and (6) C$_{1-4}$ haloalkoxy groups, wherein when two or more substituents are present on $\text{ring1}$, these substituents may form a 4- to 7-membered cyclic group together with the atoms in $\text{ring1}$ to which these substituents are bound;

$\text{ring2}$ represents a 4- to 7-membered saturated heterocycle, which may be substituted by from one to three –K–R$^2$; $K$ represents (1) a bond, (2) a C$_{1-4}$ alkyne, (3) –C(O)–, (4) –C(O)–CH$_2$–, (5) –CH$_2$–C(O)–, (6) –C(O)O–, or (7) –SO$_2$– (wherein the bond on the left is bound to the $\text{ring2}$);

$R^2$ represents (1) a C$_{1-4}$ alkyl, (2) a C$_{2-4}$ alkenyl, or (3) a C$_{2-4}$ alkynyl group, each of which may be substituted by from one to five substituents each independently selected from the group consisting of (1) NR$_3$R$^3$, (2) halogen atoms, (3) CONR$_3$R$^3$, (4) CO$_2$R$^7$, and (5) OR$^8$;

$R^3$ and $R^4$ each independently represent (1) a hydrogen atom, or (2) a C$_{1-4}$ alkyl group which may be substituted by OR$^8$ or CONR$_{10}$R$^{11}$; $R^3$ and $R^4$ may, together with the nitrogen atom to which
they are bound, form a 4- to 7-membered nitrogenous saturated heterocycle, which may be substituted by an oxo group or a hydroxyl group;

\( R^5 \) and \( R^6 \) each independently represent (1) a hydrogen atom, (2) a \( C_{1-4} \) alkyl group, or (3) a phenyl group;

\( R^7 \) represents (1) a hydrogen atom or (2) a \( C_{1-4} \) alkyl group;

\( R^8 \) represents (1) a hydrogen atom, (2) a \( C_{1-4} \) alkyl group, (3) a phenyl group, or (4) a benzotriazolyl group; \( R^9 \) represents (1) a hydrogen atom or (2) a \( C_{1-4} \) alkyl group;

\( R^{10} \) and \( R^{11} \) each independently represent (1) a hydrogen atom or (2) a \( C_{1-4} \) alkyl group;\n
\( n \) represents an integer from 0 to 4;

\( m \) represents an integer from 0 to 2; and when \( n \) is two or more, the \( R^i \)’s may be the same as each other or may differ from one another).

[00536] In an exemplary embodiment, the BTK inhibitor is a compound of Formula (XXVIII-A):

or a pharmaceutically acceptable salt, hydrate, solvate, cocystal, or prodrug thereof, wherein

\( R^1 \) represents (1) a halogen atom, (2) a \( C_{1-4} \) alkyl group, (3) a \( C_{1-4} \) alkoxy group, (4) a \( C_{1-4} \) haloalkyl group, or (5) a \( C_{1-4} \) haloalkoxy group;
ring1 represents a benzene, cyclohexane, or pyridine ring, each of which may be substituted by from one to five substituents each independently selected from the group consisting of (1) halogen atoms, (2) C\textsubscript{1-4} alkyl groups, (3) C\textsubscript{1-4} alkoxy groups, (4) nitrile, (5) CF\textsubscript{3}.

ring2 represents a 4- to 7-membered nitrogenous saturated heterocycle, which may be substituted by from one to three –K–R\textsuperscript{2}; wherein K represents (1) a bond, (2) a C\textsubscript{1-4} alkylene, (3) –C(O)–, (4) –C(O)–CH\textsubscript{2}–, (5) –CH\textsubscript{2}–C(O)–, (6) –C(O)O–, or (7) –SO\textsubscript{2}– (wherein the bond on the left is bound to the ring2);

R\textsuperscript{2} represents (1) a C\textsubscript{1-4} alkyl, (2) a C\textsubscript{2-4} alkenyl, or (3) a C\textsubscript{2-4} alkynyl group, each of which may be substituted by from one to five substituents each independently selected from the group consisting of (1) NR\textsuperscript{1}R\textsuperscript{1}, (2) halogen atoms, (3) CONR\textsuperscript{3}R\textsuperscript{3}, (4) CO\textsubscript{2}R\textsuperscript{7}, and (5) OR\textsuperscript{5};

R\textsuperscript{3} and R\textsuperscript{4} each independently represent (1) a hydrogen atom, or (2) a C\textsubscript{1-4} alkyl group which may be substituted by OR\textsuperscript{9} or CONR\textsuperscript{10}R\textsuperscript{11}; R\textsuperscript{3} and R\textsuperscript{4} may, together with the nitrogen atom to which they are bound, form a 4- to 7-membered nitrogenous saturated heterocycle, which may be substituted by an oxo group or a hydroxyl group;

R\textsuperscript{5} and R\textsuperscript{6} each independently represent (1) a hydrogen atom, (2) a C\textsubscript{1-4} alkyl group, or (3) a phenyl group;

R\textsuperscript{7} represents (1) a hydrogen atom or (2) a C\textsubscript{1-4} alkyl group;

R\textsuperscript{8} represents (1) a hydrogen atom, (2) a C\textsubscript{1-4} alkyl group, (3) a phenyl group, or (4) a benzotriazolyl group; R\textsuperscript{9} represents (1) a hydrogen atom or (2) a C\textsubscript{1-4} alkyl group;

R\textsuperscript{10} and R\textsuperscript{11} each independently represent (1) a hydrogen atom or (2) a C\textsubscript{1-4} alkyl group;

n represents an integer from 0 to 4;

m represents an integer from 0 to 2; and

when n is two or more, the R\textsuperscript{1}’s may be the same as each other or may differ from one another).

[00537] In an embodiment, the BTK inhibitor is a compound of Formula (XXVIII-B):
or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, or a hydrochloride salt thereof. The preparation of this compound is described in International Patent Application Publication No. WO 2013/081016 A1. In an embodiment, the BTK inhibitor is 6-amino-9-(1-(but-2-ynoyl)pyrrolidin-3-yl)-7-(4-phenoxyphenyl)-7,9-dihydro-8H-purin-8-one or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, or a hydrochloride salt thereof. In an embodiment, the BTK inhibitor is 6-amino-9-[(3S)-1-(2-butynoyl)-3-pyrrolidinyl]-7-(4-phenoxyphenyl)-7,9-dihydro-8H-purin-8-one or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, or a hydrochloride salt thereof.

[00538] The R-enantiomer of Formula (XXVIII-B) is also known as ONO-4059, and is given by Formula (XXVIII-R):
or a pharmaceutically acceptable salt, solvate,hydrate, cocrystal, or prodrug thereof, or a hydrochloride salt thereof.

[00539] In an embodiment, the BTK inhibitor is 6-amino-9-[(3R)-1-(2-butynoyl)-3-pyrrolidinyl]-7-(4-phenoxyphenyl)-7,9-dihydro-8\textit{H}-purin-8-one or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, or a hydrochloride salt thereof.

[00540] The preparation of Formula (XXVIII-R) is described in International Patent Application Publication No. WO 2013/081016 A1. In brief, the BTK inhibitor of Formula (XXVIII-R) can be prepared by the following procedure.

[00541] Step 1: A solution of dibenzylamine (10.2 g) in dichloromethane (30 mL) is dripped into a solution of 4,6-dichloro-5-nitropyrimidine (10 g) in dichloromethane (70 mL) on an ice bath. Then triethylamine (14.4 mL) is added, and the mixture is stirred for 1 hour. Water is added to the reaction mixture, the organic layer is washed with a saturated aqueous sodium chloride solution and dried over anhydrous sodium sulfate, and the solvent is concentrated under reduced pressure to obtain \(N,N\)-dibenzyl-6-chloro-5-nitropyrimidine-4-amine (19.2 g).

[00542] Step 2: The compound prepared in Step 1 (19 g) and tert-butyl (3R)-3-aminopyrrolidine-1-carboxylate (10.5 g) are dissolved in dioxane (58 mL). Triethylamine (8.1 mL) is added, and the mixture is stirred for 5 hours at 50°C. The reaction mixture is returned to
room temperature, the solvent is distilled off, water is added, and extraction is performed with ethyl acetate. The organic layer is washed with saturated aqueous sodium chloride solution, then dried over anhydrous sodium sulfate, and the solvent is distilled off. The residue is purified by silica gel column chromatography to obtain tert-butyl (3R)-3-[[6-(dibenzylamino)-5-nitropyrimidin-4-yl]amino]pyrrolidine-1-carboxylate (1.3 g).

[00543] Step 3: An ethyl acetate (360 mL) solution of the compound prepared in Step 2 (17.5 g) is dripped into a mixture of zinc (23.3 g) and a 3.0 M aqueous ammonium chloride solution (11.4 g) on an ice bath, and the temperature is immediately raised to room temperature. After stirring for 2 hours, the reaction mixture is filtered through CELITE and the solvent is distilled off. The residue is purified by silica gel column chromatography to obtain tert-butyl (3R)-3-[[5-amino-6-(dibenzylamino)pyrimidin-4-yl]amino]pyrrolidine-1-carboxylate (12.4 g).

[00544] Step 4: The compound prepared in Step 3 (8.4 g) and 1,1'-carbonyl diimidazole (5.9 g) are dissolved in tetrahydrofuran (120 mL) and the solution is stirred for 15 hours at 60°C. The solvent is distilled off from the reaction mixture, water is added, and extraction with ethyl acetate is performed. The organic layer is washed with saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and the solvent is distilled off. The residue is purified by silica gel column chromatography to obtain tert-butyl (3R)-3-[6-(dibenzylamino)-8-oxo-7,8-dihydro-9H-purin-9-yl]pyrrolidine-1-carboxylate (7.8 g).

[00545] Step 5: The compound prepared in Step 4 (7.8 g) is dissolved in methanol (240 mL) and ethyl acetate (50 mL), 20% Pearlman's catalyst (Pd(OH)₂/C) (8.0 g, 100 wt %) is added, hydrogen gas replacement is carried out, and stirring is performed for 7.5 hours at 60°C. The reaction mixture is filtered through CELITE and the solvent is distilled off to obtain tert-butyl (3R)-3-(6-amino-8-oxo-7,8-dihydro-9H-purin-9-yl)pyrrolidine-1-carboxylate (5.0 g).

[00546] Step 6: At room temperature p-phenoxy phenyl boronic acid (2.1 g), copper(II) acetate (1.48 g), molecular sieve 4A (2.5 g), and pyridine (0.82 mL) are added to a dichloromethane suspension (200 mL) of the compound prepared in Step 5 (2.5 g), followed by stirring for 21 hours. The reaction mixture is filtered through CELITE and the residue is purified by silica gel column chromatography to obtain tert-butyl (3R)-3-[6-amino-8-oxo-7-(4-phenoxyphenyl)-7,8-dihydro-9H-purin-9-yl]pyrrolidine-1-carboxylate (1.3 g).
Step 7: At room temperature 4 N HCl/dioxane (13 mL) is added to a methanol (13 mL) suspension of the compound prepared in Step 6 (1.3 g 2.76 mmol, 1.0 equivalent), and the mixture is stirred for 1 hour. The solvent is then distilled off to obtain (3R)-6-amino-9-pyrrolidin-3-yl-7-(4-phenoxyphenyl)-7,9-dihydro-8H-purin-8-one dihydrochloride (1.5 g).

Step 8: After 2-butylnoic acid (34 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC) (78 mg), 1-hydroxybenzotriazole (HOBt) (62 mg), and triethylamine (114 mL) are added to a solution of the compound prepared in Step 7 (100 mg) in dimethyl formamide (3 mL), the mixture is stirred at room temperature for 3 hours. Water is added to the reaction mixture and extraction with ethyl acetate is performed. The organic layer is washed with saturated sodium carbonate solution and saturated aqueous sodium chloride solution, then dried over anhydrous sodium sulfate, and the solvent is distilled off. The residue is purified by thin layer chromatography (dichloromethane:methanol:28% ammonia water=90:10:1) to obtain 6-amino-9-[(3R)-1-(2-butylnoyl)-3-pyrrolidinyl]-7-(4-phenoxyphenyl)-7,9-dihydro-8H-purin-8-one (Formula (XXVIII-R)) (75 mg).

The hydrochloride salt of the compound of Formula (XXVIII-R) can be prepared as follows: 6-amino-9-[(3R)-1-(2-butylnoyl)-3-pyrrolidinyl]-7-(4-phenoxyphenyl)-7,9-dihydro-8H-purin-8-one (3.0 g) (which may be prepared as described above) is placed in a 300 mL 3-neck pear-shaped flask, ethyl acetate (30 mL) and 1-propanol (4.5 mL) are added, and the external temperature is set at 70°C (internal temperature 61°C). After it is confirmed that the compound prepared in Step 8 has dissolved completely, 10% HCl/methanol (3.5 mL) is added, and after precipitation of crystals is confirmed, the crystals are ripened by the following sequence: external temperature 70°C for 30 min, external temperature 60°C for 30 min, external temperature 50°C for 60 min, external temperature 40°C for 30 min, room temperature for 30 min, and an ice bath for 30 min. The resulting crystals are filtered, washed with ethyl acetate (6 mL), and dried under vacuum at 50°C to obtain white crystals of 6-amino-9-[(3R)-1-(2-butylnoyl)-3-pyrrolidinyl]-7-(4-phenoxyphenyl)-7,9-dihydro-8H-purin-8-one hydrochloride (2.76 g).

In an embodiment, the BTK inhibitor is a compound selected from the structures disclosed in U.S. Patent Application Publication No. US 2014/0330015 A1, the disclosure of which is incorporated by reference herein.

In an embodiment, the BTK inhibitor is a compound of Formula (B):
or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, or a hydrochloride salt thereof, wherein:

X-Y-Z is N-C-C and R² is present, or C-N-N and R² is absent;

R¹ is a 3-8 membered, N-containing ring, wherein the N is unsubstituted or substituted with R⁴;

R² is H or lower alkyl, particularly methyl, ethyl, propyl or butyl; or

R¹ and R² together with the atoms to which they are attached, form a 4-8 membered ring, preferably a 5-6 membered ring, selected from cycloalkyl, saturated or unsaturated heterocycle, aryl, and heteroaryl rings unsubstituted or substituted with at least one substituent L-R⁴;

R³ is in each instance, independently halogen, alkyl, S-alkyl, CN, or OR⁵;

n is 1, 2, 3, or 4, preferably 1 or 2;

L is a bond, NH, heteroalkyl, or heterocyclyl;

R⁴ is COR', CO₂R', or SO₂R', wherein R' is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl;

R⁵ is H or unsubstituted or substituted heteroalkyl, alkyl, cycloalkyl, saturated or unsaturated heterocyclyl, aryl, or heteroaryl.

[00552] In some embodiments, the BTK inhibitor is one of the following particular embodiments of Formula B:
X--Y--Z is C--N--N and R\textsuperscript{2} is absent; and R\textsuperscript{1} is 3-8 membered, N-containing ring, N-substituted with R\textsuperscript{4};

X--Y--Z is N--C--C and R\textsuperscript{2} is present, R\textsuperscript{1} is 3-8 membered, N-containing ring, N-substituted with R\textsuperscript{4}; and R\textsuperscript{3} is H or lower alkyl;

X--Y--Z is N--C--C and R\textsuperscript{2} is present; and R\textsuperscript{1} and R\textsuperscript{2} together with the atoms to which they are attached, form a 4-8 membered ring selected from cycloalkyl, saturated or unsaturated heterocycle, aryl, and heteroaryl rings unsubstituted or substituted with at least one substituent L-R\textsuperscript{4}, wherein preferred rings of R\textsuperscript{1} and R\textsuperscript{2} are 5-6-membered, particularly dihydropyrrrole, tetrahydropyridine, tetrahydroazepine, phenyl, or pyridine;

X--Y--Z is N--C--C and R\textsuperscript{2} is present; and R\textsuperscript{1} and R\textsuperscript{2} together with the atoms to which they are attached, form a 5-6 membered ring, preferably (a) phenyl substituted with a single -L-R\textsuperscript{4}, or (b) dihydropyrrrole or tetrahydropyridine, N-substituted with a single -L-R\textsuperscript{4} wherein L is bond;

R\textsuperscript{1} is piperidine or azaspiro[3.3]heptane, preferably N-substituted with R\textsuperscript{4};

R\textsuperscript{2} is COR' or SO\textsubscript{2}R', particularly wherein R' is substituted or unsubstituted alkenyl, particularly substituted or unsubstituted ethenyl; or

R\textsuperscript{3} is unsubstituted or substituted alkyl or aryl, particularly substituted or unsubstituted phenyl or methyl, such as cyclopropyl-substituted methyl with or tetrabutyl-substituted phenyl.

[00553] In some embodiments, the BTK inhibitor is one of the following particular embodiments of Formula B:

R\textsuperscript{1} is piperidine or azaspiro[3.3]heptane, N-substituted with R\textsuperscript{4}, wherein R\textsuperscript{2} is H, COR' or SO\textsubscript{2}R', and R\textsuperscript{1} is substituted or unsubstituted alkenyl, particularly substituted or unsubstituted ethenyl;

R\textsuperscript{3} is –OR\textsuperscript{5}, R\textsuperscript{4} is phenyl, and n is 1;

R\textsuperscript{1} and R\textsuperscript{2}, together with the atoms to which they are attached, form a 5-6 membered ring, preferably (a) phenyl substituted with a single -L-R\textsuperscript{4}, or (b) dihydropyrrrole or
tetrahydropyridine, N-substituted with a single -L-R 4 wherein L is bond; R 3 is –OR 5; n is 1; R 4 is COR’, and R’ is ethenyl; and R 5 is phenyl; and

X--Y--Z is C--N--N and R 2 is absent; R 1 is piperidine, N-substituted with R 4; R 3 is –OR 5; n is 1; R 4 is COR’, and R’ is unsubstituted or substituted alkenyl, particularly ethenyl; and R 5 is substituted or unsubstituted aryl, particularly phenyl.

[00554] In an exemplary embodiment, the BTK inhibitor is a compound of Formula (B1), Formula (B1-2), or Formula (B1-3):
or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, or a hydrochloride salt thereof. Formula (B1-2) is also known as BGB-3111. The preparation of these compounds is described in International Patent Application Publication No. WO 2014/173289 A1 and U.S. Patent Application Publication No. US 2015/0005277 A1.

[00555] In brief, the BTK inhibitor of Formula (B1) can be prepared by the following procedure.
Step 1. Preparation of 2-(hydroxy(4-phenoxyphenyl)methylene)malononitrile:

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\begin{equation}
\text{NC\raisebox{-5.5mm}{\text{O}}\raisebox{1.5mm}{\text{C}} - \text{CN}}
\end{equation}
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A solution of 4-phenoxybenzoic acid (300 g, 1.4 mol) in SOCl₂ (1.2 L) is stirred at 80°C under N₂ for 3 hours. The mixture is concentrated in vacuum to give the intermediate (315 g) which is used for next step without further purification.

To a solution of propanedinitrile (89.5 g, 1355 mmol) and DIEA (350 g, 2710 mmol) in THF (800 mL) is dropwise a solution of the intermediate (315 g) in toluene (800 mL) at 0-5°C over 2 hours. The resultant mixture is allowed to warm to RT and stirred for 16 hours. The reaction is quenched with water (2.0 L) and extracted with EA (2.0 L x 3). The combined organic layers are washed with 1000 mL of 3 N HCl aqueous solution, brine (2.0 L x 3), dried over Na₂SO₄ and concentrated to give the crude product (330 g, 93%).

Step 2. Preparation of 2-(methoxy(4-phenoxyphenyl)methylene)malononitrile:

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\begin{equation}
\text{NC\raisebox{-5.5mm}{\text{O}}\raisebox{1.5mm}{\text{C}} - \text{CN}}
\end{equation}
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A solution of 2-(hydroxy(4-phenoxyphenyl)methylene)malononitrile (50 g, 190.8 mmol) in CH(OMe)₃ (500 mL) is heated to 75°C for 16 hours. Then the mixture is concentrated to a residue and washed with MeOH (50 mL) to give 25 g (47.5%) of 2-(methoxy(4-phenoxyphenyl)methylene)malononitrile as a yellow solid.

Step 3. Preparation of 5-amino-3-(4-phenoxyphenyl)-1H-pyrazole-4-carbonitrile:
To a solution of 2-(methoxy(4-phenoxyphenyl)methylene)malononitrile (80 g, 290 mmol) in ethanol (200 mL) is added hydrazine hydrate (20 mL). The mixture is stirred at RT for 16 hours then is concentrated to give the crude product and washed with MeOH (30 mL) to afford 55 g (68.8%) of 5-amino-3-(4-phenoxyphenyl)-1H-pyrazole-4-carbonitrile as a off-white solid.

Step 4. Preparation of tert-butyl 3-(tosyloxy)piperidine-1-carboxylate:

To a solution of tert-butyl 3-hydroxypiperidine-1-carboxylate (1.05 g, 5.0 mmol) in pyridine (8 mL) is added TsCl (1.425 g, 7.5 mmol). The mixture is stirred at RT under N₂ for two days. The mixture is concentrated and partitioned between 100 mL of EA and 100 mL of HCl (1 N) aqueous solution. The organic layer is separated from aqueous layer, washed with saturated NaHCO₃ aqueous solution (100 mL × 2), brine (100 mL × 3) and dried over Na₂SO₄. The organic layer is concentrated to afford 1.1 g (60%) of tert-butyl 3-(tosyloxy)piperidine-1-carboxylate as a colorless oil.

Step 5. Preparation of tert-butyl 3-(5-amino-4-cyano-3-(4-phenoxyphenyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate:
To a solution of tert-butyl 3-(tosyloxy)piperidine-1-carboxylate (355 mg, 1.0 mmol) and 5-amino-3-(4-phenoxyphenyl)-1H-pyrazole-4-carbonitrile (276 mg, 1.0 mmol) in 5 mL of DMF is added Cs₂CO₃ (650 mg, 2.0 mmol). The mixture is stirred at RT for 16 hours, 75°C for 3 hours and 60°C for 16 hours. The mixture is concentrated washed with brine (100 mL × 3) and dried over Na₂SO₄. The material is concentrated and purified by chromatography column on silica gel (eluted with petroleum ether/ethyl acetate = 3/1) to afford 60 mg (13%) of tert-butyl 3-(5-amino-4-cyano-3-(4-phenoxyphenyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate as a yellow oil.

Step 6. Preparation of tert-butyl 3-(5-amino-4-carbamoyl-3-(4-phenoxyphenyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate:

To a solution of tert-butyl 3-(5-amino-4-cyano-3-(4-phenoxyphenyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (100 mg, 0.22 mmol) in DMSO (2 mL) and ethanol (2 mL) was added the solution of NaOH (200 mg, 5 mmol) in water (1 mL) and H₂O₂ (1 mL). The mixture is stirred at 60°C for 15 min and concentrated to remove EtOH, after which 10 mL of water and 50 mL of ethyl acetate are added. The organic layer is separated from aqueous layer, washed with brine (30 mL × 3) and dried over Na₂SO₄. After concentration, 50 mg of residue is used
directly in the next step, wherein 50 mg of residue is purified by pre-TLC (eluted with petroleum ether/ethyl acetate = 1/1) to afford 12 mg (30%) of tert-butyl 3-(5-amino-4-carbamoyl-3-(4-phenoxyphenyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate as a white solid.

[00569] Step 7. Preparation of 5-amino-3-(4-phenoxyphenyl)-1-(piperidin-3-yl)-1H-pyrazole-4-carboxamide:

[00570] To a solution of tert-butyl 3-(5-amino-4-carbamoyl-3-(4-phenoxyphenyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (50 mg, 0.11 mmol) in ethyl acetate (1 mL) is added concentrated HCl (0.75 mL). The mixture is stirred at RT for 1 hour. Then saturated NaHCO₃ is added until pH > 7, followed by ethyl acetate (50 mL). Organic layer is separated from aqueous layer, washed with brine (50 mL × 3) and dried over Na₂SO₄. Concentrated and purified by Pre-TLC (eluted with dichloromethane/MeOH/NH₃•H₂O=5/1/0.01) to afford 10 mg (25%) of 5-amino-3-(4-phenoxyphenyl)-1-(piperidin-3-yl)-1H-pyrazole-4-carboxamide as a white solid.

[00571] Step 8. Preparation of 1-(1-acryloylpiperidin-3-yl)-5-amino-3-(4-phenoxyphenyl)-1H-pyrazole-4-carboxamide:
[00572] To a solution of 5-amino-3-(4-phenoxyphenyl)-1-(piperidin-3-yl)-1H-pyrazole-4-carboxamide (63 mg, 0.17 mmol) in dichloromethane (4 mL) is added pyridine (27 mg, 0.34 mmol). Then a solution of acryloyl chloride (12 mg, 0.17 mmol) in dichloromethane (1 mL) was added dropwise. After stirring at RT for 4 hours, the mixture is partitioned between 100 mL of dichloromethane and 100 mL of brine. Organic layer is separated from aqueous layer, washed with brine (100 mL \( \times \) 2) and dried over Na₂SO₄. Concentrated and purified by Pre-TLC (eluted with dichloromethane/MeOH=10/1) to afford 4 mg (5.5%) of 1-(1-acryloylpiperidin-3-yl)-5-amino-3-(4-phenoxyphenyl)-1H-pyrazole-4-carboxamide as a white solid.

[00573] The enantiomers of Formula (B1) provided by the procedure above may be prepared from 5-amino-3-(phenoxyphenyl)-1H-pyrazole-4-carbonitrile and (S)-tert-butyl 3-hydroxypiperidine-1-carboxylate using a similar procedure (step 4 to 8) for Formula (B1-2), or from (R)-tert-butyl 3-hydroxypiperidine-1-carboxylate using a similar procedure (step 4 to 8) for Formula (B1-3). Under appropriate conditions recognized by one of ordinary skill in the art, a racemic mixture of Formula (B1) may be separated by chiral HPLC, the crystallization of chiral salts, or other means described above to yield Formula (B1-2) and Formula (B1-3) of high enantiomeric purity.

[00574] In an embodiment, the BTK inhibitor is a compound selected from the structures disclosed in U.S. Patent Application Publication No. US 2015/0005277A1, the disclosure of which is incorporated by reference herein.

[00575] BTK inhibitors suitable for use in the described combination with a PI3K inhibitor, a PI3K-\( \gamma \) inhibitor, and/or a PI3K-\( \delta \) inhibitor also include, but are not limited to, those described in, for example, International Patent Application Publication Nos. WO 2013/010868, WO 2012/158843, WO 2012/135944, WO 2012/135937, U.S. Patent Application Publication No. 2011/0177011, and U.S. Patent Nos. 8,501,751, 8,476,284, 8,008,309, 7,960,396, 7,825,118, 7,732,454, 7,514,444, 7,459,554, 7,405,295, and 7,393,848, the disclosures of each of which are incorporated herein by reference.

**JAK-2 Inhibitors**

[00576] In some embodiments, the compositions and methods described include a JAK inhibitor or a JAK-2 inhibitor. In some embodiments, the compounds provided herein are selective for
JAK-2, in that the compounds bind or interact with JAK-2 at substantially lower concentrations than they bind or interact with other JAK receptors, including the JAK-3 receptor. In certain embodiments, the compounds bind to the JAK-3 receptor at a binding constant at least about a 2-fold higher concentration, about a 3-fold higher concentration, about a 5-fold higher concentration, about a 10-fold higher concentration, about a 20-fold higher concentration, about a 30-fold higher concentration, about a 50-fold higher concentration, about a 100-fold higher concentration, about a 200-fold higher concentration, about a 300-fold higher concentration, or about a 500-fold higher concentration.

[00577] In an embodiment, the JAK-2 inhibitor is a compound of Formula (XXIX):

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Y)n——Z
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including a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, wherein:

A<sup>1</sup> and A<sup>2</sup> are independently selected from C and N;

T, U, and V are independently selected from O, S, N, CR<sup>5</sup>, and NR<sup>6</sup>;

wherein the 5-membered ring formed by A<sup>1</sup>, A<sup>2</sup>, U, T, and V is aromatic;

X is N or CR<sup>4</sup>;

Y is C<sub>1-8</sub> alkyne, C<sub>2-8</sub> alkenylene, C<sub>2-8</sub> alkynylene, (CR<sup>11</sup>R<sup>12</sup>)<sub>p</sub>—(C<sub>3-10</sub> cycloalkylene)-(CR<sup>11</sup>R<sup>12</sup>)<sub>q</sub>, (CR<sup>11</sup>R<sup>12</sup>)<sub>p</sub>—(arylene)-(CR<sup>11</sup>R<sup>12</sup>)<sub>q</sub>, (CR<sup>11</sup>R<sup>12</sup>)<sub>p</sub>—(C<sub>1-10</sub> heterocycloalkylene)-(CR<sup>11</sup>R<sup>12</sup>)<sub>q</sub>, (CR<sup>11</sup>R<sup>12</sup>)<sub>p</sub>—(heteroarylene)-(CR<sup>11</sup>R<sup>12</sup>)<sub>q</sub>, (CR<sup>11</sup>R<sup>12</sup>)<sub>p</sub>—O(CR<sup>11</sup>R<sup>12</sup>)<sub>q</sub>, (CR<sup>11</sup>R<sup>12</sup>)<sub>p</sub>—S(CR<sup>11</sup>R<sup>12</sup>)<sub>q</sub>, (CR<sup>11</sup>R<sup>12</sup>)<sub>p</sub>C(O)(CR<sup>11</sup>R<sup>12</sup>)<sub>q</sub>, (CR<sup>11</sup>R<sup>12</sup>)<sub>p</sub>C(O)NR<sup>2</sup>(CR<sup>11</sup>R<sup>12</sup>)<sub>q</sub>.
(CR\(^1\)R\(^{12}\)\(_p\)C(O)O(CR\(^1\)R\(^{12}\)\(_q\)), (CR\(^1\)R\(^{12}\)\(_p\)OC(O)(CR\(^1\)R\(^{12}\)\(_q\)), (CR\(^1\)R\(^{12}\)\(_p\)OC(O)NR\(^q\))(CR\(^1\)R\(^{12}\)\(_q\)), (CR\(^1\)R\(^{12}\)\(_p\)NR\(^q\)(CR\(^1\)R\(^{12}\)\(_q\)h)S(O)(CR\(^1\)R\(^{12}\)\(_q\)), (CR\(^1\)R\(^{12}\)\(_p\)S(O)(CR\(^1\)R\(^{12}\)\(_q\)), or (CR\(^1\)R\(^{12}\)\(_p\)S(O)NR\(^q\)(CR\(^1\)R\(^{12}\)\(_q\)), wherein said C\(_{1-8}\) alkylene, C\(_{2-8}\) alkenylene, cycloalkylene, arylene, heterocycloalkylene, or heteroarylene, is optionally substituted with 1, 2, or 3 substituents independently selected from -D\(^1\)-D\(^2\)-D\(^3\);

Z is H, halo, C\(_{1-4}\) alkyl, C\(_{2-4}\) alkenyl, C\(_{2-4}\) alkynyl, C\(_{1-4}\) haloalkyl, halosulfanyl, C\(_{1-4}\) hydroxyalkyl, C\(_{1-4}\) cyanoalkyl, \(=\)C—R\(^1\), \(=\)N—R\(^1\), Cy\(^1\), CN, NO\(_2\), OR\(^1\), S\(^1\), C(O)R\(^1\), C(O)NR\(^1\), C(O)OR\(^1\), OC(O)R\(^1\), OC(O)NR\(^2\), NR\(^2\), NR\(^2\)C(O)R\(^3\), NR\(^2\)C(O)NR\(^3\), NR\(^2\)C(O)OR\(^3\), C(=NR\(^3\)R\(^4\)), NR\(^3\)C(=NR\(^3\)R\(^4\)), S(O)R\(^5\), S(O)NR\(^5\), S(O)OR\(^5\), NR\(^5\)S(O)R\(^2\), C(=NOH)R\(^2\), C(=NO(C\(_{1-6}\) alkyl)R\(^2\), and S(O)NR\(^5\)R\(^4\), wherein said C\(_{1-8}\) alkyl, C\(_{2-8}\) alkenyl, or C\(_{2-8}\) alkynyl, is optionally substituted with 1, 2, 3, 4, 5, or 6 substituents independently selected from halo, C\(_{1-4}\) alkyl, C\(_{2-4}\) alkenyl, C\(_{2-4}\) alkynyl, C\(_{1-4}\) haloalkyl, halosulfanyl, C\(_{1-4}\) hydroxyalkyl, C\(_{1-4}\) cyanoalkyl, Cy\(^1\), CN, NO\(_2\), OR\(^1\), S\(^1\), C(O)R\(^1\), C(O)NR\(^1\), C(O)OR\(^1\), OC(O)R\(^1\), OC(O)NR\(^2\), NR\(^2\), NR\(^2\)C(O)R\(^3\), NR\(^2\)C(O)NR\(^3\), NR\(^2\)C(O)OR\(^3\), C(=NR\(^3\)R\(^4\)), NR\(^3\)C(=NR\(^3\)R\(^4\)), S(O)R\(^5\), S(O)NR\(^5\), S(O)OR\(^5\), NR\(^5\)S(O)R\(^2\), C(=NOH)R\(^2\), C(=NO(C\(_{1-6}\) alkyl)R\(^2\), and S(O)NR\(^5\)R\(^4\);

wherein when Z is H, n is 1;

or the —(Y)—Z moiety is taken together with i) A\(^2\) to which the moiety is attached, ii) R\(^3\) or R\(^6\) of either T or V, and iii) the C or N atom to which the R\(^3\) or R\(^6\) of either T or V is attached to form a 4- to 20-membered aryl, cycloalkyl, heteroaryl, or heterocycloalkyl ring fused to the 5-membered ring formed by A\(^1\), A\(^2\), U, T, and V, wherein said 4- to 20-membered aryl, cycloalkyl, heteroaryl, or heterocycloalkyl ring is optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from —(W)\(_m\)—Q;

W is C\(_{1-8}\) alkyl, C\(_{2-8}\) alkenyl, C\(_{2-8}\) alkynyl, O, S, C(O), C(O)NR\(^3\), C(O)O, OC(O), OC(O)NR\(^3\), NR\(^3\), NR\(^3\)C(O)NR\(^3\), S(O), S(O)NR\(^3\), S(O)\(_2\), or S(O)\(_2\)NR\(^3\);

Q is H, halo, CN, NO\(_2\), C\(_{1-4}\) alkyl, C\(_{2-8}\) alkenyl, C\(_{2-8}\) alkynyl, C\(_{1-8}\) haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl, wherein said C\(_{1-8}\) alkyl, C\(_{2-8}\) alkenyl, C\(_{2-8}\) alkynyl, C\(_{1-8}\) haloalkyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted with

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1, 2, 3 or 4 substituents independently selected from halo, C\textsubscript{1-4} alkyl, C\textsubscript{2-4} alkenyl, C\textsubscript{2-4} alkylnyl, C\textsubscript{1-4} haloalkyl, halosulfanyl, C\textsubscript{1-4} hydroxyalkyl, C\textsubscript{1-4} cyanoalkyl, Cy\textsuperscript{1}, CN, NO\textsubscript{2}, OR\textsuperscript{a}, SR\textsuperscript{a}, C(O)R\textsuperscript{b}, C(O)NR\textsuperscript{b}R\textsuperscript{c}, CO(O)R\textsuperscript{d}, OC(O)NR\textsuperscript{e}R\textsuperscript{f}, NR\textsuperscript{g}C(O)R\textsuperscript{h}, NR\textsuperscript{g}C(O)NR\textsuperscript{h}R\textsuperscript{i}, NR\textsuperscript{g}C(O)OR\textsuperscript{i}, S(O)R\textsuperscript{j}, S(O)NR\textsuperscript{k}R\textsuperscript{l}, S(O)\textsubscript{2}R\textsuperscript{l}, NR\textsuperscript{m}S(O)R\textsuperscript{n}, and S(O)\textsubscript{2}NR\textsuperscript{m}R\textsuperscript{n}.

Cy\textsuperscript{1} and Cy\textsuperscript{2} are independently selected from aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, each optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from halo, C\textsubscript{1-4} alkyl, C\textsubscript{2-4} alkenyl, C\textsubscript{2-4} alkylnyl, C\textsubscript{1-4} haloalkyl, halosulfanyl, C\textsubscript{1-4} hydroxyalkyl, C\textsubscript{1-4} cyanoalkyl, CN, NO\textsubscript{2}, OR\textsuperscript{a}, SR\textsuperscript{a}, C(O)R\textsuperscript{b}, C(O)NR\textsuperscript{b}R\textsuperscript{c}, C(O)OR\textsuperscript{d}, OC(O)R\textsuperscript{e}, OC(O)NR\textsuperscript{f}R\textsuperscript{g}, NR\textsuperscript{h}C(O)R\textsuperscript{i}, NR\textsuperscript{h}C(O)OR\textsuperscript{i}, NR\textsuperscript{h}S(O)R\textsuperscript{j}, NR\textsuperscript{h}S(O)NR\textsuperscript{k}R\textsuperscript{l}, S(O)\textsubscript{2}R\textsuperscript{l}, and S(O)\textsubscript{2}NR\textsuperscript{m}R\textsuperscript{n}.

R\textsuperscript{1}, R\textsuperscript{2}, R\textsuperscript{3}, and R\textsuperscript{4} are independently selected from H, halo, C\textsubscript{1-4} alkyl, C\textsubscript{2-4} alkenyl, C\textsubscript{2-4} alkylnyl, C\textsubscript{1-4} haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO\textsubscript{2}, OR\textsuperscript{a}, SR\textsuperscript{a}, C(O)R\textsuperscript{b}, C(O)NR\textsuperscript{b}R\textsuperscript{c}, C(O)OR\textsuperscript{d}, OC(O)R\textsuperscript{e}, OC(O)NR\textsuperscript{f}R\textsuperscript{g}, NR\textsuperscript{h}C(O)R\textsuperscript{i}, NR\textsuperscript{h}C(O)OR\textsuperscript{i}, NR\textsuperscript{h}S(O)R\textsuperscript{j}, NR\textsuperscript{h}S(O)NR\textsuperscript{k}R\textsuperscript{l}, S(O)\textsubscript{2}R\textsuperscript{l}, SR\textsuperscript{a}, and S(O)\textsubscript{2}NR\textsuperscript{m}R\textsuperscript{n}.

R\textsuperscript{5} is H, halo, C\textsubscript{1-4} alkyl, C\textsubscript{2-4} alkenyl, C\textsubscript{2-4} alkylnyl, C\textsubscript{1-4} haloalkyl, halosulfanyl, CN, NO\textsubscript{2}, OR\textsuperscript{a}, SR\textsuperscript{a}, C(O)R\textsuperscript{b}, C(O)NR\textsuperscript{b}R\textsuperscript{c}, C(O)OR\textsuperscript{d}, OC(O)R\textsuperscript{e}, OC(O)NR\textsuperscript{f}R\textsuperscript{g}, NR\textsuperscript{h}C(O)R\textsuperscript{i}, NR\textsuperscript{h}C(O)OR\textsuperscript{i}, NR\textsuperscript{h}S(O)R\textsuperscript{j}, NR\textsuperscript{h}S(O)NR\textsuperscript{k}R\textsuperscript{l}, S(O)\textsubscript{2}R\textsuperscript{l}, NR\textsuperscript{g}C(O)R\textsuperscript{h}, S(O)\textsubscript{2}NR\textsuperscript{m}R\textsuperscript{n}, or S(O)\textsubscript{2}NR\textsuperscript{m}R\textsuperscript{n};

R\textsuperscript{6} is H, C\textsubscript{1-4} alkyl, C\textsubscript{2-4} alkenyl, C\textsubscript{2-4} alkylnyl, C\textsubscript{1-4} haloalkyl, halosulfanyl, OR\textsuperscript{a}, C(O)R\textsuperscript{b}, C(O)NR\textsuperscript{b}R\textsuperscript{c}, C(O)OR\textsuperscript{d}, S(O)\textsubscript{2}R\textsuperscript{l}, S(O)\textsubscript{2}NR\textsuperscript{m}R\textsuperscript{n}, or S(O)\textsubscript{2}NR\textsuperscript{m}R\textsuperscript{n};

R\textsuperscript{7} is H, C\textsubscript{1-6} alkyl, C\textsubscript{1-6} haloalkyl, C\textsubscript{2-6} alkenyl, C\textsubscript{2-6} alkylnyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl or heterocycloalkylalkyl;

R\textsuperscript{8} is H, C\textsubscript{1-6} alkyl, C\textsubscript{1-6} haloalkyl, C\textsubscript{2-6} alkenyl, C\textsubscript{2-6} alkylnyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl or heterocycloalkylalkyl;

R\textsuperscript{9} and R\textsuperscript{10} are independently selected from H, C\textsubscript{1-10} alkyl, C\textsubscript{1-4} haloalkyl, C\textsubscript{2-6} alkenyl, C\textsubscript{2-6} alkylnyl, C\textsubscript{1-6} alkylcarbonyl, arylcarbonyl, C\textsubscript{1-6} alkylsulfanyl, arylsulfanyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl and heterocycloalkylalkyl;
or \( R^9 \) and \( R^{10} \) together with the N atom to which they are attached form a 4-, 5-, 6- or 7-membered heterocycloalkyl group;

\( R^{11} \) and \( R^{12} \) are independently selected from H and -E^1-E^2-E^3-E^4;

D^1 and E^1 are independently absent or independently selected from C_{1-6} alkenylene, C_{2-6} alkyne, C_{2-6} alkynylene, C_{2-6} cycloalkylene, arylene, heteroarylene, and heterocycloalkylene, wherein each of the C_{1-6} alkenylene, C_{2-6} alkyne, C_{2-6} alkynylene, aryleno, cycloalkylene, heteroarylene, and heterocycloalkylene is optionally substituted by 1, 2 or 3 substituents independently selected from halo, CN, NO_2, N\_3, SCN, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-8} alkoxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkylamino, and C_{2-8} dialkylamino;

D^2 and E^2 are independently absent or independently selected from C_{1-6} alkenylene, C_{2-6} alkenylene, C_{2-6} alkynylene, (C_{1-4} alkenylene)\_O-(C_{1-6} alkenylene), (C_{1-6} alkenylene)-S-(C_{1-6} alkenylene), (C_{1-6} alkenylene)-NR\_e-(C_{1-6} alkenylene), (C_{1-6} alkenylene)-CO-(C_{1-6} alkenylene), and (C_{1-6} alkenylene)-CONR\_e-(C_{1-6} alkenylene), wherein each of the C_{1-6} alkenylene, C_{2-6} alkynylene, and C_{2-6} alkenylene is optionally substituted by 1, 2 or 3 substituents independently selected from halo, CN, NO_2, N\_3, SCN, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-8} alkoxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkylamino, and C_{2-8} dialkylamino;

D^3 and E^3 are independently absent or independently selected from C_{1-6} alkenylene, C_{2-6} alkenylene, C_{2-6} alkynylene, arylene, cycloalkylene, heteroarylene, and heterocycloalkylene, wherein each of the C_{1-6} alkenylene, C_{2-6} alkynylene, C_{2-6} cycloalkylene, arylene, cycloalkylene, heteroarylene, and heterocycloalkylene is optionally substituted by 1, 2 or 3 substituents independently selected from halo, CN, NO_2, N\_3, SCN, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-8} alkoxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkylamino, and C_{2-8} dialkylamino;

D^4 and E^4 are independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyln, C_{2-6} alkenyl, C_{2-6} alkoxyalkyl, halosulfanyl, C_{1-4} hydroxyalkyl, C_{1-4} cyanoalkyl, Cy\_1, CN, NO_2, OR\_e, SR\_e, C(O)R\_b, C(O)NR\_R\_R\_e, C(O)OR\_e, OC(O)R\_b, OC(O)NR\_R\_R\_e, NR\_R\_R\_e, NR\_R\_C(O)R\_b, NR\_R\_C(O)NR\_R\_R\_e, NR\_R\_C(O)OR\_e, C(=NR\_R\_)NR\_R\_R\_e, NR\_R\_C(=NR\_R\_)NR\_R\_R\_e, S(O)R\_b, S(O)NR\_R\_R\_e, S(O)\_2 R\_b, NR\_R\_S(O)\_2 R\_b, C(=NOH)R\_b, C(=NO)(C_{1-6} alkyl)R\_b, and S(O)\_2 NR\_R\_R\_e, wherein
C_{1-8} alkyl, C_{2-8} alkenyl, or C_{2-8} alkynyl, is optionally substituted with 1, 2, 3, 4, 5, or 6 substituents independently selected from halo, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} haloalkyl, halosulfanyl, C_{1-4} hydroxyalkyl, C_{1-4} cyanoalkyl, Cy, CN, NO_2, OR, SR, C(O)R, C(O)NR, OC(O)R, OC(O)NR, NR-OR, NR-C(OR), NR-C(O)R, NR-C(O)OR, C(=NR)NR, C(=NR)NR, S(O)NR, S(O)NR, S(O)NR, S(O)NR, and S(O)NR.

R is H, Cy, —(C=alkyl)-Cy, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkenyl, C_{1-6} alkynyl, wherein said C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkenyl, or C_{1-6} alkynyl is optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, halosulfanyl, aryl, aryalkyl, heteroaryl, heteroaryalkyl, cycloalkyl, and heterocycloalkyl.

R^b is H, Cy, —(C=alkyl)-Cy, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkenyl, C_{1-6} alkynyl, wherein said C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkenyl, or C_{1-6} alkynyl is optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkyl, halosulfanyl, aryl, aryalkyl, heteroaryl, heteroaryalkyl, cycloalkyl, and heterocycloalkyl.

R^r and R^s are independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkenyl, C_{1-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroaryalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkenyl, C_{1-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, aryalkyl, heteroaryalkyl, cycloalkylalkyl, and heterocycloalkylalkyl is optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, halosulfanyl, aryl, aryalkyl, heteroaryl, heteroaryalkyl, cycloalkyl, and heterocycloalkyl.

R^d and R^e are independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkenyl, C_{1-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, aryalkyl, heteroaryalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkenyl, C_{1-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, aryalkyl, heteroaryalkyl, cycloalkylalkyl, and heterocycloalkylalkyl is optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkyl, halosulfanyl, aryl, aryalkyl, heteroarylalkyl, cycloalkyl, and heterocycloalkyl;
R' and R'' are independently selected from H, Cy, 1-(C\textsubscript{1-6} alkyl)-Cy, C\textsubscript{1-10} alkyl, C\textsubscript{1-6} haloalkyl, C\textsubscript{2-6} alkenyl, C\textsubscript{2-6} alkynyl, wherein said C\textsubscript{1-10} alkyl, C\textsubscript{1-6} haloalkyl, C\textsubscript{2-6} alkenyl, or C\textsubscript{2-6} alkynyl, is optionally substituted with 1, 2, or 3 substituents independently selected from Cy, 1-(C\textsubscript{1-6} alkyl)-Cy, OH, CN, amino, halo, C\textsubscript{1-6} alkyl, C\textsubscript{1-6} haloalkyl, and halosulfanyl; or R’ and R’’ together with the N atom to which they are attached form a 4-, 5-, 6- or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 substituents independently selected from Cy, 1-(C\textsubscript{1-6} alkyl)-Cy, OH, CN, amino, halo, C\textsubscript{1-6} alkyl, C\textsubscript{1-6} haloalkyl, C\textsubscript{1-6} haloalkyl, and halosulfanyl;

R’’’ and R’’’’ are independently selected from H, C\textsubscript{1-10} alkyl, C\textsubscript{1-6} haloalkyl, C\textsubscript{2-6} alkenyl, C\textsubscript{2-6} alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl and heterocycloalkylalkyl, wherein said C\textsubscript{1-10} alkyl, C\textsubscript{1-6} haloalkyl, C\textsubscript{2-6} alkenyl, C\textsubscript{2-6} alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl or heterocycloalkylalkyl is optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C\textsubscript{1-6} alkyl, C\textsubscript{1-6} haloalkyl, C\textsubscript{1-6} haloalkyl, halosulfanyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl and heterocycloalkyl; or R’’’ and R’’’’ together with the N atom to which they are attached form a 4-, 5-, 6- or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C\textsubscript{1-6} alkyl, C\textsubscript{1-6} haloalkyl, C\textsubscript{1-6} haloalkyl, halosulfanyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl and heterocycloalkyl;

R’’’’’ and R’’’’’ are independently selected from H, C\textsubscript{1-10} alkyl, C\textsubscript{1-6} haloalkyl, C\textsubscript{2-6} alkenyl, C\textsubscript{2-6} alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl and heterocycloalkylalkyl, wherein said C\textsubscript{1-10} alkyl, C\textsubscript{1-6} haloalkyl, C\textsubscript{2-6} alkenyl, C\textsubscript{2-6} alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl or heterocycloalkylalkyl is optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C\textsubscript{1-6} alkyl, C\textsubscript{1-6} haloalkyl, halosulfanyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl and heterocycloalkyl; or R’’’’ and R’’’’ together with the N atom to which they are attached form a 4-, 5-, 6- or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 substituents
independently selected from OH, CN, amino, halo, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> haloalkyl, C<sub>1-6</sub> haloalkyl, halosulfanyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl and heterocycloalkyl;

R'<sup>i</sup> is H, CN, NO<sub>2</sub>, or C<sub>1-6</sub> alkyl;

R'<sup>i</sup> and R'<sup>i</sup> are independently selected from H and C<sub>1-6</sub> alkyl;

R'<sup>i</sup> is H, CN, or NO<sub>2</sub>;

m is 0 or 1;

n is 0 or 1;

p is 0, 1, 2, 3, 4, 5, or 6;

q is 0, 1, 2, 3, 4, 5 or 6;

r is 0 or 1; and

s is 0 or 1.

In some embodiments, when X is N, n is 1, and the moiety formed by A'<sup>1</sup>, A'<sup>2</sup>, U, T, V, and — (Y)<sup>n</sup>—Z has the formula:

![Diagram]

then Y is other than (CR'<sup>1</sup>R'<sup>2</sup>)<sub>p</sub>C(O)NR'<sub>2</sub>(CR'<sup>1</sup>R'<sup>2</sup>)<sub>q</sub>.

In some embodiments, when X is N, the 5-membered ring formed by A'<sup>1</sup>, A'<sup>2</sup>, U, T, and V is other than pyrrolyl.

In some embodiments, when X is CH, n is 1, and the moiety formed by A'<sup>1</sup>, A'<sup>2</sup>, U, T, V, and — (Y)<sup>n</sup>—Z has the formula:
then, \( -(Y)_n - Z \) is other than COOH.

In some embodiments, when \( X \) is CH or C-halo, \( R_1 \), \( R_2 \), and \( R_3 \) are each H, \( n \) is 1, and the moiety formed by \( A^1 \), \( A^2 \), \( U \), \( T \), \( V \), and \( -(Y)_n - Z \) has the formula:

\[
(Y)_n - Z
\]

then \( Z \) is other than CN, halo, or C_{1-4} alkyl.

[00578] In some embodiments, when \( X \) is CH or C-halo, \( R_1 \), \( R_2 \), and \( R_3 \) are each H, \( n \) is 0, and the moiety formed by \( A^1 \), \( A^2 \), \( U \), \( T \), \( V \), and \( -(Y)_n - Z \) has the formula:

\[
(Y)_n - Z
\]

then \( Z \) is other than CN, halo, or C_{1-4} alkyl.

[00579] In some embodiments, when \( X \) is CH or C-halo, \( R_1 \), \( R_2 \), and \( R_3 \) are each H, \( n \) is 1, and the moiety formed by \( A^1 \), \( A^2 \), \( U \), \( T \), \( V \), and \( -(Y)_n - Z \) has the formula:
then Y is other than \((\text{CR}^1 \text{R}^2)^p \text{C(O)NR}^c (\text{CR}^1 \text{R}^2)_q\) or \((\text{CR}^1 \text{R}^2)^p \text{C(O)NR}^c (\text{CR}^1 \text{R}^2)_q\).

[00580] In some embodiments, when X is CH or C-halo, \(R^1, R^2,\) and \(R^3\) are each H, n is 1, and the moiety formed by \(A^1, A^2, U, T, V,\) and \(-(Y)_n-Z\) has the formula:

then Y is other than \((\text{CR}^1 \text{R}^2)^p N^e R^c (\text{CR}^1 \text{R}^2)_q\).

[00581] In some embodiments, when X is CH or C-halo and \(R^1, R^2,\) and \(R^3\) are each H, then the moiety formed by \(A^1, A^2, U, T, V,\) and \(-(Y)_n-Z\) has a formula other than:

[00582] In some embodiments:

Z is H, halo, CN, NO2, C1-8 alkyl, C2-8 alkenyl, C2-8 alkynyl, C1-8 haloalkyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl, wherein said C1-8 alkyl, C2-8 alkenyl, C2-8 alkynyl, C1-8 haloalkyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, 3, 4, 5, or 6 substituents independently selected from halo, C1-4 alkyl, C2-4 alkenyl, C2-4 -
alkynyl, C\(_{1-4}\) haloalkyl, C\(_{1-4}\) hydroxyalkyl, C\(_{1-4}\) cyanoalkyl, Cy\(^i\), CN, NO\(_2\), OR\(^i\), SR\(^i\), C(O)R\(^b\), C(O)NR\(^i\)R\(^d\), C(O)OR\(^i\), OC(O)R\(^i\), OC(O)NR\(^i\)R\(^d\), NR\(^i\)R\(^d\), NR\(^i\)C(O)R\(^i\), NR\(^i\)C(O)NR\(^i\)R\(^d\), NR\(^i\)′C(O)OR\(^i\), C(=NR\(^i\))NR\(^i\)R\(^d\), NR\(^i\)′C(=NR\(^i\))NR\(^i\)R\(^d\), S(O)R\(^b\), S(O)NR\(^i\)R\(^d\), S(O)\(_2\)R\(^b\), NR\(^i\)′S(O)\(_2\)R\(^b\), and S(O)\(_2\)NR\(^i\)R\(^d\);

Q is H, halo, CN, NO\(_2\), C\(_{1-4}\) alkyl, C\(_{2-8}\) alkenyl, C\(_{1-8}\) haloalkyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl, wherein said C\(_{1-8}\) alkyl, C\(_{2-8}\) alkenyl, C\(_{1-8}\) haloalkyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, 3 or 4 substituents independently selected from halo, C\(_{1-4}\) alkyl, C\(_{2-4}\) alkenyl, C\(_{1-4}\) haloalkyl, C\(_{1-4}\) hydroxyalkyl, C\(_{1-4}\) cyanoalkyl, Cy\(^i\), CN, NO\(_2\), OR\(^i\), SR\(^i\), C(O)R\(^b\), C(O)NR\(^i\)R\(^d\), C(O)OR\(^i\), OC(O)R\(^i\), OC(O)NR\(^i\)R\(^d\), NR\(^i\)R\(^d\), NR\(^i\)′C(O)R\(^i\), NR\(^i\)′C(O)OR\(^i\), NR\(^i\)′S(O)R\(^i\), NR\(^i\)′S(O)\(_2\)R\(^b\), S(O)R\(^i\), S(O)NR\(^i\)R\(^d\), S(O)\(_2\)R\(^b\), and S(O)\(_2\)NR\(^i\)R\(^d\);

Cy\(^i\) and Cy\(^i\) are independently selected from aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, each optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from halo, C\(_{1-4}\) alkyl, C\(_{2-4}\) alkenyl, C\(_{1-4}\) haloalkyl, C\(_{1-4}\) hydroxyalkyl, C\(_{1-4}\) cyanoalkyl, CN, NO\(_2\), OR\(^i\), SR\(^i\), C(O)R\(^b\), C(O)NR\(^i\)R\(^d\), C(O)OR\(^i\), OC(O)R\(^i\), OC(O)NR\(^i\)R\(^d\), NR\(^i\)R\(^d\), NR\(^i\)′C(O)R\(^i\), NR\(^i\)′C(O)OR\(^i\), NR\(^i\)′S(O)R\(^i\), NR\(^i\)′S(O)\(_2\)R\(^b\), S(O)R\(^i\), S(O)NR\(^i\)R\(^d\), S(O)\(_2\)R\(^b\), and S(O)\(_2\)NR\(^i\)R\(^d\);

R\(^i\), R\(^2\), R\(^3\), and R\(^4\) are independently selected from H, halo, C\(_{1-4}\) alkyl, C\(_{2-4}\) alkenyl, C\(_{1-4}\) haloalkyl, C\(_{1-4}\) hydroxyalkyl, C\(_{1-4}\) cyanoalkyl, CN, NO\(_2\), OR\(^i\), SR\(^i\), C(O)R\(^b\), C(O)NR\(^i\)R\(^d\), C(O)OR\(^i\), OC(O)R\(^i\), OC(O)NR\(^i\)R\(^d\), NR\(^i\)R\(^d\), NR\(^i\)′C(O)R\(^i\), NR\(^i\)′C(O)OR\(^i\), NR\(^i\)′S(O)R\(^i\), NR\(^i\)′S(O)\(_2\)R\(^b\), S(O)R\(^i\), S(O)NR\(^i\)R\(^d\), S(O)\(_2\)R\(^b\), NR\(^i\)′S(O)\(_2\)R\(^b\), and S(O)\(_2\)NR\(^i\)R\(^d\);

R\(^5\) is H, halo, C\(_{1-4}\) alkyl, C\(_{2-4}\) alkenyl, C\(_{1-4}\) haloalkyl, CN, NO\(_2\), OR\(^i\), SR\(^i\), C(O)R\(^b\), C(O)NR\(^i\)R\(^d\), C(O)OR\(^i\), OC(O)R\(^i\), OC(O)NR\(^i\)R\(^d\), NR\(^i\)R\(^d\), NR\(^i\)′C(O)R\(^i\), NR\(^i\)′C(O)OR\(^i\), NR\(^i\)′S(O)R\(^i\), NR\(^i\)′S(O)\(_2\)R\(^b\), S(O)R\(^i\), S(O)NR\(^i\)R\(^d\), S(O)\(_2\)R\(^b\), NR\(^i\)′S(O)\(_2\)R\(^b\), or S(O)\(_2\)NR\(^i\)R\(^d\);

R\(^6\) is H, C\(_{1-4}\) alkyl, C\(_{2-4}\) alkenyl, C\(_{1-4}\) haloalkyl, OR\(^i\), C(O)R\(^i\), C(O)NR\(^i\)R\(^d\), C(O)OR\(^i\), S(O)R\(^i\), S(O)NR\(^i\)R\(^d\), S(O)\(_2\)R\(^b\), or S(O)\(_2\)NR\(^i\)R\(^d\);

R\(^7\) is H, C\(_{1-4}\) alkyl, C\(_{1-4}\) haloalkyl, C\(_{2-6}\) alkenyl, C\(_{1-6}\) alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl or heterocycloalkylalkyl;
R is H, C\textsubscript{1-6} alkyl, C\textsubscript{1-6} haloalkyl, C\textsubscript{2-6} alkenyl, C\textsubscript{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroaryalkyl, cycloalkylalkyl or heterocycloalkylalkyl;

R\textsuperscript{9} and R\textsuperscript{10} are independently selected from H, C\textsubscript{1-10} alkyl, C\textsubscript{1-6} haloalkyl, C\textsubscript{2-6} alkenyl, C\textsubscript{2-6} alkynyl, C\textsubscript{1-6} alkylcarbonyl, arylcarbonyl, C\textsubscript{1-6} alkylsulfonyl, arylsulfonyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroaryalkyl, cycloalkylalkyl and heterocycloalkylalkyl;

or R\textsuperscript{9} and R\textsuperscript{10} together with the N atom to which they are attached form a 4-, 5-, 6- or 7-membered heterocycloalkyl group;

R\textsuperscript{11} and R\textsuperscript{12} are independently selected from H, halo, OH, CN, C\textsubscript{1-4} alkyl, C\textsubscript{1-4} haloalkyl, C\textsubscript{2-4} alkenyl, C\textsubscript{2-4} alkynyl, C\textsubscript{1-4} hydroxyalkyl, C\textsubscript{1-4} cyanoalkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl;

R', R', and R'' are independently selected from H, C\textsubscript{1-6} alkyl, C\textsubscript{1-6} haloalkyl, C\textsubscript{2-6} alkenyl, C\textsubscript{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroaryalkyl, cycloalkylalkyl and heterocycloalkylalkyl, wherein said C\textsubscript{1-6} alkyl, C\textsubscript{1-6} haloalkyl, C\textsubscript{2-6} alkenyl, C\textsubscript{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroaryalkyl, cycloalkylalkyl and heterocycloalkylalkyl is optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C\textsubscript{1-6} alkyl, C\textsubscript{1-6} haloalkyl, aryl, arylalkyl, heteroaryl, heteroaryalkyl, cycloalkyl and heterocycloalkyl;

R', R', and R'' are independently selected from H, C\textsubscript{1-6} alkyl, C\textsubscript{1-6} haloalkyl, C\textsubscript{2-6} alkenyl, C\textsubscript{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroaryalkyl, cycloalkylalkyl and heterocycloalkylalkyl, wherein said C\textsubscript{1-6} alkyl, C\textsubscript{1-6} haloalkyl, C\textsubscript{2-6} alkenyl, C\textsubscript{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroaryalkyl, cycloalkylalkyl or heterocycloalkylalkyl is optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C\textsubscript{1-6} alkyl, C\textsubscript{1-6} haloalkyl, C\textsubscript{1-6} haloalkyl, aryl, arylalkyl, heteroaryl, heteroaryalkyl, cycloalkyl and heterocycloalkyl;

R' and R are independently selected from H, C\textsubscript{1-10} alkyl, C\textsubscript{1-6} haloalkyl, C\textsubscript{2-6} alkenyl, C\textsubscript{2-6} alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroaryalkyl, cycloalkylalkyl and heterocycloalkylalkyl, wherein said C\textsubscript{1-10} alkyl, C\textsubscript{1-6} haloalkyl, C\textsubscript{2-6} alkenyl, C\textsubscript{2-6} alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroaryalkyl, cycloalkylalkyl and heterocycloalkylalkyl.
heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl or heterocycloalkylalkyl is optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl or heterocycloalkyl;

or \( R^\prime \) and \( R^\prime \) together with the N atom to which they are attached form a 4-, 5-, 6- or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl and heterocycloalkyl;

\( R^{\prime\prime} \) and \( R^{\prime\prime} \) are independently selected from H, C_{1-10} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl and heterocycloalkylalkyl, wherein said C_{1-10} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl or heterocycloalkylalkyl is optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl and heterocycloalkyl;

or \( R^{\prime\prime} \) and \( R^{\prime\prime} \) together with the N atom to which they are attached form a 4-, 5-, 6- or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl and heterocycloalkyl;

\( R^{\prime\prime\prime} \) and \( R^{\prime\prime\prime} \) are independently selected from H, C_{1-10} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl and heterocycloalkylalkyl, wherein said C_{1-10} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl or heterocycloalkylalkyl is optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl and heterocycloalkyl; and

or \( R^{\prime\prime\prime} \) and \( R^{\prime\prime\prime} \) together with the N atom to which they are attached form a 4-, 5-, 6- or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 substituents
independently selected from OH, CN, amino, halo, C$_{1-6}$ alkyl, C$_{1-6}$ haloalkyl, C$_{1-6}$ haloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl and heterocycloalkyl.

[00583] In some embodiments, X is N.

[00584] In some embodiments, X is CR$_4$.

[00585] In some embodiments, A$_1$ is C.

[00586] In some embodiments, A$_1$ is N.

[00587] In some embodiments, A$_2$ is C.

[00588] In some embodiments, A$_2$ is N.

[00589] In some embodiments, at least one of A$_1$, A$_2$, U, T, and V is N.

[00590] In some embodiments, the 5-membered ring formed by A$_1$, A$_2$, U, T, and V is pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, thiazolyl, or oxadiazolyl.

[00591] In some embodiments, the 5-membered ring formed by A$_1$, A$_2$, U, T, and V is selected from:
wherein:

a designates the site of attachment of moiety —(Y)—Z;

b designates the site of attachment to the core moiety:

and

c and c' designate the two sites of attachment of the fused 4- to 20-membered aryl, cycloalkyl, heteroaryl, or heterocycloalkyl ring.

[00592] In some embodiments, the 5-membered ring formed by A₁, A₂, U, T, and V is selected from:
wherein:

a designates the site of attachment of moiety —(Y) —Z;

b designates the site of attachment to the core moiety.

c and c’ designate the two sites of attachment of the fused 4- to 20-membered aryl, cycloalkyl, heteroaryl, or heterocycloalkyl ring.

[00593] In some embodiments, the 5-membered ring formed by A¹, A², U, T, and V is selected from:
wherein:

a designates the site of attachment of moiety —(Y)$_n$—Z;

b designates the site of attachment to the core moiety:

and

c and c' designate the two sites of attachment of the fused 4- to 20-membered aryl, cycloalkyl, heteroaryl, or heterocycloalkyl ring.

[00594] In some embodiments, the 5-membered ring formed by $A_1$, $A_2$, U, T, and V is selected from:
wherein:

a designates the site of attachment of moiety —(Y) —Z;

b designates the site of attachment to the core moiety:

[00595] In some embodiments, the 5-membered ring formed by A₁, A₂, U, T, and V is selected from:
wherein:

a designates the site of attachment of moiety —(Y)—Z;

b designates the site of attachment to the core moiety:

[00596] In some embodiments, the 5-membered ring formed by A¹, A², U, T, and V is selected from:
wherein:

a designates the site of attachment of moiety —(Y) —Z;

b designates the site of attachment to the core moiety:

[00597] In some embodiments, n is 0.

[00598] In some embodiments, n is 1.

[00599] In some embodiments, n is 1 and Y is C1-8 alkyene, C2-8 alkenylene, (CR1 R2) p C(O)(CR1 R2) q, (CR1 R2) p C(O)NR c (CR1 R2) q, (CR1 R2) p C(O)O(CR1 R2) q, (CR1 R2) p OC(O)(CR1 R2) q, wherein said C1-8 alkyene or C2-8 alkenylene, is optionally substituted with 1, 2, or 3 halo, OH, CN, amino, C1-4 alkylamino, or C2-8 dialkylamino.

[00600] In some embodiments, n is 1 and Y is C1-8 alkyene, (CR1 R2) p C(O)(CR1 R2) q, (CR1 R2) p C(O)NR c (CR1 R2) q, (CR1 R2) p C(O)O(CR1 R2) q, wherein said C1-8 alkyene is optionally substituted with 1, 2, or 3 halo, OH, CN, amino, C1-4 alkylamino, or C2-8 dialkylamino.

[00601] In some embodiments, n is 1 and Y is C1-8 alkyene optionally substituted with 1, 2, or 3 halo, OH, CN, amino, C1-4 alkylamino, or C2-8 dialkylamino.
In some embodiments, n is 1 and Y is ethylene optionally substituted with 1, 2, or 3 halo, OH, CN, amino, C_{1-4} alkylation, or C_{2-8} dialkylamino.

In some embodiments, n is 1 and Y is (CR^{11} R^{12})_p C(O)(CR^{11} R^{12})_q, (CR^{11} R^{12})_p C(O)NR^{1} (CR^{11} R^{12})_q, or (CR^{11} R^{12})_p C(O)(CR^{11} R^{12})_q.

In some embodiments, Y is C_{1-8} alkyne, C_{2-8} alkenylene, C_{2-8} alkynylene, (CR^{11} R^{12})_p —(C_{3-10} cycloalkylene)-(CR^{11} R^{12})_q, (CR^{11} R^{12})_p-(arylene)-(CR^{11} R^{12})_q, (CR^{11} R^{12})_p —(C_{1-10} heterocycloalkylene)-(CR^{11} R^{12})_q, (CR^{11} R^{12})_p -(heteroarylene)-(CR^{11} R^{12})_q, (CR^{11} R^{12})_p O(CR^{11} R^{12})_q, or (CR^{11} R^{12})_p S(CR^{11} R^{12})_q, wherein said C_{1-8} alkyne, C_{2-8} alkenylene, C_{2-8} alkynylene, cycloalkylene, alkenylene, heterocycloalkylene, or heteroarylene, is optionally substituted with 1, 2, or 3 substituents independently selected from -D^1-D^2-D^3-D^4.

In some embodiments, Y is C_{1-8} alkyne, C_{2-8} alkenylene, C_{2-8} alkynylene, (CR^{11} R^{12})_p —(C_{3-10} cycloalkylene)-(CR^{11} R^{12})_q, (CR^{11} R^{12})_p-(arylene)-(CR^{11} R^{12})_q, (CR^{11} R^{12})_p —(C_{1-10} heterocycloalkylene)-(CR^{11} R^{12})_q, (CR^{11} R^{12})_p -(heteroarylene)-(CR^{11} R^{12})_q, (CR^{11} R^{12})_p O(CR^{11} R^{12})_q, or (CR^{11} R^{12})_p S(CR^{11} R^{12})_q, wherein said C_{1-8} alkyne, C_{2-8} alkenylene, C_{2-8} alkynylene, cycloalkylene, alkenylene, heterocycloalkylene, or heteroarylene, is optionally substituted with 1, 2, or 3 substituents independently selected from D^4.

In some embodiments, Y is C_{1-8} alkyne, C_{2-8} alkenylene, C_{2-8} alkynylene, or (CR^{11} R^{12})_p —(C_{3-10} cycloalkylene)-(CR^{11} R^{12})_q, wherein said C_{1-8} alkyne, C_{2-8} alkenylene, C_{2-8} alkynylene, or cycloalkylene, is optionally substituted with 1, 2, or 3 substituents independently selected from -D^1-D^2-D^3-D^4.

In some embodiments, Y is C_{1-8} alkyne, C_{2-8} alkenylene, C_{2-8} alkynylene, or (CR^{11} R^{12})_p —(C_{3-10} cycloalkylene)-(CR^{11} R^{12})_q, wherein said C_{1-8} alkyne, C_{2-8} alkenylene, C_{2-8} alkynylene, or cycloalkylene, is optionally substituted with 1, 2, or 3 substituents independently selected from D^4.

In some embodiments, Y is C_{1-8} alkyne, C_{2-8} alkenylene, or C_{2-8} alkynylene, each optionally substituted with 1, 2, or 3 substituents independently selected from -D^1-D^2-D^3-D^4.

In some embodiments, Y is C_{1-8} alkylene optionally substituted with 1, 2, or 3 substituents independently selected from -D^1-D^2-D^3-D^4.

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[00610] In some embodiments, $Y$ is C$_{1-8}$ alkylene optionally substituted with 1, 2, or 3 substituents independently selected from D'.

[00611] In some embodiments, $Y$ is C$_{1-8}$ alkylene, C$_{2-8}$ alkenylene, C$_{2-8}$ alkynylene, (CR$_{11}$R$_{12}$)$_{p}$O—(CR$_{11}$R$_{12}$)$_{q}$, (CR$_{11}$R$_{12}$)$_{p}$S(CR$_{11}$R$_{12}$)$_{q}$, (CR$_{11}$R$_{12}$)$_{p}$C(O)(CR$_{11}$R$_{12}$)$_{q}$, (CR$_{11}$R$_{12}$)$_{p}$C(O)NR$_{3-10}$, (CR$_{11}$R$_{12}$)$_{p}$C(O)(CR$_{11}$R$_{12}$)$_{q}$, (CR$_{11}$R$_{12}$)$_{p}$C(O)NR$_{3-10}$, (CR$_{11}$R$_{12}$)$_{p}$C(O)(CR$_{11}$R$_{12}$)$_{q}$, or

[00612] In some embodiments, $Y$ is C$_{1-8}$ alkylene, C$_{2-8}$ alkenylene, C$_{2-8}$ alkynylene, (CR$_{11}$R$_{12}$)$_{p}$—(C$_{3-10}$ cycloalkylene)-(CR$_{11}$R$_{12}$)$_{q}$, (CR$_{11}$R$_{12}$)$_{p}$—(arylene)-(CR$_{11}$R$_{12}$)$_{q}$, (CR$_{11}$R$_{12}$)$_{p}$—(heteroarylene)-(CR$_{11}$R$_{12}$)$_{q}$, (CR$_{11}$R$_{12}$)$_{p}$O(CR$_{11}$R$_{12}$)$_{q}$, (CR$_{11}$R$_{12}$)$_{p}$S(CR$_{11}$R$_{12}$)$_{q}$, (CR$_{11}$R$_{12}$)$_{p}$C(O)(CR$_{11}$R$_{12}$)$_{q}$, or

[00613] In some embodiments, $p$ is 0.

[00614] In some embodiments, $p$ is 1.

[00615] In some embodiments, $p$ is 2.

[00616] In some embodiments, $q$ is 0.

[00617] In some embodiments, $q$ is 1.

[00618] In some embodiments, $q$ is 2.
In some embodiments, one of p and q is 0 and the other of p and q is 1, 2, or 3.

In some embodiments, Z is H, halo, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} haloalkyl, halosulfanyl, C_{1-4} hydroxyalkyl, C_{1-4} cyanoalkyl, C\{\text{y}^i\}, CN, NO\{\text{2}\}, OR\{\text{r}\}, C(O)R\{\text{b}\}, C(O)NR\{\text{r}\}^d, C(O)OR\{\text{b}\}, OC(O)R\{\text{b}\}, OC(O)NR\{\text{r}\}^d, NR\{\text{r}\}C(O)R\{\text{b}\}, NR\{\text{r}\}C(O)NR\{\text{r}\}^d, NR\{\text{r}\}C(O)OR\{\text{b}\}, C(=NR\{\text{r}\})R\{\text{b}\}, S(O)R\{\text{b}\}, S(O)NR\{\text{r}\}^d, S(O)\_2 R\{\text{b}\}, NR\{\text{s}\}S(O)\_2 R\{\text{b}\}, C(=NOH)R\{\text{b}\}, C(=NO(C\{\text{i}\}_4 alkyl)R\{\text{b}\}, and S(O)\_2 NR\{\text{r}\}^d.

In some embodiments, Z is aryl, cycloalkyl, heteroaryl, or heterocycloalkyl, each optionally substituted with 1, 2, 3, 4, 5, or 6 substituents selected from halo, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} haloalkyl, halosulfanyl, C_{1-4} hydroxyalkyl, C_{1-4} cyanoalkyl, C\{\text{y}^i\}, CN, NO\{\text{2}\}, OR\{\text{r}\}, SR\{\text{r}\}, C(O)R\{\text{b}\}, C(O)NR\{\text{r}\}^d, C(O)OR\{\text{b}\}, OC(O)R\{\text{b}\}, OC(O)NR\{\text{r}\}^d, NR\{\text{r}\}C(O)R\{\text{b}\}, NR\{\text{r}\}C(O)NR\{\text{r}\}^d, NR\{\text{r}\}C(O)OR\{\text{b}\}, C(=NR\{\text{r}\})NR\{\text{r}\}^d, NR\{\text{r}\}C(=NR\{\text{r}\})NR\{\text{r}\}^d, S(O)R\{\text{b}\}, S(O)NR\{\text{r}\}^d, S(O)\_2 R\{\text{b}\}, NR\{\text{s}\}S(O)\_2 R\{\text{b}\}, and S(O)\_2 NR\{\text{r}\}^d.

In some embodiments, Z is aryl, cycloalkyl, heteroaryl, or heterocycloalkyl, each optionally substituted with 1, 2, 3, 4, 5, or 6 substituents selected from halo, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} haloalkyl, halosulfanyl, C_{1-4} hydroxyalkyl, C_{1-4} cyanoalkyl, C\{\text{y}^i\}, CN, NO\{\text{2}\}, OR\{\text{r}\}, SR\{\text{r}\}, C(O)R\{\text{b}\}, C(O)NR\{\text{r}\}^d, C(O)OR\{\text{b}\}, OC(O)R\{\text{b}\}, OC(O)NR\{\text{r}\}^d, NR\{\text{r}\}C(O)R\{\text{b}\}, NR\{\text{r}\}C(O)NR\{\text{r}\}^d, NR\{\text{r}\}C(O)OR\{\text{b}\}, C(=NR\{\text{r}\})NR\{\text{r}\}^d, NR\{\text{r}\}C(=NR\{\text{r}\})NR\{\text{r}\}^d, S(O)R\{\text{b}\}, S(O)NR\{\text{r}\}^d, S(O)\_2 R\{\text{b}\}, NR\{\text{s}\}S(O)\_2 R\{\text{b}\}, and S(O)\_2 NR\{\text{r}\}^d.

In some embodiments, Z is aryl or heteroaryl, each optionally substituted with 1, 2, 3, 4, 5, or 6 substituents selected from halo, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} haloalkyl, halosulfanyl, C_{1-4} hydroxyalkyl, C_{1-4} cyanoalkyl, C\{\text{y}^i\}, CN, NO\{\text{2}\}, OR\{\text{r}\}, SR\{\text{r}\}, C(O)R\{\text{b}\}, C(O)NR\{\text{r}\}^d, C(O)OR\{\text{b}\}, OC(O)R\{\text{b}\}, OC(O)NR\{\text{r}\}^d, NR\{\text{r}\}C(O)R\{\text{b}\}, NR\{\text{r}\}C(O)NR\{\text{r}\}^d, NR\{\text{r}\}C(O)OR\{\text{b}\}, C(=NR\{\text{r}\})NR\{\text{r}\}^d, NR\{\text{r}\}C(=NR\{\text{r}\})NR\{\text{r}\}^d, S(O)R\{\text{b}\}, S(O)NR\{\text{r}\}^d, S(O)\_2 R\{\text{b}\}, NR\{\text{s}\}S(O)\_2 R\{\text{b}\}, and S(O)\_2 NR\{\text{r}\}^d.
In some embodiments, Z is aryl or heteroaryl, each optionally substituted with 1, 2, 3, 4, 5, or 6 substituents selected from halo, C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl, C<sub>1-4</sub> haloalkyl, C<sub>1-4</sub> hydroxyalkyl, C<sub>1-4</sub> cyanoalkyl, Cy<sup>i</sup>, CN, NO<sub>2</sub>, OR<sup>i</sup>, SR<sup>i</sup>, C(O)R<sup>i</sup>, C(O)NR<sup>i</sup>R<sup>j</sup>, C(O)OR<sup>i</sup>, OC(O)R<sup>i</sup>, OC(O)NR<sup>i</sup>R<sup>j</sup>, NR<sup>i</sup>C(O)NR<sup>i</sup>R<sup>j</sup>, NR<sup>i</sup>C(O)OR<sup>i</sup>, C(=NR<sup>i</sup>)NR<sup>i</sup>R<sup>j</sup>, NR<sup>i</sup>C(=NR<sup>i</sup>)NR<sup>i</sup>R<sup>j</sup>, S(O)R<sup>b</sup>, S(O)NR<sup>i</sup>R<sup>j</sup>, S(O)OR<sup>i</sup>, NR<sup>i</sup>S(O)<sub>2</sub>R<sup>b</sup>, and S(O)<sub>2</sub>NR<sup>i</sup>R<sup>j</sup>.

In some embodiments, Z is phenyl or 5- or 6-membered heteroaryl, each optionally substituted with 1, 2, 3, 4, 5, or 6 substituents selected from halo, C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl, C<sub>1-4</sub> haloalkyl, halosulfanyl, C<sub>1-4</sub> hydroxyalkyl, C<sub>1-4</sub> cyanoalkyl, Cy<sup>i</sup>, CN, NO<sub>2</sub>, OR<sup>i</sup>, SR<sup>i</sup>, C(O)R<sup>i</sup>, C(O)NR<sup>i</sup>R<sup>j</sup>, C(O)OR<sup>i</sup>, OC(O)R<sup>i</sup>, OC(O)NR<sup>i</sup>R<sup>j</sup>, NR<sup>i</sup>C(O)NR<sup>i</sup>R<sup>j</sup>, NR<sup>i</sup>C(O)OR<sup>i</sup>, C(=NR<sup>i</sup>)NR<sup>i</sup>R<sup>j</sup>, NR<sup>i</sup>C(=NR<sup>i</sup>)NR<sup>i</sup>R<sup>j</sup>, S(O)R<sup>b</sup>, S(O)NR<sup>i</sup>R<sup>j</sup>, S(O)OR<sup>i</sup>, NR<sup>i</sup>S(O)<sub>2</sub>R<sup>b</sup>, and S(O)<sub>2</sub>NR<sup>i</sup>R<sup>j</sup>.

In some embodiments, Z is phenyl optionally substituted with 1, 2, 3, 4, 5, or 6 substituents selected from halo, C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl, C<sub>1-4</sub> haloalkyl, halosulfanyl, C<sub>1-4</sub> hydroxyalkyl, C<sub>1-4</sub> cyanoalkyl, Cy<sup>i</sup>, CN, NO<sub>2</sub>, OR<sup>i</sup>, SR<sup>i</sup>, C(O)R<sup>i</sup>, C(O)NR<sup>i</sup>R<sup>j</sup>, C(O)OR<sup>i</sup>, OC(O)R<sup>i</sup>, OC(O)NR<sup>i</sup>R<sup>j</sup>, NR<sup>i</sup>C(O)NR<sup>i</sup>R<sup>j</sup>, NR<sup>i</sup>C(O)OR<sup>i</sup>, C(=NR<sup>i</sup>)NR<sup>i</sup>R<sup>j</sup>, NR<sup>i</sup>C(=NR<sup>i</sup>)NR<sup>i</sup>R<sup>j</sup>, S(O)R<sup>b</sup>, S(O)NR<sup>i</sup>R<sup>j</sup>, S(O)OR<sup>i</sup>, NR<sup>i</sup>S(O)<sub>2</sub>R<sup>b</sup>, and S(O)<sub>2</sub>NR<sup>i</sup>R<sup>j</sup>.

In some embodiments, Z is phenyl optionally substituted with 1, 2, 3, 4, 5, or 6 substituents selected from halo, C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl, C<sub>1-4</sub> haloalkyl, C<sub>1-4</sub> hydroxyalkyl, C<sub>1-4</sub> cyanoalkyl, Cy<sup>i</sup>, CN, NO<sub>2</sub>, OR<sup>i</sup>, SR<sup>i</sup>, C(O)R<sup>i</sup>, C(O)NR<sup>i</sup>R<sup>j</sup>, C(O)OR<sup>i</sup>, OC(O)R<sup>i</sup>, OC(O)NR<sup>i</sup>R<sup>j</sup>, NR<sup>i</sup>C(O)NR<sup>i</sup>R<sup>j</sup>, NR<sup>i</sup>C(O)OR<sup>i</sup>, C(=NR<sup>i</sup>)NR<sup>i</sup>R<sup>j</sup>, NR<sup>i</sup>C(=NR<sup>i</sup>)NR<sup>i</sup>R<sup>j</sup>, S(O)R<sup>b</sup>, S(O)NR<sup>i</sup>R<sup>j</sup>, S(O)OR<sup>i</sup>, NR<sup>i</sup>S(O)<sub>2</sub>R<sup>b</sup>, and S(O)<sub>2</sub>NR<sup>i</sup>R<sup>j</sup>.

In some embodiments, Z is cycloalkyl or heterocycloalkyl, each optionally substituted with 1, 2, 3, 4, 5, or 6 substituents selected from halo, C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl, C<sub>1-4</sub> hydroxyalkyl, C<sub>1-4</sub> cyanoalkyl, Cy<sup>i</sup>, CN, NO<sub>2</sub>, OR<sup>i</sup>, SR<sup>i</sup>, C(O)R<sup>i</sup>, C(O)NR<sup>i</sup>R<sup>j</sup>, C(O)OR<sup>i</sup>, OC(O)R<sup>i</sup>, OC(O)NR<sup>i</sup>R<sup>j</sup>, NR<sup>i</sup>C(O)NR<sup>i</sup>R<sup>j</sup>, NR<sup>i</sup>C(O)OR<sup>i</sup>, C(=NR<sup>i</sup>)NR<sup>i</sup>R<sup>j</sup>, NR<sup>i</sup>C(=NR<sup>i</sup>)NR<sup>i</sup>R<sup>j</sup>, S(O)R<sup>b</sup>, S(O)NR<sup>i</sup>R<sup>j</sup>, S(O)OR<sup>i</sup>, NR<sup>i</sup>S(O)<sub>2</sub>R<sup>b</sup>, and S(O)<sub>2</sub>NR<sup>i</sup>R<sup>j</sup>.
haloalkyl, halosulfanyl, C_{1-4} hydroxyalkyl, C_{1-4} cyanoalkyl, Cy^i, CN, NO_2, OR^a, SR^a, C(O)R^b, C(O)NR^c, OC(O)R^b, OC(O)NR^c, NR^c R^d, NR^c C(O)R^b, NR^c C(O)NR^c R^d, NR^c C(O)OR^c, C(=NR^c)NR^c R^d, NR^c C(=NR^c)NR^c R^d, S(O)R^b, S(O)NR^c R^d, S(O)_2 R^b, NR^c S(O) R^b, and S(O)_2 NR^d.

In some embodiments, Z is cycloalkyl or heterocycloalkyl, each optionally substituted with 1, 2, 3, 4, 5, or 6 substituents selected from halo, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} cyanoalkyl, C_{1-4} alkenyl, C_{1-4} alkyl, CN, NO_2, OR^a, SR^a, C(O)R^b, C(O)NR^c, OC(O)R^b, OC(O)NR^c, NR^c R^d, NR^c C(O)R^b, NR^c C(O)NR^c R^d, NR^c C(O)OR^c, C(=NR^c)NR^c R^d, NR^c C(=NR^c)NR^c R^d, S(O)R^b, S(O)NR^c R^d, S(O)_2 R^b, NR^c S(O) R^b, and S(O)_2 NR^d.

In some embodiments, Z is cycloalkyl, cycloalkyl, cycloalkyl, or cycloalkyl, each optionally substituted with 1, 2, 3, 4, 5, or 6 substituents selected from halo, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} haloalkyl, C_{1-4} cyanoalkyl, C_{1-4} alkenyl, Cy^i, CN, NO_2, OR^a, SR^a, C(O)R^b, C(O)NR^c, OC(O)R^b, OC(O)NR^c, NR^c R^d, NR^c C(O)R^b, NR^c C(O)NR^c R^d, NR^c C(O)OR^c, C(=NR^c)NR^c R^d, NR^c C(=NR^c)NR^c R^d, S(O)R^b, S(O)NR^c R^d, S(O)_2 R^b, NR^c S(O) R^b, and S(O)_2 NR^d.

In some embodiments, Z is C_{1-8} alkyl, C_{2-8} alkenyl, or C_{2-8} alkynyl, each optionally substituted with 1, 2, 3, 4, 5, or 6 substituents selected from halo, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} haloalkyl, C_{1-4} cyanoalkyl, C_{1-4} alkenyl, Cy^i, CN, NO_2, OR^a, SR^a, C(O)R^b, C(O)NR^c, OC(O)R^b, OC(O)NR^c, NR^c R^d, NR^c C(O)R^b, NR^c C(O)NR^c R^d, NR^c C(O)OR^c, C(=NR^c)NR^c R^d, NR^c C(=NR^c)NR^c R^d, S(O)R^b, S(O)NR^c R^d, S(O)_2 R^b, NR^c S(O) R^b, and S(O)_2 NR^d.
In some embodiments, Z is aryl, cycloalkyl, heteroaryl, or heterocycloalkyl, each optionally substituted with 1, 2, 3, 4, 5, or 6 substituents independently selected from halo, C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl, C<sub>1-4</sub> haloalkyl, halosulfanyl, C<sub>1-4</sub> hydroxyalkyl, C<sub>1-4</sub> cyanoalkyl, Cy<sup>i</sup>, CN, NO<sub>2</sub>, OR<sup>e</sup>, SR<sup>e</sup>, C(O)R<sup>b</sup>, C(O)NR<sup>d</sup>R<sup>d</sup>, C(O)OR<sup>e</sup>, OC(O)R<sup>b</sup>, OC(O)NR<sup>d</sup>R<sup>d</sup>, NR<sup>e</sup>R<sup>d</sup>, NR<sup>e</sup>C(O)R<sup>b</sup>, NR<sup>e</sup>C(O)NR<sup>d</sup>R<sup>d</sup>, NR<sup>e</sup>C(O)OR<sup>e</sup>, S(O)R<sup>b</sup>, S(O)NR<sup>d</sup>R<sup>d</sup>, S(O)<sub>2</sub>R<sup>b</sup>, NR<sup>e</sup>S(O)<sub>2</sub>R<sup>b</sup>, and S(O)<sub>2</sub>NR<sup>e</sup>R<sup>d</sup>.

In some embodiments, Z is aryl, cycloalkyl, heteroaryl, or heterocycloalkyl, each optionally substituted with 1, 2, 3, 4, 5, or 6 substituents independently selected from halo, C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl, C<sub>1-4</sub> haloalkyl, C<sub>1-4</sub> hydroxyalkyl, C<sub>1-4</sub> cyanoalkyl, Cy<sup>i</sup>, CN, NO<sub>2</sub>, OR<sup>e</sup>, SR<sup>e</sup>, C(O)R<sup>b</sup>, C(O)NR<sup>d</sup>R<sup>d</sup>, C(O)OR<sup>e</sup>, OC(O)R<sup>b</sup>, OC(O)NR<sup>d</sup>R<sup>d</sup>, NR<sup>e</sup>R<sup>d</sup>, NR<sup>e</sup>C(O)R<sup>b</sup>, NR<sup>e</sup>C(O)NR<sup>d</sup>R<sup>d</sup>, NR<sup>e</sup>C(O)OR<sup>e</sup>, S(O)R<sup>b</sup>, S(O)NR<sup>d</sup>R<sup>d</sup>, S(O)<sub>2</sub>R<sup>b</sup>, NR<sup>e</sup>S(O)<sub>2</sub>R<sup>b</sup>, and S(O)<sub>2</sub>NR<sup>e</sup>R<sup>d</sup>.

In some embodiments, Z is aryl or heteroaryl, each optionally substituted with 1, 2, 3, 4, 5, or 6 substituents independently selected from halo, C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl, C<sub>1-4</sub> haloalkyl, halosulfanyl, C<sub>1-4</sub> hydroxyalkyl, C<sub>1-4</sub> cyanoalkyl, Cy<sup>i</sup>, CN, NO<sub>2</sub>, OR<sup>e</sup>, SR<sup>e</sup>, C(O)R<sup>b</sup>, C(O)NR<sup>d</sup>R<sup>d</sup>, C(O)OR<sup>e</sup>, OC(O)R<sup>b</sup>, OC(O)NR<sup>d</sup>R<sup>d</sup>, NR<sup>e</sup>R<sup>d</sup>, NR<sup>e</sup>C(O)R<sup>b</sup>, NR<sup>e</sup>C(O)NR<sup>d</sup>R<sup>d</sup>, NR<sup>e</sup>C(O)OR<sup>e</sup>, S(O)R<sup>b</sup>, S(O)NR<sup>d</sup>R<sup>d</sup>, S(O)<sub>2</sub>R<sup>b</sup>, NR<sup>e</sup>S(O)<sub>2</sub>R<sup>b</sup>, and S(O)<sub>2</sub>NR<sup>e</sup>R<sup>d</sup>.

In some embodiments, Z is aryl or heteroaryl, each optionally substituted with 1, 2, 3, 4, 5, or 6 substituents independently selected from halo, C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl, C<sub>1-4</sub> haloalkyl, halosulfanyl, C<sub>1-4</sub> hydroxyalkyl, C<sub>1-4</sub> cyanoalkyl, Cy<sup>i</sup>, CN, NO<sub>2</sub>, OR<sup>e</sup>, SR<sup>e</sup>, C(O)R<sup>b</sup>, C(O)NR<sup>d</sup>R<sup>d</sup>, C(O)OR<sup>e</sup>, OC(O)R<sup>b</sup>, OC(O)NR<sup>d</sup>R<sup>d</sup>, NR<sup>e</sup>R<sup>d</sup>, NR<sup>e</sup>C(O)R<sup>b</sup>, NR<sup>e</sup>C(O)NR<sup>d</sup>R<sup>d</sup>, NR<sup>e</sup>C(O)OR<sup>e</sup>, S(O)R<sup>b</sup>, S(O)NR<sup>d</sup>R<sup>d</sup>, S(O)<sub>2</sub>R<sup>b</sup>, NR<sup>e</sup>S(O)<sub>2</sub>R<sup>b</sup>, and S(O)<sub>2</sub>NR<sup>e</sup>R<sup>d</sup>.

In some embodiments, Z is phenyl or 5- or 6-membered heteroaryl, each optionally substituted with 1, 2, 3, 4, 5, or 6 substituents independently selected from halo, C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl, C<sub>1-4</sub> haloalkyl, halosulfanyl, C<sub>1-4</sub> hydroxyalkyl, C<sub>1-4</sub> cyanoalkyl, Cy<sup>i</sup>, CN, NO<sub>2</sub>, OR<sup>e</sup>, SR<sup>e</sup>, C(O)R<sup>b</sup>, C(O)NR<sup>d</sup>R<sup>d</sup>, C(O)OR<sup>e</sup>, OC(O)R<sup>b</sup>, OC(O)NR<sup>d</sup>R<sup>d</sup>, NR<sup>e</sup>R<sup>d</sup>, NR<sup>e</sup>C(O)R<sup>b</sup>, NR<sup>e</sup>C(O)NR<sup>d</sup>R<sup>d</sup>, NR<sup>e</sup>C(O)OR<sup>e</sup>, S(O)R<sup>b</sup>, S(O)NR<sup>d</sup>R<sup>d</sup>, S(O)<sub>2</sub>R<sup>b</sup>, NR<sup>e</sup>S(O)<sub>2</sub>R<sup>b</sup>, and S(O)<sub>2</sub>NR<sup>e</sup>R<sup>d</sup>.

In some embodiments, Z is phenyl or 5- or 6-membered heteroaryl, each optionally substituted with 1, 2, 3, 4, 5, or 6 substituents independently selected from halo, C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl, C<sub>1-4</sub> haloalkyl, C<sub>1-4</sub> hydroxyalkyl, C<sub>1-4</sub> cyanoalkyl, Cy<sup>i</sup>, CN, NO<sub>2</sub>, OR<sup>e</sup>, SR<sup>e</sup>,
C(O)R, C(O)NR R, C(O)OR, OC(O)R, OC(O)NR R, NR R, NR C(O)R, NR C(O)NR R, NR C(O)OR, S(O)R, S(O)NR R, S(O)2 R, NR S(O)2 R, and S(O)2 NR R.

[00638] In some embodiments, Z is phenyl optionally substituted with 1, 2, 3, 4, 5, or 6 substituents independently selected from halo, C1-4 alkyl, C1-4 alkenyl, C1-4 alkynyl, C1-4 haloalkyl, halosulfanyl, C1-4 hydroxyalkyl, C1-4 cyanoalkyl, Cy, CN, NO2, OR, SR, C(O)R, C(O)NR R, C(O)OR, OC(O)R, OC(O)NR R, NR R, NR C(O)R, NR C(O)NR R, NR C(O)OR, S(O)R, S(O)NR R, S(O)2 R, NR S(O)2 R, and S(O)2 NR R.

[00639] In some embodiments, Z is phenyl optionally substituted with 1, 2, 3, 4, 5, or 6 substituents independently selected from halo, C1-4 alkyl, C1-4 alkenyl, C1-4 alkynyl, C1-4 haloalkyl, C1-4 hydroxyalkyl, C1-4 cyanoalkyl, Cy, CN, NO2, OR, SR, C(O)R, C(O)NR R, C(O)OR, OC(O)R, OC(O)NR R, NR R, NR C(O)R, NR C(O)NR R, NR C(O)OR, S(O)R, S(O)NR R, S(O)2 R, NR S(O)2 R, and S(O)2 NR R.

[00640] In some embodiments, Z is cycloalkyl or heterocycloalkyl, each optionally substituted with 1, 2, 3, 4, 5, or 6 substituents independently selected from halo, C1-4 alkyl, C1-4 alkenyl, C1-4 alkynyl, C1-4 haloalkyl, halosulfanyl, C1-4 hydroxyalkyl, C1-4 cyanoalkyl, Cy, CN, NO2, OR, SR, C(O)R, C(O)NR R, C(O)OR, OC(O)R, OC(O)NR R, NR R, NR C(O)R, NR C(O)NR R, NR C(O)OR, S(O)R, S(O)NR R, S(O)2 R, NR S(O)2 R, and S(O)2 NR R.

[00641] In some embodiments, Z is cycloalkyl or heterocycloalkyl, each optionally substituted with 1, 2, 3, 4, 5, or 6 substituents independently selected from halo, C1-4 alkyl, C1-4 alkenyl, C1-4 alkynyl, C1-4 haloalkyl, C1-4 hydroxyalkyl, C1-4 cyanoalkyl, Cy, CN, NO2, OR, SR, C(O)R, C(O)NR R, C(O)OR, OC(O)R, OC(O)NR R, NR R, NR C(O)R, NR C(O)NR R, NR C(O)OR, S(O)R, S(O)NR R, S(O)2 R, NR S(O)2 R, and S(O)2 NR R.

[00642] In some embodiments, Z is C1-8 alkyl, C2-8 alkenyl, or C2-8 alkynyl, each optionally substituted with 1, 2, 3, 4, 5, or 6 substituents independently selected from halo, C1-4 alkyl, C1-4 alkenyl, C1-4 alkynyl, C1-4 haloalkyl, halosulfanyl, C1-4 hydroxyalkyl, C1-4 cyanoalkyl, Cy, CN, NO2, OR, SR, C(O)R, C(O)NR R, C(O)OR, OC(O)R, OC(O)NR R, NR R, NR C(O)R, NR C(O)NR R, NR C(O)OR, S(O)R, S(O)NR R, S(O)2 R, NR S(O)2 R, and S(O)2 NR R.
In some embodiments, Z is C₈₋₁₈ alkyl, C₂₋₈ alkenyl, or C₂₋₈ alkynyl, each optionally substituted with 1, 2, 3, 4, 5, or 6 substituents independently selected from halo, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ haloalkyl, C₁₋₄ hydroxyalkyl, C₁₋₄ cyanoalkyl, Cy¹, CN, NO₂, OR¹, SR¹, C(O)R², C(O)NR³, OR², OC(O)R², OC(O)NR³, NR²R³, NR³C(O)R⁴, NR⁴C(O)NR⁵R⁶, NR⁴C(O)OR⁷, S(O)R⁸, S(O)NR⁹, C(O)OR¹⁰, NR⁴R⁹R¹¹, NR⁴C(O)R¹², and S(O)₂R¹³.

In some embodiments, Z is C₈₋₁₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl, each optionally substituted with 1, 2, 3, 4, 5, or 6 substituents independently selected from halo, C₁₋₄ alkyl, C₁₋₄ haloalkyl, halosulfanyl, C₁₋₄ hydroxyalkyl, C₁₋₄ cyanoalkyl, Cy¹, CN, NO₂, OR¹, C(O)NR³, C(O)OR¹⁰, NR⁴R⁹, NR⁴C(O)R¹², and S(O)₂R¹³.

In some embodiments, Z is C₈₋₁₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl, each optionally substituted with 1, 2, 3, 4, 5, or 6 substituents independently selected from halo, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ hydroxyalkyl, C₁₋₄ cyanoalkyl, Cy¹, CN, NO₂, OR¹, C(O)NR³, C(O)OR¹⁰, NR⁴R⁹, NR⁴C(O)R¹², and S(O)₂R¹³.

In some embodiments, Z is C₈₋₁₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl, each optionally substituted with 1, 2, or 3 substituents independently selected from halo, C₁₋₄ alkyl, C₁₋₄ haloalkyl, halosulfanyl, C₁₋₄ hydroxyalkyl, C₁₋₄ cyanoalkyl, Cy¹, CN, NO₂, OR¹, C(O)NR³, C(O)OR¹⁰, NR⁴R⁹, NR⁴C(O)R¹², and S(O)₂R¹³.

In some embodiments, Z is C₈₋₁₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl, each optionally substituted with 1, 2, or 3 substituents independently selected from halo, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ hydroxyalkyl, C₁₋₄ cyanoalkyl, Cy¹, CN, NO₂, OR¹, C(O)NR³, C(O)OR¹⁰, NR⁴R⁹, NR⁴C(O)R¹², and S(O)₂R¹³.

In some embodiments, Z is substituted with at least one substituent comprising at least one CN group.

In some embodiments, Z is C₈₋₁₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl, each substituted with at least one CN or C₁₋₄ cyanoalkyl and optionally substituted with 1, 2, 3, 4, or 5 further substituents selected from halo, C₁₋₄ alkyl, C₂₋₈ alkenyl, C₂₋₄ alkynyl, C₁₋₄ haloalkyl, halosulfanyl, C₁₋₄ hydroxyalkyl, C₁₋₄ cyanoalkyl, Cy¹, CN,
NO₂, OR', SR', C(O)R', C(O)NR'R', C(O)OR', OC(O)R', OC(O)NR'R', NR'R', NR'C(O)R',
NR'C(O)NR'R', NR'C(O)OR', S(O)R', S(O)NR'R', S(O)₂R', NR'S(O)₂R', and S(O)₂NR'R'.

[00650] In some embodiments, Z is C₁₋₈ alkyl, C₂₋₈ alkenyl, C₃₋₈ alkynyl, aryl, cycloalkyl,
heteroaryl, or heterocycloalkyl, each substituted with at least one CN or C₁₋₄ cyanoalkyl and
optionally substituted with 1, 2, 3, or 5 further substituents selected from halo, C₁₋₄ alkyl, C₂₋₄
alkenyl, C₃₋₄ alkynyl, C₂₋₈ haloalkyl, C₂₋₄ hydroxalkyl, C₂₋₄ cyanoalkyl, Cy¹, CN, NO₂, OR², SR²,
C(O)R², C(O)NR², C(O)OR², OC(O)R², OC(O)NR², NR², NR'C(O)R², NR'C(O)NR², NR'C(O)OR²,
NR'C(O)OR², S(O)R², S(O)NR²R², S(O)₂R², NR'S(O)₂R², and S(O)₂NR²R².

[00651] In some embodiments, wherein the —(Y)n—Z moiety is taken together with i) A² to
which said moiety is attached, ii) R₅ or R⁶ of either T or V, and iii) the C or N atom to which said
R₅ or R⁶ of either T or V is attached to form a 4- to 20-membered aryl, cycloalkyl, heteroaryl, or
heterocycloalkyl ring fused to the 5-membered ring formed by A¹, A², U, T, and V, wherein said
4- to 20-membered aryl, cycloalkyl, heteroaryl, or heterocycloalkyl ring is optionally substituted
by 1, 2, 3, 4, or 5 substituents independently selected from —(W)m-Q.

[00652] In some embodiments, wherein the —(Y)n—Z moiety is taken together with i) A² to
which said moiety is attached, ii) R₅ or R⁶ of either T or V, and iii) the C or N atom to which said
R₅ or R⁶ of either T or V is attached to form a 4- to 8-membered aryl, cycloalkyl, heteroaryl, or
heterocycloalkyl ring fused to the 5-membered ring formed by A¹, A², U, T, and V, wherein said
4- to 8-membered aryl, cycloalkyl, heteroaryl, or heterocycloalkyl ring is optionally substituted
by 1, 2, 3, 4, or 5 substituents independently selected from —(W)m-Q.

[00653] In some embodiments, the —(Y)n—Z moiety is taken together with i) A² to which said
moiety is attached, ii) R₅ or R⁶ of either T or V, and iii) the C or N atom to which said R₅ or R⁶ of
either T or V is attached to form a 6-membered aryl, cycloalkyl, heteroaryl, or heterocycloalkyl
ring fused to the 5-membered ring formed by A¹, A², U, T, and V, wherein said 6-membered
aryl, cycloalkyl, heteroaryl, or heterocycloalkyl ring is optionally substituted by 1, 2, or 3
substituents independently selected from halo, CN, NO₂, C₁₋₈ alkyl, C₂₋₈ alkenyl, C₃₋₈ alkynyl, C₁₋₈
haloalkyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl wherein said C₁₋₈ alkyl, C₂₋₈ alkenyl,
C₃₋₈ alkynyl, C₁₋₈ haloalkyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally
substituted by 1, 2 or 3 CN.
[00654] In some embodiments, C y 1 and C y 2 are independently selected from aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, each optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from halo, C 1-4 alkyl, C 2-4 alkenyl, C 2-4 alkynyl, C 1-4 haloalkyl, C 1-4 hydroxyalkyl, C 1-4 cyanoalkyl, CN, NO 2 , OR 2 , SR 2 , C(O)R 2 , C(O)NR 2 R 2b , C(O)OR 2 , OC(O)R 2 , OC(O)NR 2 R 2b , NR 2 C(O)R 2 , NR 2 C(O)OR 2 , S(O)R 2b , S(O)NR 2 R 2b , S(O) 2 R 2b , and S(O) 2 NR 2 R 2b .

[00655] In some embodiments, R 1 , R 2 , R 3 , and R 4 are each H.

[00656] In some embodiments, C y 1 and C y 2 are independently selected from aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, each optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from halo, C 1-4 alkyl, C 2-4 alkenyl, C 2-4 alkynyl, C 1-4 haloalkyl, CN, NO 2 , OR 2 , SR 2 , C(O)R 2 , C(O)NR 2 R 2b , C(O)OR 2 , OC(O)R 2 , OC(O)NR 2 R 2b , OC(O)NR 2 R 2b , OC(O)NR 2 R 2b , OC(O)NR 2 R 2b , S(O)R 2b , S(O)NR 2 R 2b , S(O) 2 R 2b , and S(O) 2 NR 2 R 2b .

[00657] In some embodiments, C y 1 and C y 2 are independently selected from cycloalkyl optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from halo, C 1-4 alkyl, C 2-4 alkenyl, C 2-4 alkynyl, C 1-4 haloalkyl, CN, NO 2 , OR 2 , SR 2 , C(O)R 2 , C(O)NR 2 R 2b , C(O)OR 2 , OC(O)R 2 , OC(O)NR 2 R 2b , OC(O)NR 2 R 2b , NR 2 R 2b , NR 2 C(O)R 2 , NR 2 C(O)OR 2 , S(O)R 2b , S(O)NR 2 R 2b , S(O) 2 R 2b , and S(O) 2 NR 2 R 2b .

[00658] In some embodiments, R 1 , R 2 , R 3 , and R 4 are independently selected from H, halo, C 1-4 alkyl, C 2-4 alkenyl, C 2-4 alkynyl, C 1-4 haloalkyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO 2 , OR 2 , SR 2 , C(O)R 2 , C(O)NR 2 R 2b , C(O)OR 2 , OC(O)R 2 , OC(O)NR 2 R 2b , NR 2 OR 2 , NR 2 C(O)R 2 , NR 2 C(O)OR 2 , S(O)R 2b , S(O)NR 2 R 2b , S(O) 2 R 2b , and S(O) 2 NR 2 R 2b .

[00659] In some embodiments, R 1 , R 2 , R 3 , and R 4 are independently selected from H, halo, and C 1-4 alkyl.

[00660] In some embodiments, R 1 , R 2 , R 3 , and R 4 are each H.
In some embodiments, $R^1$ is H, halo, or C$_{1-4}$ alkyl.

In some embodiments, $R^5$ is H, halo, C$_{1-4}$ alkyl, C$_{2-4}$ alkenyl, C$_{2-4}$ alkynyl, C$_{1-4}$ halooalkyl, CN, NO$_2$, OR', SR', C(O)R', C(O)NR'R', C(O)OR', OC(O)R', OC(O)NR'R', NR'R', NR'C(O)R', NR'C(O)OR', C(=NR')NR'R', NR'C(=NR')(NR')', S(O)R', S(O)NR'R', S(O)$_2$R', C(=NOH)R, C(=NO(C$_{1-6}$ alkyl))R', and S(O)$_2$NR'R', where $R'$ is H, halo, C$_{1-4}$ alkyl, C$_{2-4}$ alkenyl, or C$_{2-8}$ alkynyl, is optionally substituted with 1, 2, 3, 4, 5, or 6 substituents independently selected from halo, C$_{1-4}$ alkyl, C$_{2-4}$ alkenyl, C$_{2-4}$ alkynyl, C$_{1-4}$ haloalkyl, halosulfany1, C$_{1-4}$ hydroxyalkyl, C$_{1-4}$ cyanoalkyl, Cy', CN, NO$_2$, OR', SR', C(O)R', C(O)NR'R', C(O)OR', OC(O)R', OC(O)NR'R', NR'R', NR'C(O)R', NR'C(O)OR', C(=NR')NR'R', NR'C(=NR')(NR')', S(O)R', S(O)NR'R', S(O)$_2$R', C(=NOH)R, C(=NO(C$_{1-6}$ alkyl))R', and S(O)$_2$NR'R'.

In some embodiments, $R^{11}$ and $R^{12}$ are independently selected from H, halo, OH, CN, (C$_{1-4}$)alkyl, (C$_{1-4}$)haloalkyl, halosulfany1, SCN, (C$_{2-4}$)alkenyl, (C$_{1-4}$)alkynyl, (C$_{1-4}$)hydroxyalkyl, (C$_{1-4}$)cyanoalkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl.

In some embodiments, $R^{11}$ and $R^{12}$ are independently selected from H, halo, OH, CN, (C$_{1-4}$)alkyl, (C$_{1-4}$)haloalkyl, (C$_{2-4}$)alkenyl, (C$_{1-4}$)alkynyl, (C$_{1-4}$)hydroxyalkyl, (C$_{1-4}$)cyanoalkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl.
In an embodiment, the JAK-2 inhibitor is ruxolitinib (available from Incyte Corp. and Novartis AG). In an embodiment, the JAK-2 inhibitor is ruxolitinib phosphate (available from Incyte Corp. and Novartis AG). In an embodiment, the JAK-2 inhibitor is \((R)-3-(4-(7H\text{-}\text{pyrrolo}[2,3-d]\text{pyrimidin}-4\text{-}y1)-1\text{H}\text{-}\text{pyrazol}-1\text{-}y1)-3\text{-}\text{cyclopentylpropanenitrile}\). In an embodiment, the JAK-2 inhibitor is the phosphate salt of \((R)-3-(4-(7H\text{-}\text{pyrrolo}[2,3-d]\text{pyrimidin}-4\text{-}y1)-1\text{H}\text{-}\text{pyrazol}-1\text{-}y1)-3\text{-}\text{cyclopentylpropanenitrile}\). In an embodiment, the JAK-2 inhibitor is \((3R)-3\text{-}\text{cyclopentyl}-3-[4-(7H\text{-}\text{pyrrolo}[2,3-d]\text{pyrimidin}-4\text{-}y1)-1\text{H}\text{-}\text{pyrazol}-1\text{-}y1]\text{propanenitrile}\). In an embodiment, the JAK-2 inhibitor has the chemical structure shown in Formula (XXX):

![Formula (XXX)](image)

Ruxolitinib may be prepared according to the procedures given in the references above, or by the procedure of Example 67 of U.S. Patent No. 7598257, the disclosure of which is specifically incorporated by reference herein. Briefly, the preparation is as follows:

Step 1. (2E)- and (2Z)-3-Cyclopentylacrylonitrile. To a solution of 1.0 M potassium tert-butoxide in THF (235 mL) at 0° C. was added dropwise a solution of diethyl cyanomethylphosphonate (39.9 mL, 0.246 mol) in TBF (300 mL). The cold bath was removed and the reaction was warmed to room temperature followed by recooling to 0° C., at which time a solution of cyclopentanecarbaldehyde (22.0 g, 0.224 mol) in THF (60 mL) was added dropwise. The bath was removed and the reaction warmed to ambient temperature and stirred for 64 hours. The mixture was partitioned between diethyl ether and water, the aqueous was extracted with three portions of ether, followed by two portions of ethyl acetate. The combined extracts were washed with brine, then dried over sodium sulfate, filtered and concentrated in vacuo to afford a mixture containing 24.4 g of olefin isomers which was used without further purification (89%). 1H NMR (400 MHz, CDCl3): δ 6.69 (dd, 1H, trans olefin), 6.37 (t, 1H, cis olefin), 5.29 (dd, 1H, trans olefin), 5.20 (d, 1H, cis olefin), 3.07-2.95 (m, 1H, cis product), 2.64-2.52 (m, 1H, trans product), 1.98-1.26 (m, 16H).

Step 2. (3R)- and (3S)-3-Cyclopentyl-3-[4-(7-(2-(trimethylsilyl)ethoxy)methyl-7H-pyrrolo[2,3-d]-pyrimidin-4-yl)-1H-pyrazol-1-yl]propanenitrile. To a solution of 4-(1H-pyrazol-4-yl)-7-[2-(trimethylsilyl)ethoxy]methyl-7H-pyrrolo[2,3-d]-pyrimidine (15.0 g, 0.0476 mol) in ACN (300 mL) was added 3-cyclopentylacrylonitrile (15 g, 0.12 mol) (as a mixture of cis and trans isomers), followed by DBU (15 mL, 0.10 mol). The resulting mixture was stirred at room temperature overnight. The ACN was evaporated. The mixture was diluted with ethyl acetate, and the solution was washed with 1.0 N HCl. The aqueous layer was back-extracted with three portions of ethyl acetate. The combined organic extracts were washed with brine, dried over sodium sulfate, filtered and concentrated. The crude product was purified by silica gel chromatography (gradient of ethyl acetate/hexanes) to yield a viscous clear syrup, which was dissolved in ethanol and evaporated several times to remove ethyl acetate, to afford 19.4 g of racemic adduct (93%). The enantiomers were separated by preparative-HPLC, (OD-H column, 15% ethanol/hexanes) and used separately in the next step to generate their corresponding final product. The final products (see Step 3) stemming from each of the separated enantiomers were
found to be active JAK inhibitors; however, the final product stemming from the second peak to elute from the preparative-HPLC was more active than its enantiomer. The products may be isolated by preparative HPLC or other means known to those of skill in the art for use in Step 3 below. \(^\text{1}^\)H NMR (300 MHz, CDCl3): \(\delta\) 8.85 (s, 1H), 8.32 (s, 2H), 7.39 (d, 1H), 6.80 (d, 1H), 5.68 (s, 2H), 4.26 (dt, 1H), 3.54 (t, 2H), 3.14 (dd, 1H), 2.95 (dd, 1H), 2.67-2.50 (m, 1H), 2.03-1.88 (m, 1H), 1.80-1.15 (m, 7H), 0.92 (t, 2H), −0.06 (s, 9H); MS(ES): 437 (M+).

[00675] Step 3. To a solution of 3-cyclopentyl-3-[4-(7-[2-(trimethylsilyl)ethoxy]methyl-7H-pyrrolo[2,3-d]-pyrimidin-4-yl]-1H-pyrazol-1-yl]propanenitrile (6.5 g, 0.015 mol, \(R\) or \(S\) enantiomer as isolated above) in DCM (40 mL) was added TFA (16 mL) and this was stirred for 6 hours. The solvent and TFA were removed in vacuo. The residue was dissolved in DCM and concentrated using a rotary evaporator two further times to remove as much as possible of the TFA. Following this, the residue was stirred with ethylenediamine (4 mL, 0.06 mol) in methanol (30 mL) overnight. The solvent was removed in vacuo, water was added and the product was extracted into three portions of ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate, decanted and concentrated to afford the crude product which was purified by flash column chromatography (eluting with a gradient of methanol/DCM). The resulting mixture was further purified by preparative-HPLC/MS (C18 eluting with a gradient of ACN/H2O containing 0.15% NH4OH) to afford product (2.68 g, 58%). \(^\text{1}^\)H NMR (400 MHz, D6-dmso): \(\delta\) 12.11 (br s, 1H), 8.80 (s, 1H), 8.67 (s, 1H), 8.37 (s, 1H), 7.60 (d, 1H), 6.98 (d, 1H), 4.53 (dt, 1H), 3.27 (dd, 1H), 3.19 (dd, 1H), 2.48-2.36 (m, 1H), 1.86-1.76 (m, 1H), 1.68-1.13 (m, 7H); MS(ES): 307 (M+).

[00676] Ruxolitinib prepared according to the steps above, or any other procedure, may be used as its free base for the compositions and methods described here. Ruxolitinib may also be used in a salt form. For example, a crystalline phosphoric acid salt of \((R)-3-(4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl)-3-cyclopentylpropanenitrile\ may be prepared from the free base as follows according to the procedure given in Example 2 of U.S. Patent No. 8,722,693, the disclosure of which is specifically incorporated herein by reference. To a test tube was added \((R)-3-(4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl)-3-cyclopentylpropanenitrile\ (153.5 mg) and phosphoric acid (56.6 mg) followed by isopropyl alcohol (IPA) (5.75 mL). The resulting mixture was heated to clear, cooled to room temperature, and then stirred for another 2
hours. The precipitate was collected by filtration and the cake was washed with 0.6 mL of cold IPA. The cake was dried under vacuum to constant weight to provide the final salt product (171.7 mg). The phosphoric acid salt is a 1:1 salt by $^1$H NMR and crystallinity is confirmed by X-ray powder diffraction (XRPD). Differential scanning calorimetry (DSC) of the produce yields a sharp melting peak at about 198.7°C.

[00677] In an embodiment, the JAK-2 inhibitor is a compound of Formula (XXXI):

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, wherein:
L is SO$_2$ or CO;
R' is C$_{1-6}$ alkyl, C$_{3-7}$ cycloalkyl, phenyl, 5- or 6-membered heteroaryl, indolyl, NR$_2$R$^3$, or OR$^4$, wherein said alkyl, cycloalkyl, phenyl, or heteroaryl is optionally substituted with 1, 2, or 3 substituents independently selected from F, CN, and C$_{1-4}$ alkyl;
R$^2$ and R$^3$ are independently selected from H, C$_{1-4}$ alkyl, and phenyl; and
R$^4$ is C$_{1-6}$ alkyl, phenyl, or benzyl.
In some embodiments, when L is SO$_2$, then R$^1$ is other than OR$^4$.
In some embodiments, when L is SO$_2$, then R$^1$ is C$_{1-6}$ alkyl, C$_{3-7}$ cycloalkyl, phenyl, 5- or 6-membered heteroaryl, or NR$_2$R$^3$, wherein said alkyl, cycloalkyl, phenyl, or heteroaryl is optionally substituted with 1, 2, or 3 substituents independently selected from F and C$_{1-4}$ alkyl.
In some embodiments, when L is CO, then R$^1$ is C$_{3-7}$ cycloalkyl, phenyl, 5- or 6-membered heteroaryl, indolyl, NR$_2$R$^3$, or OR$^4$, wherein said cycloalkyl, phenyl, or heteroaryl is optionally substituted with 1, 2, or 3 substituents independently selected from CN and C$_{1-4}$ alkyl.
In some embodiments, L is SO$_2$.
In some embodiments, L is CO.
In some embodiments, R$^1$ is methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, 2-methylprop-1-yl, 1-methylprop-1-yl, each optionally substituted with 1, 2, or 3 F.
In some embodiments, $R_1^1$ is $C_{1-4}$ alkyl.
In some embodiments, $R_1^1$ is ethyl.
In some embodiments, $R_1^1$ is $C_{3-7}$ cycloalkyl optionally substituted by $C_{1-4}$ alkyl.
In some embodiments, $R_1^1$ is phenyl optionally substituted with F, methyl, or CN.
In some embodiments, $R_1^1$ is 5-membered heteroaryl selected from thienyl, pyrazolyl, pyrrolyl, 1,2,4-oxadiazolyl, and isoxazolyl, each optionally substituted with $C_{1-4}$ alkyl.
In some embodiments, $R_1^1$ is pyridinyl.
In some embodiments, $R_1^1$ is $N R_2^2 R_3^3$ or $O R_4^4$.
In some embodiments, $L$ is $SO_2$ and $R_1^1$ is $C_{1-6}$ alkyl.

[00678] In an embodiment, the JAK-2 inhibitor is baricitinib (available from Incyte Corp. and Eli Lilly & Co.). In an embodiment, the JAK-2 inhibitor is 2-(3-(4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl)-1-(ethylsulfonyl)azetidin-3-yl)acetonitrile. In an embodiment, the JAK-2 inhibitor has the chemical structure shown in Formula (XXXII):

![Formula (XXXII)](image)


[00679] In an embodiment, the JAK-2 inhibitor is a compound of Formula (XXXIII):
or pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, wherein: Q and Z are independently selected from N and CR¹; n is 1, 2 or 3;

R¹ is independently selected from hydrogen, halogen, R², OR², OH, R³, OR³, CN, CF₃, (CH₂)ₙN(R³)₂, NO₂, R²R³, SO₂R¹, NR²SO₂R¹, COR¹, NR²COR¹, CO₂H, CO₂R¹, NR²COR¹, R²CN, R²CN, R²OH, R²OR³ and OR³R¹; or two R¹ substituents together with the carbons which they are attached to form an unsaturated 5 or 6 membered heterocyclyl;

R² is substituted or unsubstituted Ci^alkyl or substituted or unsubstituted Cj₄ alkylene where up to 2 carbon atoms can be optionally replaced with CO, NR¹, C0NR¹, S, SO₂ or O;

R³ is R², C₂-₄ alkenyl or substituted or unsubstituted aryl;

R⁴ is NH₂, NHR¹, N(R¹)₂, substituted or unsubstituted morpholino, substituted or unsubstituted thiomorpholino, substituted or unsubstituted thiomorpholino-1-oxide, substituted or unsubstituted thiomorpholino-1, 1-dioxide, substituted or unsubstituted piperazinyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted pyridinyl, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted tetrahydrofuranyl and substituted or unsubstituted tetrahydropyranyl;

R⁵ is substituted or unsubstituted Ci^alkylene;

R⁶-R¹⁰ are independently selected from H, R⁷ CN, halogen, substituted or unsubstituted Ci₆ alkyl, OR¹, CO₂R¹, N(R¹)₂, NO₂, CON(R¹)₂, SO₂N(R¹)₂, N(SO₂R¹)₂, substituted or unsubstituted piperazinyl, N(R⁷)SO₂R² and CF₃; R² is absent or substituted or unsubstituted Ci₆ alkylene

Formula (XXXIII)
wherein up to 2 carbon atoms can be optionally replaced with CO, NSO$_2$R$^1$, NR$^Y$, CO$_2$R$^Y$, S, SO$_2$ or O; R$^1$ is H or substituted or unsubstituted C$_{1-4}$ alkyl; and R$^{11}$ is selected from H, halogen, substituted or unsubstituted C$_{1-4}$ alkyl, OR$^2$, CO$_2$R$^2$, CN, CO$_2$NR$^Y$, S, SO$_2$, or O; or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. The preparation of this compound is described in U.S. Patent No. 8,486,941 and U.S. Patent Application Publication Nos. 2010/0197671 A1; 2014/0005180 A1; 2014/0011803 A1; and, 2014/0073643 A1, the disclosures of which are incorporated by reference herein. In an embodiment, the JAK-2 inhibitor is a compound described in U.S. Patent No. 8,486,941 and U.S. Patent Application Publication Nos. 2010/0197671 A1; 2014/0005180 A1; 2014/0011803 A1; and, 2014/0073643 A1, the disclosures of which are incorporated by reference herein.

[00681] In an embodiment, the JAK-2 inhibitor is a compound of Formula (XXXV):
or a tautomer thereof, or a clathrate thereof, or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, wherein:

\[ X_{41} \text{ is } O, S, \text{ or } NR_{42}; \]

\[ X_{42} \text{ is } CR_{44} \text{ or } N; \]

\[ Y_{40} \text{ is } N \text{ or } CR_{45}; \]

\[ Y_{41} \text{ is } N \text{ or } CR_{46}; \]

\[ Y_{42}, \text{ for each occurrence, is independently } N, C \text{ or } CR_{46}; \]

\[ Z \text{ is } OH, SH, \text{ or } NHR_{47}; \]

\( R_{43} \) is —H, —OH, —SH, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, halo, cyano, nitro, guanadino, a haloalkyl, a heteroalkyl, an alkoxy or cycloalkoxy, a haloalkoxy, —NR_{10}R_{11}, —OR_{8}, —C(O)R_{7}, —C(O)OR_{7}, —C(S)R_{7}, —C(O)SR_{8}, —C(S)OR_{8}, —C(S)NR_{10}R_{11}, —C(NR_{8})OR_{7}, —C(NR_{8})R_{7}, —C(NR_{8})NR_{10}R_{11}, —C(NR_{8})SR_{8}, —OC(O)R_{7}, —OC(O)OR_{7}, —OC(S)OR_{7}, —OC(O)OR_{7}, —SC(O)R_{7}, —SC(O)OR_{7}, —SC(NR_{8})OR_{7}, —OC(S)R_{7}, —SC(S)R_{7}, —SC(S)OR_{7}, —OC(O)NR_{10}R_{11}, —OC(S)NR_{10}R_{11}, —OC(NR_{8})NR_{10}R_{11}, —SC(O)NR_{10}R_{11}, —SC(NR_{8})NR_{10}R_{11}, —OC(NR_{8})R_{7}, —SC(NR_{8})R_{7}, —OC(O)NR_{10}R_{11}, —NR_{7}C(O)R_{7}, —NR_{7}C(S)R_{7}, —NR_{7}C(S)OR_{7}, —NR_{7}C(NR_{8})R_{7}, —NR_{7}C(O)OR_{7}, —
NR_7 C(NR_8 )OR_9 , —NR_7 C(O)NR_8 R_10 R_11 , —NR_7 C(NR_8 )NR_10 R_11 , —SR_7 ,
—S(O)_p R_9 , —OS(O)_p R_9 , —OS(O)_p NR_10 R_11 , —S(O) OR_9 , —NR_8 S(O) R_9 , —
NR_8 S(O) NR_10 R_11 , —NR_8 S(O) OR_9 , —S(O) NR_10 R_11 , —SS(O) R_9 , —SS(O) OR_9 , —
SS(O) NR_10 R_11 , —OP(O)(OR_9 )_2 , or —SP(O)(OR_9 )_2 ;

R_{42} is —H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally
substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocycl, an optionally substituted aryl, an
optionally substituted heteroaryl, hydroxyalkyl, haloalkyl, a heteroalkyl, a heteroaryl, C(O)R_7 , —
(CH_2)_m C(O)OR_7 , —C(O)OR_7 , —OC(O)R_7 , —C(O)NR_10 R_11 , —S(O) R_7 , —S(O) OR_9 , or —
S(O) NR_10 R_11 ;

R_{43} and R_{44} are, independently, —H, —OH, an optionally substituted alkyl, an optionally
substituted alkenyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an
optionally substituted heterocycl, an optionally substituted aryl, an
optionally substituted heteroaryl, hydroxyalkyl, haloalkyl, a heteroalkyl, a heteroaryl, C(O)R_7 , —
(CH_2)_m C(O)OR_7 , —C(O)OR_7 , —OC(O)R_7 , —C(O)NR_10 R_11 , —
NR_8 C(O)R_7 , —SR_7 , —S(O) R_7 , —OS(O) R_9 , —S(O) OR_9 , or —NR_8 S(O) R_7 , —
S(O) NR_10 R_11 , or R_{43} and R_{44} taken together with the carbon atoms to which they are attached
form an optionally substituted cycloalkyl, an optionally substituted aryl, an optionally
substituted heterocyclic, or an optionally substituted heteroaryl;

R_{45} is —H, —OH, —SH, —NR_H, —OR_2_2b, —SR_2_2b, —NHR_2_2b, —O(CH_2)_m OH, —O(CH_2)_m SH,
—O(CH_2)_m NR_H, —S(CH_2)_m OH, —S(CH_2)_m SH, —S(CH_2)_m NR_H, —OC(O)NR_10 R_11 , —
SC(O)NR_10 R_11 , —NR_9 C(O)NR_10 R_11 , —OC(O)R_9 , —SC(O)R_9 , —NR_9 C(O)R_9 , —
OC(O)OR_9 , —SC(O)OR_9 , —NR_9 C(O)OR_9 , —OCH_2 C(O)R_7 , —SCH_2 C(O)R_7 , —
NR_9 CH_2 C(O)R_7 , —OCH_2 C(O)OR_9 , —SCR_2 C(O)OR_9 , —NR_9 CH_2 C(O)OR_9 , —
OCH_2 C(O)NR_10 R_11 , —SCH_2 C(O)NR_10 R_11 , —NR_9 CH_2 C(O)NR_10 R_11 , —OS(O) R_9 , —
SS(O) R_9 , —NR_9 S(O) R_9 , —OS(O) NR_10 R_11 , —SS(O) NR_10 R_11 , —NR_9 S(O) NR_10 R_11 , —
OS(O) OR_9 , —SS(O) OR_9 , —NR_9 S(O) OR_9 , —OC(S)R_9 , —SC(S)R_9 , —NR_9 C(S)R_9 , —
OC(S)OR_9 , —SC(S)OR_9 , —NR_9 C(S)OR_9 , —OC(S)NR_10 R_11 , —SC(S)NR_10 R_11 , —
NR_7 C(S)NR_{10} R_{11}, —OC(NR_8 )R_7, —SC(NR_8 )R_7, —NR_7 C(N_8 )R_2, —OC(NR_8 )OR_7, —SC(NR_8 )OR_7, —NR_7 C(N_8 )OR_7, —OC(NR_8 )_R_{10} R_{11}, —SC(NR_8 )NR_7 R_{10} R_{11}, or —NR_7 C(N_8 )NR_7 R_{10} R_{11};

R_{14}, for each occurrence, is independently, selected from the group consisting of H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, halo, cyano, nitro, guanadino, a haloalkyl, a heteroalkyl, —NR_10 R_{11}, —OR_7, —C(O)R_7, —C(O)OR_7, —OC(O)R_7, —C(O)NR_7 R_{10}, —NR_7 C(O)R_7, —SR_7, —S(O)_p R_7, —OS(O)_p R_7, —S(O) OR_7, —NR_7 S(O) R_7, or —S(O) NR_{10} R_{11};

R_7 and R_8, for each occurrence, are, independently, —H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl;

R_{10} and R_{11}, for each occurrence, are independently —H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl; or R_{10} and R_{11}, taken together with the nitrogen to which they are attached, form an optionally substituted heterocyclyl or an optionally substituted heteroaryl;

R_{26}, for each occurrence is, is independently, a lower alkyl;

p, for each occurrence, is, independently, 1 or 2; and

m, for each occurrence, is independently, 1, 2, 3, or 4.

[00682] In an embodiment, the JAK-2 inhibitor is a compound of Formula (XXXVI):
or a tautomer thereof, or a clathrate thereof, or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, wherein:

X_{45} is CR_{54} or N;

Z_{1} is —OH or —SH;

R_{56} is selected from the group consisting of —H, methyl, ethyl, isopropyl, and cyclopropyl;

R_{52} is selected from the group consisting of —H, methyl, ethyl, n-propyl, isopropyl, n-butyl, n-pentyl, n-hexyl, —(CH_{2})_{2}OCH_{3}, —CH_{2}C(O)OH, and —C(O)N(CH_{3})_{2};

R_{53} and R_{54} are each, independently, —H, methyl, ethyl, or isopropyl; or R_{53} and R_{54} taken together with the carbon atoms to which they are attached form a phenyl, cyclohexenyl, or cyclooctenyl ring; and

R_{55} is selected from the group consisting of —H, —OH, —OCH_{3}, and —OCH_{2}CH_{3}.

[00683] In an embodiment, the JAK-2 inhibitor is ganetespib. In an embodiment, the JAK-2 inhibitor is 5-(2,4-dihydroxy-5-isopropylphenyl)-4-(1-methyl-1H-indol-5-yl)-2,4-dihydro-3H-1,2,4-triazol-3-one. In an embodiment, the JAK-2 inhibitor has the chemical structure shown in Formula (XXXVII):

[00684] In an embodiment, the JAK-2 inhibitor is a compound of Formula (XXXVIII):
or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, wherein the compound is defined by the following (I) or (II).

(I): X represents CH or N; $R^1$ represents a halogen; $R^2$ represents: (1) H, (2) a halogen, (3) cyano, (4) a group represented by the following general formula [2]:

\[
\begin{array}{c}
  * \\
  \text{Rc} \\
  \text{Rd} \\
  \text{Re}
\end{array}
\]

(wherein * indicates the binding position; and $R^C$, $R^D$ and $R^E$ are the same or different and each represents (a) H, or (b) alkyl optionally substituted by hydroxy or alkoxy, or alternatively two of $R^C$, $R^D$ and $R^E$ are taken together with the adjacent C to represent a N-containing saturated heterocyclic group and the other one is H, the saturated heterocyclic group optionally substituted by alkylsulfonyl).

(5) a group represented by the following general formula [3]:

\[
\begin{array}{c}
  * \\
  \text{N} \\
  \text{Rf} \\
  \text{Rg}
\end{array}
\]

(wherein * has the same meaning as described above; and $R^F$ and $R^G$ are the same or different and each represents (a) H, (b) alkyl optionally substituted by one or two groups selected from the group consisting of hydroxy, amino, dialkylamino, a saturated cyclic amino group, alkylcarbonylamino, alkylsulfonylamino, aryl, heteroaryl optionally substituted by alkyl,
tetrahydrofuranyl, and carbamoyl, (c) alkylcarbonyl, (d) alkylsulfonyl, (e) carbamoyl, or (f) heteroaryl optionally substituted by alkyl, or alternatively R^1 and R^2 are taken together with the adjacent N to represent a saturated cyclic amino group, which may optionally be substituted by one or two groups selected from the group consisting of (a) halogen, (b) cyano, (c) hydroxy, (d) alkyl optionally substituted by one or two groups selected from the group consisting of hydroxy, alkoxy, amino, alkoxycarbonylamino, alkylsulfonylamino, and alkylcarbonylamino, (e) cycloalkyl, (f) haloalkyl, (g) alkoxy, (h) oxo, (i) a group represented by the following general formula [4]:

![Formula 4](image)

(wherein * has the same meaning as described above; and R^w represents alkyl or aryl). (j) a group represented by the following general formula [5]:

![Formula 5](image)

(wherein * has the same meaning as described above; and RI and RJ are the same or different and each represents H, alkyl, carbamoyl, alkylcarbonyl, or alkylsulfonyl), (k) a group represented by the following general formula [6]:

![Formula 6](image)

(wherein * has the same meaning as described above; and RK represents alkyl, hydroxy, amino, alkylamino, dialkylamino, cycloalkylamino, (cycloalkyl)alkylamino, (hydroxyalkyl)amino, (alkoxyalkyl)amino, alkoxy, alkylsulfonylamino, or a saturated cyclic amino group), and (l) a saturated cyclic amino group optionally substituted by hydroxy; and the saturated cyclic amino
group, which is formed by combining RF, RG and the adjacent N, may form a spiro-linkage with a group represented by the following general formula [7A] or [7B]:

![Diagram of spiro-linkage](7A)

![Diagram of spiro-linkage](7B)

(wherein has the same meaning as described above),

(6) a group represented by the following general formula [8]:

![Diagram of general formula](8)

(wherein * has the same meaning as described above; and R₁ represents (a) alkyl, (b) hydroxy, (c) alkoxy, (d) saturated cyclic amino group optionally substituted by alkyl or alkylsulfonyl, or (e) an amino optionally substituted by one or two groups selected from the group consisting of alkyl, cycloalkyl, (cycloalkyl)alkyl, aralkyl; haloalkyl, dialkylaminoalkyl, alkoxyalkyl, and hydroxyalkyl),

(7) a group represented by the following general formula [9]:

![Diagram of general formula](9)

(wherein * has the same meaning as described above; and Rₘ, Rₙ and Rₒ are the same or different and each represents H, halogen, cyano, alkoxy, carbamoyl, sulfamoyl, monoalkylaminosulfonyl, or alkylsulfonyl, or alternatively two of Rₘ, Rₙ and Rₒ are taken together to represent methylenedioxy).
(8) —OR^p (R^p represents an alkyl optionally substituted by a group selected from the group consisting of hydroxy, dialkylamino, alkoxy, tetrahydrofuranyl, and cycloalkyl, or an optionally O-containing saturated cyclic group optionally substituted by hydroxy), or

(9) a heteroaryl optionally substituted by one or two groups selected from the group consisting of cyano, halogen, hydroxy, alkoxy, alkylcarbonyl, carbamoyl, alkyl, cycloalkyl, (cycloalkyl)alkyl, aralkyl, hydroxycarbonyl and alkoxyalkyl;

R^3 represents H or hydroxy;
R^2 represents H or alkyl; and
R^1 represents H or alkyl;

(II): X represents —CR^A;
R^A represents a group represented by the following general formula [10]:

![General formula [10]](image)

(wherein * has the same meaning as described above; and R^B represents (a) amino optionally substituted by one or two groups selected from the group consisting of alkyl, cycloalkyl, (cycloalkyl)alkyl, and alkoxyalkyl, (b) alkoxy, (c) hydroxy, or (d) a saturated cyclic amino group);

R^1 represents a halogen;
R^2 represents H;
R^3 represents E or hydroxy;
R^4 represents H or alkyl; and
R^5 represents H or alkyl.

[00685] In an embodiment, the JAK-2 inhibitor is NS-018. In an embodiment, the JAK-2 inhibitor is (S)-N^2-(1-(4-fluorophenyl)ethyl)-6-(1-methyl-1H-pyrazol-4-yl)-N^4-(pyrazin-2-yl)pyrimidine-2,4-diamine. In an embodiment, the JAK-2 inhibitor has the chemical structure shown in Formula (XXXIX):

[00686] In an embodiment, the JAK-2 inhibitor is a compound of Formula (XL):

\[
\text{Formula (XL)}
\]

or a stereoisomer, tautomer, or pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, wherein:

Y is C\textsubscript{1-4} alkyl.
X is C\textsubscript{1-4} alkyl;

R is

any of which are optionally fused with a 5 or 6 membered carbocycle or heterocycle having one heteroatom selected from NR\textsuperscript{3} or S, said fused carbocycle or heterocycle being optionally substituted with 0-3 R\textsuperscript{1}.

R\textsuperscript{1} is H, halo, CN, C\textsubscript{1-6} alkyl substituted with 0-3 R\textsuperscript{e}, CF\textsubscript{3}, CONR\textsuperscript{1}R\textsuperscript{1}, NR\textsuperscript{1}R\textsuperscript{1}, COOR\textsuperscript{1}, SO\textsubscript{2}-(C\textsubscript{1-4})alkyl, C(O)R\textsuperscript{1}, cycloalkyl substituted with 0-3 R\textsuperscript{e}, furanyl, tetrahydropyranyl, or pyridinyl;
R₂ is absent, H, C₁₋₆ alkyl substituted with 0-3 R', C(O)O—(C₁₋₄)alkyl, SO₂—(C₁₋₄)alkyl, cycloalkyl substituted with 0-3 R⁵, or tetrahydropyranyl;

R³ is absent, H, or C(O)O—(C₁₋₄)alkyl;

R' is H, C₁₋₆ alkyl substituted with 0-3 R', C₃₋₆ cycloalkyl substituted with 0-3 R⁵, tetrahydropyranyl, or dioxotetrahydrothiophenyl;

R⁵ is H or C₁₋₆ alkyl;

R' is H, halo, CN, OH, O—(C₁₋₄)alkyl, O—(C₁₋₄)alkyl-O—(C₁₋₄)alkyl, NH₂, N(C₁₋₄ alkyl)₂, C(O)N(C₁₋₄ alkyl)₂, SO₂—(C₁₋₄)alkyl, or morpholinyl or piperazinyl, either of which are optionally substituted with 0-1 C₁₋₄ alkyl;

R⁶ is C₁₋₆ alkyl, or azeridinyl, azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, dioxidothiomorpholinyl or tetrahydropyranyl, any of which are substituted with 0-2 R⁷; and

R⁷ is H, halo, CN, C₁₋₄ alkyl, OH, O—(C₁₋₄)alkyl, SO₂—(C₁₋₄)alkyl, NHC(O)—(C₁₋₄)alkyl, morpholinyl, OC(O)—(C₁₋₄)alkyl, C(O)N(C₁₋₄ alkyl)₂, or O—(C₁₋₄)alkyl-O—(C₁₋₄)alkyl.

In another embodiment are compounds of Formula (XL), wherein:

R is:
any of which are optionally substituted with 0-3 $R^1$.
In another embodiment are compounds of Formula (XL), wherein:
Y is methyl; and
X is ethyl.
In another embodiment are compounds of Formula (XL), wherein:
R is:
In another embodiment are compounds of Formula (XL), wherein:

R is:
any of which are optionally substituted with 0-2 R₁
In another embodiment are compounds of Formula (XL), wherein

\[ R \text{ is:} \]

\[ R_1 \text{ is } H, \text{ halo, CN, } C_{1-6} \text{ alkyl substituted with 0-3 } R^d, \text{ CF}_3, \text{ CONR}^a R^e, \text{ COOR}^b, \text{ SO}_2 -(C_{1-4}) \text{ alkyl,} \]
\[ C(O)R^d, \text{ cycloalkyl substituted with 0-3 } R^e, \text{ or pyridinyl;} \]

\[ R^d \text{ is } H, \text{ C}_{1-6} \text{ alkyl substituted with } 0-3 \text{ R}^f, \text{ C}_{3-6} \text{ cycloalkyl substituted with } 0-3 \text{ R}^f, \]
\[ \text{ tetrahydropyranyl or dioxotetrahydrothiophenyl;} \]

\[ R^e \text{ is } H \text{ or } C_{1-6} \text{ alkyl;} \]

\[ R^f \text{ is } H, \text{ halo, OH, } O-(C_{1-4}) \text{ alkyl, } \text{ SO}_2 -(C_{1-4}) \text{ alkyl or morpholinyl;} \]

\[ R^g \text{ is } C_{1-6} \text{ alkyl, or azetidinyl, pyrrolidinyl, morpholinyl, piperazinyl or dioxidothiomorpholinyl,} \]
\[ \text{any of which are substituted with 0-2 } R^e; \]

\[ R^h \text{ is } H, \text{ halo, CN, OH, } O-(C_{1-4}) \text{ alkyl, } \text{ SO}_2 -(C_{1-4}) \text{ alkyl, } \text{ NHC(O)-(C_{1-4}) alkyl or morpholinyl.} \]

In another embodiment are compounds of Formula (XL), wherein:

\[ R \text{ is:} \]

\[ R_1 \text{ is } H, \text{ halo, } C_{1-6} \text{ alkyl substituted with } 0-3 \text{ R}^i, \text{ CF}_3, \text{ CONR}^e R^f, \text{ COOR}^b, \text{ C(O)R}^d, \text{ cycloalkyl} \]
\[ \text{substituted with } 0-3 \text{ R}^e \text{ or furanyl;} \]
R² is H, C₁-₆ alkyl substituted with 0-3 R', SO₂—(C₁-₄)alkyl, cycloalkyl substituted with 0-3 R', or tetrahydropyranyl;

R¹ is H, or C₁-₆ alkyl substituted with 0-3 R';

R³ is H or C₁-₆ alkyl;

R² is H, halo, CN, OH, O—(C₁-₄)alkyl, O—(C₁-₄)alkyl-O—(C₁-₄)alkyl, NH₂, N(C₁-₄ alkyl)₂, C(O)N(C₁-₄ alkyl)₂, SO₂—(C₁-₄)alkyl, or morpholinyl or piperazinyl, either of which are optionally substituted with 0-1 C₁-₄ alkyl;

R² is C₁-₆ alkyl, or morpholinyl, piperazinyl or dihydrothiomorpholinyl, any of which are substituted with 0-2 R'; and

R¹ is H, C₁-₄ alkyl, CN, OH, NHC(O)—(C₁-₄)alkyl or morpholinyl.

In another embodiment are compounds of Formula (XL), wherein:

R is:

![Chemical Structure](attachment:image)

R¹ is C₁-₆ alkyl substituted with 0-3 R'; and

R² is C₁-₆ alkyl.

[00687] In an embodiment, the JAK-2 inhibitor is BMS-911543. In an embodiment, the JAK-2 inhibitor is N,N-dicyclopentyl-4-((1,5-dimethyl-1H-pyrazol-3-yl)amino)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide. In an embodiment, the JAK-2 inhibitor has the chemical structure shown in Formula (XLI):
or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. The preparation of this compound is described in U.S. Patent Nos. 8,673,933 and 8,202,881 and U.S. Patent Application Publication Nos. 2013/0225551 A1 and 2011/0059943 A1, the disclosures of which are incorporated by reference herein. In an embodiment, the JAK-2 inhibitor is a compound described in U.S. Patent Nos. 8,673,933 and 8,202,881 and U.S. Patent Application Publication Nos. 2013/0225551 A1 and 2011/0059943 A1, the disclosures of which are incorporated by reference herein.

[00688] In an embodiment, the JAK-2 inhibitor is gandotinib. In an embodiment, the JAK-2 inhibitor is 3-(4-chloro-2-fluorobenzyl)-2-methyl- N-(5-methyl-1 H-pyrazol-3-yl)-8-(morpholinomethyl)imidazo[1,2-b]pyridazin-6-amine. In an embodiment, the JAK-2 inhibitor has the chemical structure shown in Formula (XLII):
or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. The preparation of this compound is described in U.S. Patent No. 7,897,600 and U.S. Patent Application Publication Nos. 2010/0152181 A1 and 2010/0286139 A1, the disclosures of which are incorporated by reference herein. In an embodiment, the JAK-2 inhibitor is a compound described in U.S. Patent No. 7,897,600 and U.S. Patent Application Publication Nos. 2010/0152181 A1 and 2010/0286139 A1, the disclosures of which are incorporated by reference herein.

[00689] In an embodiment, the JAK-2 inhibitor is a compound of Formula (XLIII):

![Formula (XLIII)](image)

or a pharmaceutically acceptable derivative or prodrug thereof, wherein:

R’ and R’ are independently selected from the group consisting of -T-R’ and -L-Z-R’;

Q’ is selected from the group consisting of —CR’ — and wherein said —CR’ — may be a cis or trans double bond or a mixture thereof,

R’ is -T-(Ring D);

Ring D is a 5-7 membered monocyclic ring or 8-10 membered bicyclic ring selected from the group consisting of aryl, heteroaryl, heterocyclyl, and carbocyclyl, said heteroaryl or heterocyclyl ring having 1-4 ring heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, wherein each substitutable ring carbon of Ring D is independently
substituted by oxo, -T-R′ or —V-Z-R′, and each substitutable ring nitrogen of Ring D is independently substituted by —R″;

T is a valence bond or —(C(R‴)″)₅-A—;

A is a valence bond or a C₁₋₃ alkylidene chain wherein a methylene unit of said C₁₋₃ alkylidene chain is optionally replaced by —O—, —S—, —N(R‴)₅—, —CO—, —CONH—, —NHCO—, —SO₂—, —SO₂NH—, —NHSO₂—, —CO₂—, —OC(O)—, —OC(O)NH—, or —NHCO₂—;

Z is a C₁₋₄ alkylidene chain;

L is selected from the group consisting of —O—, —S—, —SO—, —SO₂—, —N(R‴)SO₂—, —SO₂N(R‴)₂—, —N(R‴)CON(R‴)₂—, —N(R‴)SO₂N(R‴)₂—, —N(R‴)SO₂R—, and —OC(═O)N(R‴)₂—;

R′ and R″ are independently selected from the group consisting of —R and -T-W—R‴, or R′ and R″ taken together with their intervening atoms form a fused, 5-8 membered, unsaturated or partially unsaturated ring having 0-3 ring heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, wherein each substitutable ring carbon of said fused ring formed by R′ and R″ is independently substituted by halo, oxo, —CN, —NO₂, R‴, or —V—R‴, and each substitutable ring nitrogen of said ring formed by R′ and R″ is independently substituted by —R‴;

R‴ is selected from the group consisting of —R, -halo, —OR, —C(═O)R, —CO₂R, —COCOR, —COCH₂COR, —NO₂, —CN, —S(O)R, —S(O)₂R, —SR, —N(R‴)₂, —CON(R‴)₂, —SO₂N(R‴)₂, —OC(═O)R, —N(R‴)COR, —N(R‴)CO₂(C₆₋₁₅ aliphatic), —N(R‴)N(R‴)₂, —C═NN(R‴)₂, —C═N—OR, —N(R‴)CON(R‴)₂, —N(R‴)SO₂N(R‴)₂, —N(R‴)SO₂R, and —OC(═O)N(R‴)₂.
each R is independently hydrogen or an optionally substituted group selected from the group consisting of C\textsubscript{1-6} aliphatic, C\textsubscript{6-10} aryl, a heteroaryl ring having 5-10 ring atoms, and a heterocyclyl ring having 5-10 ring atoms;

each R\textsuperscript{4} is independently selected from the group consisting of —R\textsuperscript{7}, —COR\textsuperscript{7}, —CO\textsubscript{2}(optionally substituted C\textsubscript{1-6} aliphatic), —CON(R\textsuperscript{7})\textsubscript{2}, and —SO\textsubscript{2}R\textsuperscript{7};

each R\textsuperscript{5} is independently selected from the group consisting of —R, halo, —OR, —C(=O)R, —CO\textsubscript{2}R, —COCOR, —NO\textsubscript{2}, —CN, —S(O)R, —SO\textsubscript{2}R, —SR, —N(R\textsuperscript{4}), —CON(R\textsuperscript{4})\textsubscript{2}, —SO\textsubscript{2}N(R\textsuperscript{4})\textsubscript{2}, —OC(=O)R, —N(R\textsuperscript{4})COR, —N(R\textsuperscript{4})CO\textsubscript{2}(optionally substituted C\textsubscript{1-6} aliphatic), —N(R\textsuperscript{4})N(R\textsuperscript{4})\textsubscript{2}, —C═NN(R\textsuperscript{4})\textsubscript{2}, —C═N—OR, —N(R\textsuperscript{4})CON(R\textsuperscript{4})\textsubscript{2}, —N(R\textsuperscript{4})SO\textsubscript{2}N(R\textsuperscript{4})\textsubscript{2}, —N(R\textsuperscript{4})SO\textsubscript{2}R, and —OC(=O)N(R\textsuperscript{4})\textsubscript{2};

V is selected from the group consisting of —O—, —S—, —SO—, —SO\textsubscript{2}—, —N(R\textsuperscript{6})SO\textsubscript{2}—, —SO\textsubscript{2}N(R\textsuperscript{6})—, —N(R\textsuperscript{6})—, —CO—, —CO\textsubscript{2}—, —N(R\textsuperscript{6})CO—, —N(R\textsuperscript{6})C(O)O—, —N(R\textsuperscript{6})CON(R\textsuperscript{6})—, —N(R\textsuperscript{6})SO\textsubscript{2}N(R\textsuperscript{6})—, —N(R\textsuperscript{6})N(R\textsuperscript{6})—, —C(O)N(R\textsuperscript{6})—, —OC(O)N(R\textsuperscript{6})—, —C(R\textsuperscript{6})\textsubscript{2}O—, —C(R\textsuperscript{6})\textsubscript{2}S—, —C(R\textsuperscript{6})\textsubscript{2}SO—, —C(R\textsuperscript{6})\textsubscript{2}SO\textsubscript{2}—, —C(R\textsuperscript{6})\textsubscript{2}SO\textsubscript{2}N(R\textsuperscript{6})—, —C(R\textsuperscript{6})\textsubscript{2}N(R\textsuperscript{6})C(O)O—, —C(R\textsuperscript{6})\textsubscript{2}NC\textsubscript{1-4}C(R\textsuperscript{6})\textsubscript{2}—, —C(R\textsuperscript{6})\textsubscript{2}N(R\textsuperscript{6})SO\textsubscript{2}N(R\textsuperscript{6})—, and —C(R\textsuperscript{6})\textsubscript{2}N(R\textsuperscript{6})CON(R\textsuperscript{6})—;

W is selected from the group consisting of —C(R\textsuperscript{6})O—, —C(R\textsuperscript{6})S—, —C(R\textsuperscript{6})SO—, —C(R\textsuperscript{6})\textsubscript{2}SO—, —C(R\textsuperscript{6})\textsubscript{2}SO\textsubscript{2}N(R\textsuperscript{6})—, —C(R\textsuperscript{6})\textsubscript{2}N(R\textsuperscript{6})—, —C(O)C(R\textsuperscript{6})—, —C(R\textsuperscript{6})\textsubscript{2}OC(O)N(R\textsuperscript{6})—, —C(R\textsuperscript{6})\textsubscript{2}N(R\textsuperscript{6})CO—, —C(R\textsuperscript{6})\textsubscript{2}N(R\textsuperscript{6})C(O)O—, —C(R\textsuperscript{6})═C\textsubscript{1-4}C(R\textsuperscript{6})═NN(R\textsuperscript{6})—, —C(R\textsuperscript{6})═NN═O—, —C(R\textsuperscript{6})\textsubscript{2}N(R\textsuperscript{6})N(R\textsuperscript{6})—, —C(R\textsuperscript{6})\textsubscript{2}N(R\textsuperscript{6})SO\textsubscript{2}N(R\textsuperscript{6})—, —C(R\textsuperscript{6})\textsubscript{2}N(R\textsuperscript{6})CON(R\textsuperscript{6})—, and —CON(R\textsuperscript{6})—;

each R\textsuperscript{6} is independently selected from the group consisting of hydrogen and an optionally substituted C\textsubscript{1-4} aliphatic group, or two R\textsuperscript{6} groups on the same nitrogen atom may be taken together with the nitrogen atom to form a 3-6 membered heterocyclyl or heteroaryl ring;

each R\textsuperscript{6} is independently selected from the group consisting of hydrogen and a C\textsubscript{1-4} aliphatic group, or two R\textsuperscript{6} on the same carbon atom are taken together to form a 3-8 membered carbocyclic ring;
each \( R_6 \) is independently selected from the group consisting of hydrogen, a \( C_{1-4} \) aliphatic group, halogen, optionally substituted aryl, and optionally substituted heteroaryl, or two \( R_6 \) on adjacent carbon atoms are taken together to form a 5-7 membered carbocyclic ring; and each \( R_7 \) is independently selected from the group consisting of hydrogen and an optionally substituted \( C_{1-6} \) aliphatic group, or two \( R_7 \) on the same nitrogen are taken together with the nitrogen to form a 5-8 membered heterocyclyl or heteroaryl ring.

[00690] In an embodiment, the JAK-2 inhibitor is ENMD-2076. In an embodiment, the JAK-2 inhibitor is \((E)-N'-(5\text{-}methyl-1\text{-}H\text{-}pyrazol-3\text{-}yl)-6-(4\text{-}methylpiperazin-1\text{-}yl)-2\text{-}styrylpyrimidin-4\text{-}amine\). In an embodiment, the JAK-2 inhibitor has the chemical structure shown in Formula (XLIV):

![Formula (XLIV) Image]

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. The preparation of this compound is described in U.S. Patent Nos. 8,153,630; 7,563,787; and, 8,114,870 and U.S. Patent Application Publication Nos. 2008/0200485 A1; 2007/0142368 A1; 2009/0264422 A1; 2011/0318393 A1; and, 2009/0029992 A1, the disclosures of which are incorporated by reference herein.

[00691] In an embodiment, the JAK-2 inhibitor is a compound of Formula (XLV):
or a salt, solvate, tautomer or N-oxide thereof,

wherein M is selected from a group D1 and a group D2:

and wherein:

(A) when M is a group D1:

X is selected from O, NH and NCH₃;

A is selected from a bond and a group NR₂ where R₂ is hydrogen or methyl;

E is selected from a bond, CH₂, CH(CN) and C(CH₃)₂;

R₁ is selected from:

(i) a cycloalkyl group of 3 to 5 ring members optionally substituted by hydroxy, fluorine, amino, methylamino, methyl or ethyl;

(ii) a saturated heterocyclic group of 4 to 6 ring members containing 1 or 2 heteroatom ring members selected from O, N, S and SO₂, the heterocyclic group being optionally substituted...
by (C\textsubscript{1-4})alkyl, amino or hydroxy; but excluding unsubstituted 4-morpholinyl, unsubstituted tetrahydropyran-4-yl, unsubstituted 2-pyrrolidinyl, and unsubstituted and 1-substituted piperidine-4-yl;

(iii) a 2,5-substituted phenyl group of the formula:

\[
\begin{array}{c}
\text{R}_3 \\
\text{OMe}
\end{array}
\]

wherein (a) when X is NH or N—CH\textsubscript{3}, R\textsubscript{3} is selected from chlorine and cyano;

and (b) when X is O, R\textsubscript{3} is CN;

(iv) a group CR\textsubscript{6}R\textsubscript{7}R\textsubscript{8} wherein R\textsubscript{6} and R\textsubscript{7} are each selected from hydrogen and methyl, and R\textsubscript{8} is selected from hydrogen, methyl, (C\textsubscript{1-4})alkylsulphonylmethyl, hydroxymethyl and cyano;

(v) a pyridazin-4-yl group optionally substituted by one or two substituents selected from methyl, ethyl, methoxy and ethoxy;

(vi) a substituted imidazothiazole group wherein the substituents are selected from methyl, ethyl, amino, fluorine, chlorine, amino and methylamino; and

(vii) an optionally substituted 1,3-dihydro-isooindol-2-yl or optionally substituted 2,3-dihydroindol-1-yl group wherein the optional substituents in each case are selected from halogen, cyano, amino, C\textsubscript{1-4} mono- and dialkylamino, CONH\textsubscript{2} or CONH—(C\textsubscript{1-4})alkyl, C\textsubscript{1-4} alkyl and C\textsubscript{1-4} alkoxy wherein the C\textsubscript{1-4} alkyl and C\textsubscript{1-4} alkoxy groups are optionally substituted by hydroxy, methoxy, or amino;

(viii) 3-pyridyl optionally substituted by one or two substituents selected from hydroxy, halogen, cyano, amino, C\textsubscript{1-4} mono- and dialkylamino, CONH\textsubscript{2} or CONH—C\textsubscript{1-4} alkyl, C\textsubscript{1-4} alkyl and C\textsubscript{1-4} alkoxy wherein the C\textsubscript{1-4} alkyl and C\textsubscript{1-4} alkoxy groups are optionally substituted by hydroxy, methoxy, or amino, but excluding the compounds 2-oxo-1,2-dihydro-pyridine-3-carboxylic acid [3-(5-morpholin-4-ylmethyl-1\textsubscript{H}-benzoimidazol-2-yl)-1\textsubscript{H}-pyrazol-4-yl]-amide and 2,6-
dimethoxy-N-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-nicotinamide;

(ix) thiomorpholine or an S-oxide or S,S-dioxide thereof optionally substituted by one or two substituents selected from halogen, cyano, amino, C<sub>1-4</sub> mono- and dialkylamino, CONH<sub>2</sub> or CONH—C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkyl and C<sub>1-4</sub> alkoxy wherein the C<sub>1-4</sub> alkyl and C<sub>1-4</sub> alkoxy groups are optionally substituted by hydroxy, methoxy, or amino; and

when E-A is NR<sub>1</sub>, R<sub>1</sub> is additionally selected from:

(x) 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,4-difluorophenyl, 3,4-difluorophenyl, 2,5-difluorophenyl, 3,5-difluorophenyl, 2,4,6-trifluorophenyl, 2-methoxyphenyl, 5-chloro-2-methoxyphenyl, cyclohexyl, unsubstituted 4-tetrahydropyranyl and tert-butyl;

(xi) a group NR<sub>10</sub>R<sub>11</sub> where R<sub>10</sub> and R<sub>11</sub> are each C<sub>1-4</sub> alkyl or R<sub>10</sub> and R<sub>11</sub> are linked so that NR<sub>10</sub>R<sub>11</sub> forms a saturated heterocyclic group of 4 to 6 ring members optionally containing a second heteroatom ring member selected from O, N, S and SO<sub>2</sub>, the heterocyclic group being optionally substituted by C1-4 alkyl, amino or hydroxy;

(xii) pyridone optionally substituted by one or two substituents selected from hydroxy, halogen, cyano, amino, C<sub>1-4</sub> mono- and dialkylamino, CONH<sub>2</sub>, CONH—C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkyl and C<sub>1-4</sub> alkoxy wherein the C<sub>1-4</sub> alkyl and C<sub>1-4</sub> alkoxy groups are optionally substituted by hydroxy, methoxy, or amino;

when E-A is C(CH<sub>3</sub>),NR<sub>2</sub> or CH<sub>2</sub>-NR<sub>2</sub>, R<sub>1</sub> is additionally selected from:

(xiii) unsubstituted 2-furyl and 2,6-difluorophenyl; and

when E-A is C(CH<sub>3</sub>),NR<sub>2</sub>, R<sub>1</sub> is additionally selected from:

(xiv) unsubstituted phenyl; and

when E is CH<sub>3</sub>, R<sub>1</sub> is additionally selected from:

(xv) unsubstituted tetrahydropyran-4-yl; and

(B) when M is a group D2:
A is selected from a bond and a group NR₂ where R₂ is hydrogen or methyl;

E is selected from a bond, CH₂, CH(CN) and C(CH₃)₂;

R₁ is selected from:

(xvi) a 2-substituted 3-furyl group of the formula:

\[
\begin{align*}
&\text{N} - R_4 \\
&\text{O} \\
&\text{R}_5
\end{align*}
\]

wherein R₄ and R₅ are the same or different and are selected from hydrogen and C₁₋₄ alkyl, or R₄ and R₅ are linked so that NR₄R₅ forms a 5- or 6-membered saturated heterocyclic group optionally containing a second heteroatom or group selected from O, NH, NMe, S or SO₂, the 5- or 6-membered saturated ring being optionally substituted by hydroxy, fluorine, amino, methylamino, methyl or ethyl; (xvii) a 5-substituted 2-furyl group of the formula:

\[
\begin{align*}
&R_4 \\
&\text{N} - R_4 \\
&\text{O} \\
&R_5
\end{align*}
\]

wherein R₄ and R₅ are the same or different and are selected from hydrogen and C₁₋₄ alkyl, or R₄ and R₅ are linked so that NR₄R₅ forms a 5- or 6-membered saturated heterocyclic group optionally containing a second heteroatom or group selected from O, NH, NMe, S or SO₂, the 5- or 6-membered saturated heterocyclic group being optionally substituted by hydroxy, fluorine, amino, methylamino, methyl or ethyl;

with the proviso that the compound is not 5-piperidin-1-ylmethyl-furan-2-carboxylic acid [3-(5,6-dimethoxy-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-amide;

(xviii) a group of the formula:
wherein \( R_9 \) is hydrogen, methyl, ethyl or isopropyl; \( G \) is \( \text{CH, O, S, SO, SO}_2 \) or \( \text{NH} \) and the group is optionally substituted by one, two or three substituents selected from \( \text{C}_{1-4} \) hydrocarbyl, hydroxy, \( \text{C}_{1-4} \) hydrocarbyloxy, fluorine, amino, mono- and di-\( \text{C}_{1-4} \) alkylamino and wherein the \( \text{C}_{1-4} \) hydrocarbyl and \( \text{C}_{1-4} \) hydrocarbyloxy groups are each optionally substituted by hydroxy, fluorine, amino, mono- or di-\( \text{C}_{1-4} \) alkylamino; and

(xix) a 3,5-disubstituted phenyl group of the formula:

![Chemical structure](attachment:image)

wherein \( X \) is selected from \( \text{O, NH and NCH}_3 \); and

(C) when \( M \) is a group D1:

and \( X \) is \( \text{O} \); \( A \) is a group \( \text{NR}_2 \) where \( R_2 \) is hydrogen; \( E \) is a bond; and \( R_1 \) is 2,6-difluorophenyl; then the compound of the Formula (XLV) is an acid addition salt selected from salts formed with an acid selected from the group consisting of acetic, adipic, alginic, ascorbic (e.g. \( \text{L-ascorbic} \)), aspartic (e.g. \( \text{L-aspartic} \)), benzenesulphonic, benzoic, camphoric (e.g. (\(+\)) camphoric), capric, caprylic, carbonic, citric, cyclamic, dodecanoate, dodecylsulphuric, ethane-1,2-disulphonic, ethanesulphonic, fumaric, galactaric, gentisic, glucoheptonic, D-glucuronic, glucuronic (e.g. \( \text{D-glucuronic} \)), glutamic (e.g. \( \text{L-glutamic} \)), \( \alpha \)-oxoglutaric, glycolic, hippuric, hydrochloric, isethionic, isobutyric, lactic (e.g. (\(+\))-L-lactic and (\(\pm\))-DL-lactic), lactobionic, laurysulphonic, maleic, malic, (\(-\))-L-malic, malonic, methanesulphonic, mucic, naphthalenesulphonic (e.g. naphthalene-2-sulphonic), naphthalene-1,5-disulphonic, nicotinic, oleic, orotic, oxalic, palmitic,
pamoic, phosphoric, propionic, sebacic, stearic, succinic, sulphuric, tartaric (e.g. (+)-L-tartaric), thiocyanic, toluenesulphonic (e.g. p-toluenesulphonic), valeric and xinafoic acids.

[00692] In an embodiment, the JAK-2 inhibitor is AT-9283. In an embodiment, the JAK-2 inhibitor is 1-cyclopropyl-3-(3-(5-(morpholinomethyl)-1H-benzo[d]imidazol-2-yl)-1H-pyrazol-4-yl)urea. In an embodiment, the JAK-2 inhibitor has the chemical structure shown in Formula (XLVI):

![Formula (XLVI)](image)


[00693] In an embodiment, the JAK-2 inhibitor is a compound of Formula (XLVII):

![Formula (XLVII)](image)

wherein:
R₁ and R₂ are each independently selected from the group consisting of: H, halogen, alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl, heteroalkyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, cycloalkylheteroalkyl, heterocycloalkylheteroalkyl, heteroarylheteroalkyl, arylheteroalkyl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, alkoxyaryl, alkenyloxy, alkynyloxy, cycloalkylkxyo, heterocycloalkyloxy, aryloxy, aryalkyloxy, phenoxy, benzylloxy, heteroaryloxy, amino, alkylamino, aminoaalkyl, acylamino, arylamino, sulfonylamino, sulfinylamino, —COOH, —COR, —COOR, —CONHR, —NHCOO, —NHCOOR, —NHCONHR, alkoxycarbonyl, alkylaminocarbonyl, sulfonyl, alkysulfanyl, alkylsulfonyl, arylsulfonyl, arylsulfanyl, aminosulfonyl, —SR, R'S(O)R, R'S(O)₂R, R'C(O)N(R₃)R⁴, R'SO₂N(R₃)R⁴, R'C(O)R₅—, R₆N(R₅)C(O)R₆, R₆N(SO₂)R₆, R₆N(R₅)C(O)N(R₅)R₆ and acyl, each of which may be optionally substituted;

each R₁, R₂, and R₃ is independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, arylalkyl, heteroarylalkyl and acyl, each of which may be optionally substituted;

each R₄ is independently selected from the group consisting of a bond, alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, arylalkyl, heteroarylalkyl and acyl, each of which may be optionally substituted;

Z is independently selected from the group consisting of a bond, O, S, —N(R₇)—, —N(R₇)C₁₋₂alkyl—, and —C₁₋₂alkylN(R₇)—;

each R₇ is independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, arylalkyl, heteroarylalkyl and acyl, each of which may be optionally substituted;

Ar¹ and Ar² are each independently selected from the group consisting of aryl and heteroaryl, each of which may be optionally substituted;
L is a group of formula:

\[ -X^1 - Y - X^2 - \]

wherein \( X^1 \) is attached to \( Ar^1 \) and \( X^2 \) is attached to \( Ar^2 \), and wherein \( X^1, X^2 \) and \( Y \) are selected such that the group \( L \) has between 5 and 15 atoms in the normal chain.

\( X^1 \) and \( X^2 \) are each independently a heteroalkyl group containing at least one oxygen atom in the normal chain.

\( Y \) is a group of formula \(-\text{CR}^=\text{CR}^k-\) or an optionally substituted cycloalkyl group,

wherein \( \text{R}^k \) and \( \text{R}^h \) are each independently selected from the group consisting of \( H \), alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, arylalkyl, heteroarylalkyl and acyl, each of which may be optionally substituted, or

\( \text{R}^k \) and \( \text{R}^h \) may be joined such that when taken together with the carbon atoms to which they are attached they form a cycloalkenyl or cycloheteroalkenyl group;

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, or an N-oxide thereof.

In certain embodiments \( Z^2 \) is selected from the group consisting of a bond, \(-\text{N(}^{R'})\-\), and \(-\text{S}-\). In one specific embodiment \( Z^2 \) is \(-\text{N(}^{R'})\-\). In an even more specific embodiment \( Z^2 \) is \(-\text{N(H)}\-\).

\( Ar^1 \) and \( Ar^2 \) are each independently selected from the group consisting of aryl and heteroaryl and may be monocyclic, bicyclic or polycyclic moieties. In certain embodiments each of \( Ar^1 \) and \( Ar^2 \) is a monocyclic or bicyclic moiety. In certain embodiments each of \( Ar^1 \) and \( Ar^2 \) are a monocyclic moiety.

In certain embodiments \( Ar^1 \) is selected from the group consisting of:
wherein $V_1$, $V_2$, $V_3$ and $V_4$ are each independently selected from the group consisting of $N$, and $C(R^{10})$;

$W$ is selected from the group consisting of $O$, $S$ and $NR^{10}$;

$W^1_1$ and $W^2$ are each independently selected from the group consisting of $N$ and $CR^{10}$;

wherein each $R^{10}$ is independently selected from the group consisting of: $H$, halogen, alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl, heteroalkyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, cycloalkylheteroalkyl, heterocycloalkylheteroalkyl, heteroarylheteroalkyl, arylheteroalkyl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, alkoxyaryl, alkenyloxy, alkynyloxy, cycloalkylkoxy, heterocycloalkyloxy, aryloxy,
arylalkyloxy, phenoxy, benzyloxy, heteroaryloxy, amino, alkylamino, aminoalkyl, acylamino, arylamino, sulfonlamino, sulfinylamino, —COOH, —COR, —COOR, —CONHR, —NHCOR, —NHCOOR, —NHCONHR, alkoxy carbonyl, alkylaminocarbonyl, sulfonyl, alkylsulfonyl, alkylsulfinyl, arylsulfonyl, arylsulfinyl, aminosulfonyl, —SR, R'S(O)R —, R'S(O)2 R —, R'C(O)N(R')R —, R'SO2 N(R')R —, R'N(R')C(O)R —, R'N(R')SO2 R —, R'N(R')C(O)N(R')R — and acyl, each of which may be optionally substituted,

wherein R', R', R' and R' are as defined above.

In certain embodiments Ar' is selected from the group consisting of:

wherein V', V', V', V', W, W', W', R', R', R' and R' are as defined above.

In certain embodiments Ar' is selected from the group consisting of:
wherein each $R^{i0}$ is independently as defined above,

$k$ is an integer selected from the group consisting of 0, 1, 2, 3, and 4; and

$n$ is an integer selected from the group consisting of 0, 1, and 2.

In yet an even further embodiment $A_r^1$ is selected from the group consisting of:

wherein $R^{10}$ is as defined above.

In certain embodiments $A_r^1$ is selected from the group consisting of:

wherein each $R^{10}$ is independently as defined above, and
q is an integer selected from the group consisting of 0, 1 and 2.

In certain embodiments Ar\(^1\) is selected from the group consisting of:

In certain embodiments Ar\(^1\) is selected from the group consisting of:
In certain embodiments $\text{Ar}^2$ is selected from the group consisting of:
wherein V^5, V^6, V^7 and V^8 are independently selected from the group consisting of N, and C(R^{11});

wherein each R^{11} is independently selected from the group consisting of: H, halogen, alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl, heteroalkyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, cycloalkylheteroalkyl, heterocycloalkylheteroalkyl, heteroarylheteroalkyl, arylheteroalkyl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, alkoxyaryl, alkenyloxy, alkynyl, cycloalkylkoxy, heterocycloalkyloxy, arloxy, arylalkyloxy, phenoxy, benzyloxy, heteroaryloxy, amino, alkylamino, aminoalkyl, acylamino, arylamino, sulfonylamino, sulfanylamo, —COOH, —COR^3, —COOR^3, —CONHR^3, —NHCOR^3, —NHCOOR^3, —NHCONHR^3, alkoxy, alkylaminocarbonyl, sulfonyl, alkylsulfonyl, alkylsulfinyl, arylsulfonyl, arylsulfinyl, aminosulfon, —SR^3, R^4S(O)R^6 —, R^4S(O)_2R^6 —, R^4C(O)N(R^5)R^6 —, R^4SO_2N(R^5)R^6 —, R^4N(R^5)C(O)R^6 —, R^4N(R^5)SO_2R^6 —, R^4N(R^5)C(O)N(R^7)R^6 — and acyl, each of which may be optionally substituted.

In certain embodiments Ar^2 is selected from the group consisting of:

![Diagram]

wherein each R^{11} is independently as defined above

o is an integer selected from the group consisting of 0, 1, 2, 3, and 4; and

p is an integer selected from the group consisting of 0, 1, 2, and 3.

In certain embodiments Ar^2 is selected from the group consisting of:
wherein each \( R^{11} \) is as defined above.

In an even further embodiment \( A_r^2 \) is selected from the group consisting of:
In an embodiment, the JAK-2 inhibitor is a compound of Formula (XLVIII):

![Chemical Structure](image)

Formula (XLVIII)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof

wherein $R^1$, $R^2$, $R^{10}$, $R^{11}$, $X^1$, $X^2$, $Y$, $k$ and $o$ are as defined above.

In an embodiment, the JAK-2 inhibitor is a compound of Formula (XLIX):
or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof

wherein $R_1$, $R_2$, $R_{10}$, $R_{11}$, $X_1$, $X_2$, $Y$, q and o are as defined above.

[00696] In an embodiment, the JAK-2 inhibitor is a compound of Formula (L):

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof

wherein $R^i$, $R^j$, $R^{10}$, $R^{11}$, $X^i$, $X^j$, $Y$, q and o are as defined above.

[00697] In an embodiment, the JAK-2 inhibitor is a compound of Formula (LI):
or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof
wherein $R^1$, $R^2$, $R^{10}$, $R^{11}$, $X^1$, $X^2$, $Y$, $q$ and $o$ are as defined above.

[00698] In an embodiment, the JAK-2 inhibitor is a compound of Formula (LII):

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof
wherein $R^1$, $R^2$, $R^{10}$, $R^{11}$, $X^1$, $X^2$, $Y$, $q$ and $o$ are as defined above.

[00699] In an embodiment, the JAK-2 inhibitor is a compound of Formula (LIII):

281
or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof

wherein R¹, R², R¹⁰, R¹¹, X¹, X², Y, q and o are as defined above.

[00700] In embodiments where the JAK-2 inhibitor has a compound of Formulas (XLVII)-(LIII), X¹, X² and Y are chosen such that there are between 5 and 15 atoms in the normal chain. In one embodiment, X¹, X² and Y are chosen such that there are between 6 and 15 atoms in the normal chain. In one specific embodiment, X¹, X² and Y are chosen such that there are 7 atoms in the normal chain. In another specific embodiment, X¹, X² and Y are chosen such that there are 8 atoms in the normal chain.

[00701] In embodiments where the JAK-2 inhibitor has a compound of Formulas (XLVII)-(LIII), X¹ and X² are each independently a heteroalkyl group containing at least one oxygen atom in the normal chain. In certain embodiments X¹ is selected from the group consisting of: (a) —O(C₁₅)alkyl-, (b) —(C₁₋₅)alkylO-, and (c) —(C₁₋₅)alkylO(C₁₋₅)alkyl. In certain embodiments X¹ is selected from the group consisting of: (a) —OCH₂— (b) —CH₂O—, (c) —OCH₂CH₂—, (d) —CH₂CH₂O—, (e) —CH₂OCH₂—, and (f) —CH₂CH₂OCH₂—. In one specific embodiment X¹ is —OCH₂—. In another specific embodiment X¹ is —CH₂O—. In another specific embodiment X¹ is —CH₂OCH₂—. In another specific embodiment X¹ is —CH₂CH₂OCH₂—. In certain embodiments X² is selected from the group consisting of: (a) —O(C₁₋₅)alkyl-, (b) —(C₁₋₅)alkylO-, and (c) —(C₁₋₅)alkylO(C₁₋₅)alkyl. In certain embodiments X² is selected from the group consisting of: (a) —OCH₂— (b) —CH₂O—, (c) —OCH₂CH₂—, (d) —CH₂CH₂O—, (e) —CH₂OCH₂—, and (f) —CH₂CH₂OCH₂—. In one specific embodiment X² is —OCH₂—. In
another specific embodiment $X^1$ is —CH$_2$O—. In another specific embodiment $X^2$ is —OCH$_2$CH$_2$—. In another specific embodiment $X^3$ is —CH$_2$CH$_2$O—. In another specific embodiment $X^4$ is —CH$_2$OCH$_2$—. In another specific embodiment $X^5$ is —CH$_2$CH$_2$OCH$_2$—.

[00702] In an embodiment, the JAK-2 inhibitor is pacritinib. In an embodiment, the JAK-2 inhibitor is $\text{(E)-4}^4\text{-(2-(pyrrolidin-1-yl)ethoxy)-6,11-dioxo-3-aza-2(4,2)-pyrimidina-1,4(1,3)-dibenzenacyclododecaphan-8-ene.}$ In an embodiment, the JAK-2 inhibitor is the chemical structure shown in Formula (LIV):

![Formula (LIV)](image)


[00703] In an embodiment, the JAK-2 inhibitor is selected from the structures disclosed in U.S. Patent Nos. 8,143,255; 8,153,632; and 8,415,338 and U.S. Patent Application Publication Nos. 2009/0258886 A1; 2012/0142680 A1; 2012/0196855 A1; and 2013/0172338 A1, the disclosures of which are incorporated by reference herein.

[00704] In an embodiment, the JAK-2 inhibitor is (E)-4\(^{-}\)-(2-(pyrrolidin-1-yl)ethoxy)-6,11-dioxo-3-aza-2(4,2)-pyrimidina-1(2,5)-furana-4(1,3)-benzenacyclododephan-8-ene. In an embodiment, the JAK-2 inhibitor is (9E)-15-(2-(pyrrolidin-1-yl)ethoxy)-7,12,25-trioxo-19,21,24-triaza-tetracyclo[18.3.1.1(2,5).1(14,18)]hexacosa-1(24),2,4,9,14(26),15,17,20,22-nonaene. In an embodiment, the JAK-2 inhibitor is the chemical structure shown in Formula (LIV-A):

![Formula (LIV-A)](image)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. The preparation and properties of this JAK-2 inhibitor are known to those of ordinary skill in the art, and for example are described in: Madan et al., SB1578, a novel inhibitor of JAK2, FLT3, and c-Fms for the treatment of rheumatoid arthritis, *J. Immunol.* 2012, 189, 4123-4134 and William et al., Discovery of the macrocycle (9E)-15-(2-(pyrrolidin-1-yl)ethoxy)-7,12,25-trioxo-19,21,24-triaza-tetracyclo[18.3.1.1(2,5).1(14,18)]hexacosa-1(24),2,4,9,14(26),15,17,20,22-nonaene (SB1578), a potent inhibitor of janus kinase 2/fms-like tyrosine kinase-3 (JAK2/FLT3) for the treatment of rheumatoid arthritis. *J. Med. Chem.* 2012, 55, 2623-2640.
In an embodiment, the JAK-2 inhibitor is a compound selected from the structures disclosed in U.S. Patent No. 8,349,851 and U.S. Patent Application Publication Nos. 2010/0317659 A1, 2013/0245014, 2013/0296363 A1, the disclosures of which are incorporated by reference herein. In an embodiment, the JAK-2 inhibitor is a compound of Formula (LV):

![Formula (LV)](image_url)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, wherein 

R¹ and R² are selected from (i), (ii), (iii), (iv), and (v) as follows:

(i) R¹ and R² together form =O, =S, =NR⁹ or =CR¹⁰R¹¹;

(ii) R¹ and R² are both —OR⁸, or R¹ and R², together with the carbon atom to which they are attached, form dioxacycloalkyl;

(iii) R¹ is hydrogen or halo; and R² is halo; and

(iv) R¹ is alkyl, alkenyl, alkynyl, cycloalkyl or aryl, wherein the alkyl, alkenyl, alkynyl, cycloalkyl and aryl is optionally substituted with one or more substituents selected from halo, cyano, alkyl, —R¹OR₈, —R¹S(O) R₉, —R¹NR²R² and —C(O)OR₈; and R² is halo or —OR⁸; and

(v) R¹ is halo, deuto, —OR¹², —NR¹³R¹⁴, or —S(O) R₁⁵; and R² is hydrogen, deuto, alkyl, alkenyl, alkynyl, cycloalkyl or aryl, wherein the alkyl, alkenyl, alkynyl, cycloalkyl and aryl, is optionally substituted with one or more substituents selected from halo, cyano, alkyl, —R¹OR₈, —R¹S(O) R₉ and —R¹NR²R²;
R₃ is hydrogen, halo, alkyl, cyano, haloalkyl, cycloalkyl, cycloalkylalkyl, hydroxy or alkoxy.

R⁴ and R⁵ are each independently hydrogen or alkyl;

each R⁶ is independently selected from halo, alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, —R⁶ OR¹⁸, —R⁶ NR¹⁹ R²⁰, and —R⁶ S(O)ₐ Rᵶ;

each R⁷ is independently halo, alkyl, haloalkyl or —R⁷ ORᵶ;

R⁸ is alkyl, alkenyl or alkynyl;

R⁹ is hydrogen, alkyl, haloalkyl, hydroxy, alkoxy or amino;

R¹⁰ is hydrogen or alkyl;

R¹¹ is hydrogen, alkyl, haloalkyl or —C(O)OR⁸;

R¹² is selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, —C(O)R⁻, —C(O)OR⁻ and —C(O)NR⁻ R⁻, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl and heteroaralkyl are each optionally substituted with one or more substituents independently selected from halo, oxo, alkyl, hydroxy, alkoxy, amino and alkylthio;

R¹³ and R¹⁴ are selected as follows:

(i) R¹³ is hydrogen or alkyl; and R¹⁴ is selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, alkoxy, —C(O)R⁻, —C(O)OR⁻, —C(O)NR⁻ R⁻ and —S(O) R⁻, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl and heteroaralkyl are each optionally substituted with one or more substituents independently selected from halo, oxo, alkyl, hydroxy, alkoxy, amino and alkylthio; or

(ii) R¹³ and R¹⁴, together with the nitrogen atom to which they are attached, form heterocyclyl or heteroaryl wherein the heterocyclyl or heteroaryl is optionally substituted with one or more substituents independently selected from halo, alkyl, hydroxy, alkoxy, amino and alkylthio and wherein the heterocyclyl is also optionally substituted with oxo;
R^{15} is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, —C(O)NR^{y}R^{z} or —NR^{y}R^{z}, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl and heteroaralkyl are each optionally substituted with one or more substituents independently selected from halo, oxo, alkyl, hydroxy, alkoxy, amino and alkylthio;

R^{18} is hydrogen, alkyl, haloalkyl, hydroxy(C_{2-6})alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl or heteroarylalkyl; wherein R^{18} is optionally substituted with 1 to 3 groups Q^{1}, each Q^{1} independently selected from alkyl, hydroxyl, halo, haloalkyl, alkoxy, aryloxy, alkoxyalkyl, alkoxy carbonyl, alkoxy sulfonyl, hydroxycarbonyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, haloaryl and amino;

R^{19} and R^{20} are selected as follows:

(i) R^{19} and R^{20} are each independently hydrogen or alkyl; or

(ii) R^{19} and R^{20}, together with the nitrogen atom to which they are attached, form a heterocyclyl or heteroaryl which is optionally substituted with 1 to 2 groups each independently selected from halo, alkyl, haloalkyl, hydroxyl and alkoxy;

each R^{x} is independently alkylene or a direct bond;

R^{2} is hydrogen, alkyl, alkenyl or alkynyl;

R^{2} is independently hydrogen, alkyl, alkenyl, alkynyl or haloalkyl;

R^{2} and R^{2} are selected as follows:

(i) R^{2} and R^{2} are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl or haloalkyl;

(ii) R^{2} and R^{2}, together with the nitrogen atom to which they are attached, form a heterocyclyl or heteroaryl which is optionally substituted with 1 to 2 groups each independently selected from halo, alkyl, haloalkyl, hydroxyl and alkoxy;

n is 0-4;
p is 0-5; and each q is independently 0, 1 or 2.

[00706] In an embodiment, the JAK-2 inhibitor is AC-410 (available from Ambit Biosciences). In an embodiment, the JAK-2 inhibitor is (S)-(4-fluorophenyl)(4-((5-methyl-1H-pyrazol-3-yl)amino)quinazolin-2-yl)methanol. In an embodiment, the JAK-2 inhibitor has the chemical structure of Formula (LVI):

![Chemical Structure](image)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. The preparation of racemic (4-fluorophenyl)(4-((5-methyl-1H-pyrazol-3-yl)amino)quinazolin-2-yl)methanol hydrochloride is described in Examples 3 and 12 of U.S. Patent No. 8,349,851, the disclosure of which is incorporated by reference herein. Other preparation methods known to one of skill in the art also may be used. The preparation of Formula (LVI) is also described in the following paragraphs.

[00707] The preparation of (4-fluorophenyl)(4-(5-methyl-1H-pyrazol-3-ylamino)quinazolin-2-yl)methanone is accomplished by the following two steps (A and B). Step A: To a solution of ethyl 4-chloroquinazoline-2-carboxylate (0.6 g, 2.53 mmol) in THF (6 mL) at −40° C., was added dropwise a 1 M solution of 4-fluorophenylmagnesium bromide in THF (3 mL, 3.0 mmol, 1.2 eq). The mixture was stirred at −40 C for 4 h. The reaction was quenched by adding 0.5 N HCl solution (5 mL) and the mixture was extracted with EtOAc (2×10 mL). The combined organic layers were washed with brine and dried over MgSO₄. The crude product was purified on a silica gel column using a mixture of EtOAc-hexanes as eluent. (4-chloroquinazoline-2-yl)(4-
fluorophenyl)methanone was obtained as a light yellow solid (440 mg, 60%). $^1$H NMR (300 MHz, DMSO-d6) δ 7.45–740 (m, 2H), 8.07–8.03 (m, 1H), 8.17–8.13 (m, 2H), 8.23 (m, 2H), 8.42 (d, 1H); LC-MS (ESI) m/z 287 (M+H)$^+$. Step B: To a solution of (4-chloroquinazolin-2-yl)(4-fluorophenyl)methanone (84 mg, 0.30 mmol) in DMF (3mL) were added DIEA (0.103 mL, 0.6 mmol) and 5-methyl-1 H-pyrazol-3-amino (88 mg, 0.9 mmol) at rt. The reaction mixture was heated at 40° C. overnight. The reaction was quenched by adding water and the yellow precipitate was collected by filtration and washed with water. The crude product was purified by silica gel chromatography eluting with DCM/MeOH to give (4-fluorophenyl)(4-(5-methyl-1 H-pyrazol-3-ylamino)quinazolin-2-yl)methanone (30 mg, 29%). $^1$H NMR (300 MHz, DMSO-d6) δ 2.19 (s, 3H), 6.54 (s, 1H), 7.40 (m, 2H), 7.68 (t, 1H), 7.9–7.7 (m, 2H), 8.08 (m, 2H), 8.74 (d, 1H), 10.66 (s, 1H), 12.20 (s, 1H); LC-MS (ESI) m/z 348 (M+H)$^+$. 

**[00708]** To a solution of 4-fluorophenyl)(4-(5-methyl-1 H-pyrazol-3-ylamino)quinazolin-2-yl)methanone (60 mg, 0.172 mmol) in 1:1 MeOH/THF (10 mL) at 0° C., was added NaBH$_4$ (64 mg, 1.69 mmol). The reaction mixture was stirred at 0° C. for 1.5 h. The reaction mixture was quenched by adding a few drops of acetone and concentrated to dryness. The crude solid was purified on HPLC to afford (4-fluorophenyl)(4-(5-methyl-1 H-pyrazol-3-ylamino)quinazolin-2-yl)methanol (18 mg, 30%); $^1$H NMR (300 MHz, DMSO-d6) δ 2.25 (s, 3H), 5.67 (s, 1H), 5.83 (bs, 1H), 6.40 (bs, 1H), 7.13 (m, 2H), 7.55–7.53 (m, 3H), 7.79 (s, 2H), 8.57 (bs, 1H), 10.43 (s, 1H), 12.12 (bs, 1H); LC-MS (ESI) m/z 350 (M+H)$^+$. 

**[00709]** To a suspension of (4-fluorophenyl)(4-(5-methyl-1 H-pyrazol-3-ylamino)quinazolin-2-yl)methanone (2.3 g) in 30% MeOH/DCM (60 mL) at 0° C. was added dropwise 4M HCl/1,4-dioxane (10 mL). After all solid material had dissolved, the mixture was concentrated under reduced pressure, and to the residue was added 30% CH$_3$CN/H$_2$O (80 mL) and the mixture was sonicated until all solid material had dissolved. The mixture was frozen and lyophilized overnight to afford (4-fluorophenyl)(4-(5-methyl-1 H-pyrazol-3-ylamino)quinazolin-2-yl)methanol hydrochloride (100%). $^1$H NMR (300 MHz, DMSO-d6) δ 2.25 (s, 3H), 6.02 (s, 1H), 6.20 (s, 1H), 7.27 (t, 2H), 7.60 (qt, 2H), 7.80 (t, 1H), 8.08 (t, 1H), 8.23 (d, 1H), 8.83 (d, 1H), 12.16 (s, 1H), 14.51 (b, 1H); LC-MS (ESI) m/z 350 (M+H)$^+$. Formula LVI, (S)-(4-fluorophenyl)(4-(5-methyl-1 H-pyrazol-3-yl)amino)quinazolin-2-yl)methanol, may be obtained from this preparation by chiral liquid chromatographic separation of the enantiomers, or by other
well known techniques for resolution of enantiomers, such as those described in: Eliel et al., *Stereochemistry of Organic Compounds*, Wiley-Interscience, New York, 1994.

[00710] In another embodiment, the JAK-2 inhibitor is (R)-(4-fluorophenyl)(4-((5-methyl-1H-pyrazol-3-yl)amino)quinazolin-2-yl)methanol, which is also known in the art to be active as a JAK-2 inhibitor. In an embodiment, the JAK-2 inhibitor is racemic (4-fluorophenyl)(4-((5-methyl-1H-pyrazol-3-yl)amino)quinazolin-2-yl)methanol, which is also known in the art to be active as a JAK-2 inhibitor.

[00711] In some preferred embodiments, JAK-2 inhibitors having Formulas (LV) or (LVI) can be prepared, isolated, or obtained by any method known to one of skill in the art, including, but not limited to, synthesis from a suitable optically pure precursor, asymmetric synthesis from an achiral starting material, or resolution of a racemic or enantiomeric mixture, for example, chiral chromatography, recrystallization, resolution, diastereomeric salt formation, or derivatization into diastereomeric adducts followed by separation.

[00712] In one embodiment, provided herein is a method for preparation of the compound of Formula (LVI), which comprises resolving racemic (4-fluorophenyl)(4-(5-methyl-1H-pyrazol-3-ylamino)quinazolin-2-yl)methanol with chiral chromatography. In certain embodiments, as shown in Scheme I, the two individual enantiomers are separated using a chiral column, wherein the stationary phase is silica gel coated with a chiral selector such as tris-(3,5-dimethylphenyl)carbamoyl cellulose.

[00713] In another embodiment, provided herein is a method for preparation of the compound of Formula (LVI), comprising the step of reducing the achiral ketone (4-fluorophenyl)(4-(5-methyl-1H-pyrazol-3-ylamino)quinazolin-2-yl)methanone, prepared as described above or by other methods known to one of skill in the art, with hydrogen in the present of a chiral catalyst. The achiral ketone (4-fluorophenyl)(4-(5-methyl-1H-pyrazol-3-ylamino)quinazolin-2-yl)methanone may be reduced to predominantly a single enantiomeric product with a chiral reducing system of “type A” or “type B,” wherein type A and type B differ from each other solely by having chiral auxiliaries of opposite chiralities. In certain embodiments, the chiral catalyst is [(S)—P-Phos RuCl₂ (S)-DAIPEN].
In certain embodiments, the reduction of the achiral ketone (4-fluorophenyl)(4-(5-methyl-1H-pyrazol-3-ylamino)quinazolin-2-yl)methanone in presence of a chiral catalyst is carried out in isopropyl alcohol as a solvent. In certain embodiments, the reduction of achiral ketone (4-fluorophenyl)(4-(5-methyl-1H-pyrazol-3-ylamino)quinazolin-2-yl)methanone in the presence of a chiral catalyst is carried out in isopropyl alcohol and water mixture as a solvent. In certain embodiments, isopropyl alcohol and water are used in a ratio of 1:1, 8:1 or 9:1. In one embodiment, DMSO is used as a cosolvent in the reaction. In one embodiment, DMSO is used in 10, 20 or 30% based on the total amount of isopropyl alcohol and water mixture. In certain embodiments, isopropyl alcohol, DMSO and water are used in a ratio of 1:1:1, 4:4:0.5, 8:1:1, 47:47:6, 41:58:1, 44:50:6, or 18:79:3. In certain embodiments, isopropyl alcohol, DMSO and water are used in a ratio of 41:58:1. In certain embodiments, isopropyl alcohol, and DMSO are used in a ratio of 1:1. In certain embodiments, the reduction is carried out in presence of a base, such as potassium hydroxide, potassium tert butoxide and others. In certain embodiments, the base is used in 2-15 mol %, in one embodiment, 2 mol %, 5 mol %, 10 mol %, 12.5 mol % or 15 mol %.

In certain embodiments, the reduction is carried out at a temperature of 40-80° C, in one embodiment, 40° C, 50° C, 60° C, 70° C or 80° C. In certain embodiments, the reduction is carried out at a temperature of 70° C. In certain embodiments, the reduction is carried out at a pressure of 4 bar to 30 bar, in one embodiment, 4, 5, 10, 15, 20, 25 or 30 bar. In certain embodiments, the reduction is carried out at a pressure of 4 bar. In certain embodiments, the catalyst loading in the reaction is 100/1, 250/1, 500/1, 1000/1, 2000/1, 3000/1, 4000/1, 5000/1, 7000/1, 10,000/1 or 20,000/1. In certain embodiments, the catalyst loading in the reaction is 2000/1 or 4000/1.

In another embodiment, provided herein is a method for preparation of the compound of Formula (LVI), which comprises the step of reducing the achiral ketone (4-fluorophenyl)(4-(5-methyl-1H-pyrazol-3-ylamino)quinazolin-2-yl)methanone with a ketoreductase (e.g., alcohol dehydrogenase). See Moore et al., Acc. Chem. Res. 2007, 40, 1412-1419; Daussmann et al., Engineering in Life Sciences 2006, 6, 125-129; Schlummer et al., Specialty Chemicals Magazine 2008, 28, 48-49; Osswald et al., Chimica Oggi 2007, 25(Suppl.), 16-18; and Kambourakis et al., PharmaChem 2006, 5(9), 2-5.
[00716] In yet another embodiment, provided herein is a method for preparation of the compound of Formula (LVI), comprising the step of reducing the achiral ketone (4-fluorophenyl)(4-(5-methyl-1H-pyrazol-3-ylamino)quinazolin-2-yl)methanone with a reducing reagent (e.g., borane or borohydride reagents) in the presence of a chiral catalyst. In certain embodiments, the reducing agent is borane or a borohydride reagent. In certain embodiments, the chiral catalyst is a chiral oxazaborolidine. See, Cory et al., *Tetrahedron Letters* 1996, 37, 5675; and Cho, *Chem. Soc. Rev.* 2009, 38, 443.

[00717] In another embodiment, provided herein is a method for preparation of the compound of Formula (LVI) comprising the step of reducing the achiral ketone (4-fluorophenyl)(4-(5-methyl-1H-pyrazol-3-ylamino)quinazolin-2-yl)methanone via asymmetric hydrosilylation, as described in U.S. Patent Application Publication No. 2008/0269490, the disclosure of which is specifically incorporated herein by reference in its entirety.

[00718] In still another embodiment, provided herein is a method for preparation of the compound of Formula (LVI), comprising the step of reducing the achiral ketone (4-fluorophenyl)(4-(5-methyl-1H-pyrazol-3-ylamino)quinazolin-2-yl)methanone via transfer hydrogenation catalyzed by an iridium complex, as described in Malacea et al., *Coordination Chemistry Reviews* 2010, 254, 729-752.

[00719] The starting materials used in the synthesis of the compound of Formula LVI provided herein are either commercially available or can be prepared by a method known to one of skill in the art. For example, the achiral ketone (4-fluorophenyl)(4-(5-methyl-1H-pyrazol-3-ylamino)quinazolin-2-yl)methanone can be prepared according to the methods described in U.S. Patent Nos. 8,349,851, issued January 8, 2013; and 8,703,943, issued April 22, 2014, the disclosures of which are incorporated herein by reference in their entireties.

[00720] In some embodiments, the compositions and methods described include one or more JAK-2 inhibitors described in PCT Application Publication No. 2012/030914, published March 8, 2012, contents of which are incorporated herein in their entireties. In some embodiments, the JAK-2 inhibitors have the structure of Formula (LV-A):
or a pharmaceutically acceptable salt, solvate or hydrate thereof, wherein

A is azolyl other than pyrazolyl;

R¹ and R² are selected from (i), (ii), (iii), (iv) and (v) as follows:

(i) R¹ and R² together form =0, =S, =NR³ or =CR⁴R⁵;

(ii) R¹ and R² are both -OR⁶, or R¹ and R², together with the carbon atom to which they are attached, form cycloalkyl or heterocyclyl wherein the cycloalkyl is substituted with one to four substituents selected from halo, deuter, alkyl, haloalkyl, -OR⁶, -N(R⁷)², and -S(O)³R⁸ and wherein the heterocyclyl contains one to two heteroatoms wherein each heteroatom is independently selected from O, NR²⁴, S, S(O) and S(O)²;

(iii) R¹ is hydrogen or halo; and R² is halo;

(iv) R¹ is alkyl, alkenyl, alkynyl, cycloalkyl or aryl, wherein the alkyl, alkenyl, alkynyl, cycloalkyl and aryl are each optionally substituted with one to four substituents selected from halo, deuter, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, cyano, =0, =N-OR²¹, -R¹OR²¹, -R¹N(R²¹)², -R¹S(O)³R²³, -C(O)R²¹, -C(O)OR²¹ and -C(O)N(R²²)²; and

(v) R¹ is halo, deuter, -OR¹², -NR¹³R¹⁴, or -S(O)⁴R¹⁵; and R² is hydrogen, deuter, alkyl, alkenyl, alkynyl, cycloalkyl or aryl, wherein the alkyl, alkenyl, alkynyl, cycloalkyl and aryl are each optionally substituted with one to four substituents selected from halo, cyano, alkyl, -R³OR²¹, -R³S(O)⁴R¹ and -R³NR³R³;
R¹ is hydrogen, deuto, halo, alkyl, cyano, haloalkyl, deutoalkyl, cycloalkyl, cycloalkylalkyl, hydroxy or alkoxy;

R² is hydrogen or alkyl; each R⁶ is independently selected from halo, alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, -R⁸OR¹⁸, -R⁸NR¹⁹R²⁰, and -R⁸S(O)₉R²¹;

each R⁷ is independently halo, alkyl, haloalkyl or -R⁹OR²²;

R is alkyl, alkenyl or alkynyl;

R⁵ is hydrogen, alkyl, haloalkyl, hydroxy, alkoxy or amino;

R¹⁰ is hydrogen or alkyl;

R¹¹ is hydrogen, alkyl, haloalkyl or -C(O)OR⁴;

R¹² is selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, -C(O)R⁷, -C(O)OR⁸ and -C(O)NR⁹R¹⁰, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl and heteroaralkyl are each optionally substituted with one or more, in one embodiment, one to four, in one embodiment, one to three, in one embodiment, one, two or three, substituents independently selected from halo, oxo, alkyl, hydroxy, alkoxy, amino and alkylthio;

R¹³ and R¹⁴ are selected as follows:

(i) R¹³ is hydrogen or alkyl; and R¹⁴ is selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, alkoxy, -C(O)R¹⁵, -C(O)OR¹⁶, -C(O)NR¹⁷R¹⁸ and -S(O)R¹⁹, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl and heteroaralkyl are each optionally substituted with one or more, in one embodiment, one to four, in one embodiment, one to three, in one embodiment, one, two or three, substituents independently selected from halo, oxo, alkyl, hydroxy, alkoxy, amino and alkylthio; or
(ii) $R_{13}$ and $R_{14}$, together with the nitrogen atom to which they are attached, form heterocyclyl or heteroaryl wherein the heterocyclyl or heteroaryl are substituted with one or more, in one embodiment, one to four, in one embodiment, one to three, in one embodiment, one, two or three, substituents independently selected from halo, alkyl, hydroxy, alkoxy, amino and alkylthio and wherein the heterocyclyl is optionally substituted with oxo; $R_{15}$ is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, $-\text{C(O)NR}_y\text{R}_z$ or $-\text{NR}_y\text{R}_z$, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl and heteroaralkyl are each optionally substituted with one or more, in one embodiment, one to four, in one embodiment, one to three, in one embodiment, one, two or three, substituents independently selected from halo, oxo, alkyl, hydroxy, alkoxy, amino and alkylthio;

$R_{18}$ is hydrogen, alkyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl or heteroarylalkyl; wherein $R_{18}$ is optionally substituted with 1 to 3 groups $Q_1$, each $Q_1$ independently selected from alkyl, hydroxyl, halo, oxo, haloalkyl, alkoxy, aryloxy, alkoxyalkyl, alkoxycarbonyl, alkoxy sulfonyl, carboxyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, haloaryl and amino;

$R_{19}$ and $R_{20}$ are selected as follows:

(i) $R_{19}$ and $R_{20}$ are each independently hydrogen or alkyl; or

(ii) $R_{19}$ and $R_{20}$, together with the nitrogen atom to which they are attached, form a heterocyclyl or heteroaryl which are each optionally substituted with 1 to 2 groups each independently selected from halo, oxo, alkyl, haloalkyl, hydroxyl and alkoxy;

$R_{21}$ is hydrogen, alkyl, alkenyl, alkynyl, haloalkyl or cycloalkyl;

each $R_{22}$ is independently hydrogen, alkyl, alkenyl, alkynyl, haloalkyl or cycloalkyl; or both $R_{22}$, together with the nitrogen atom to which they are attached, form a heterocyclyl optionally substituted with oxo;

$R_{23}$ is alkyl, alkenyl, alkynyl or haloalkyl;

$R_{24}$ is hydrogen or alkyl.
each $R^i$ is independently alkylene or a direct bond;

$R^*$ is hydrogen, alkyl, alkenyl or alkynyl;

$R^+$ is independently hydrogen, alkyl, alkenyl, alkynyl or haloalkyl;

$R^-$ and $R^+$ are selected as follows:

(i) $R^*$ and $R^+$ are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl or haloalkyl; or

(ii) $R^-$ and $R^+$, together with the nitrogen atom to which they are attached, form a heterocyclol or heteroaryl which are optionally substituted with 1 to 2 groups each independently selected from halo, alkyl, haloalkyl, hydroxyl and alkoxy;

n is 0-4;

p is 0-5;

each q is independently 0, 1 or 2; and

r is 1-3.

[00721] In some embodiments, the JAK-2 inhibitor of Formula (LV-A) has the structure of Formula (LV-B):

![Formula (LV-B)](image)

or a pharmaceutically acceptable salt, solvate or hydrate thereof, wherein
A is imidazolyl, oxazolyl, thiazolyl, thiadiazolyl, or triazolyl;

R\(^3\) is hydrogen, alkyl, haloalkyl or cycloalkyl;

each R\(^6\) is independently selected from halo, alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, -R\(^1\)OR\(^1\), -R\(^x\)NR\(^1\)R\(^2\), and -R\(^x\)S(O)\(^q\)R\(^v\);

R\(^7\) is halo;

R\(^{18}\) is hydrogen, alkyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl or heteroarylalkyl; wherein each R\(^{18}\) is optionally substituted with 1 to 3 groups Q\(^j\), each Q\(^j\) independently selected from alkyl, hydroxyl, halo, oxo, haloalkyl, alkoxy, arylalkyl, alkoxyalkyl, alkoxy, alkoxy, sulfonyl, carboxyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, haloaryl and amino;

R\(^{19}\) and R\(^{20}\) are selected as follows:

(i) R\(^{19}\) and R\(^{20}\) are each independently hydrogen or alkyl; or

(ii) R\(^{19}\) and R\(^{20}\), together with the nitrogen atom to which they are attached, form a heterocyclyl or heteroaryl which are each optionally substituted with 1 to 2 groups each independently selected from halo, oxo, alkyl, haloalkyl, hydroxyl and alkoxy;

each R\(^x\) is independently alkylene or a direct bond;

R\(^1\) is hydrogen, alkyl, alkenyl or alkynyl;

R\(^5\) and R\(^2\) are selected as follows:

(i) R\(^5\) and R\(^2\) are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl or haloalkyl; or

(ii) R\(^5\) and R\(^2\), together with the nitrogen atom to which they are attached, form a heterocyclyl or heteroaryl which are optionally substituted with 1 to 2 groups each independently selected from halo, alkyl, haloalkyl, hydroxyl and alkoxy;

n is 0-3;
each q is independently 0, 1 or 2; and
r is 1-3.

[00722] In some preferred embodiments of the JAK-2 inhibitor of Formula (LV-A) or (LV-B),
R' is hydrogen or alkyl.

[00723] In some preferred embodiments of the JAK-2 inhibitor of Formula (LV-A) or (LV-B),
A is imidazolyl, oxazolyl, thiazolyl, thiadiazolyl, or triazolyl.

[00724] In some preferred embodiments of the JAK-2 inhibitor of Formula (LV-A) or (LV-B),
R’ is fluro.

[00725] In some preferred embodiments, JAK-2 inhibitor of Formula (LV-A) has the structure
of Formula (LV-C):

![Formula (LV-C)](image)

or a pharmaceutically acceptable salt, solvate or hydrate thereof, where
R’ and R’’ are selected as follows:

(i) R’ and R’’ together form =0;

(ii) R’ and R’’, together with the carbon atom to which they are attached, form
dioxacycloalkyl or cycloalkyl wherein the cycloalkyl is substituted with one to four
substituents selected from halo, deutero, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, cyano, =0, and hydroxy;

(iii) $R^1$ is hydrogen or halo; and $R^2$ is halo;

(iv) $R^1$ is alkyl, and $R^2$ is hydrogen, alkyl, halo, hydroxy or alkoxy; or

(v) $R^1$ is halo, hydroxy or alkoxy; and $R^2$ is hydrogen or alkyl;

$R^3$ is hydrogen, alkyl or cycloalkyl,

$R^4$ is hydrogen or alkyl;

$R^5$ is hydrogen or alkyl;

$R^7$ is halo; and

$n$ is 0-3.

[00726] In some preferred embodiments of the JAK-2 inhibitor of Formula (LV-C), $n$ is 0.

[00727] In some preferred embodiments, JAK-2 inhibitor of Formula (LV-A) has the structure of Formula (LV-D):

or a pharmaceutically acceptable salt, solvate or hydrate thereof, where:

$R^1$ and $R^2$ are selected as follows:

(i) $R^1$ and $R^2$ together form $=0$;
(ii) \( R^1 \) and \( R^2 \), together with the carbon atom to which they are attached, form dioxacycloalkyl or cycloalkyl wherein the cycloalkyl is substituted with one to four substituents selected from halo, deuto, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, cyano, \( =0 \), and hydroxy;

(iii) \( R^1 \) is hydrogen or halo; and \( R^2 \) is halo;

(iv) \( R^1 \) is alkyl, and \( R^2 \) is hydrogen, alkyl, halo, hydroxy or alkoxy; or

(v) \( R^1 \) is halo, hydroxy or alkoxy; and \( R^2 \) is hydrogen or alkyl; \( R^3 \) is hydrogen, alkyl or cycloalkyl,

\( R^4 \) is hydrogen or alkyl;

\( R^5 \) is halo;

and

\( n \) is 0-3.

[00728] In some preferred embodiments of the JAK-2 inhibitor of Formula (LV-D), \( n \) is 0.

[00729] In some preferred embodiments, JAK-2 inhibitor of Formula (LV-D) is selected from the group consisting of:

- (4-fluorophenyl)(4-((1-methyl-1\( H \)-imidazol-4-yl)amino)quinazolin-2-yl)methanol;
- (4-((1\( H \)-imidazol-4-yl)amino)quinazolin-2-yl)(4-fluorophenyl)methanol;
- (4-fluorophenyl)(4-((thiazol-4-ylamino)quinazolin-2-yl)methanol;
- (4-fluorophenyl)(4-((5-methylthiazol-2-yl)amino)quinazolin-2-yl)methanol;
- 2-(difluoro(4-fluorophenyl)methyl)-N-(1-methyl-1\( H \)-imidazol-4-yl)quinazolin-4-amine,

or a pharmaceutically acceptable salt, solvate or hydrate thereof.

[00730] In an embodiment, the JAK-2 inhibitor is a compound of Formula (LVII):
including a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof,

wherein:

$R_1$ is selected from hydrogen, hydroxy, amino, mercapto, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_1$ alkoxy, $C_1$ alkanoyloxy, $N$—($C_{1-6}$ alkyl)amino, $N,N$—($C_{1-6}$ alkyl) amino, $C_1$ alkanoylamino, $C_1$ alkylsulphonylamino, 3-5-membered carbocyclyl or 3-5-membered heterocyclyl; wherein $R_1$ may be optionally substituted on carbon by one or more $R^6$; and wherein if said heterocyclyl contains an —NH— moiety that nitrogen may be optionally substituted by a group selected from $R^7$;

$R_2$ and $R_3$ are independently selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_1$ alkoxy, $C_1$ alkanoyl, $C_1$ alkanoyloxy, $N$—($C_{1-6}$ alkyl)amino, $N,N$—($C_{1-6}$ alkyl) amino, $C_1$ alkanoylamino, $C_1$ alkylsulphonylamino, $N$—($C_{1-6}$ alkyl)carbamoyl, $N,N$—($C_{1-6}$ alkyl) carbamoyl, $C_1$ alkylS(O)$_a$ wherein a is 0 to 2, $C_1$ alkoxy carbonyl, $N$—($C_{1-6}$ alkyl)sulphamoyl, $N,N$—($C_{1-6}$ alkyl)sulphamoyl, $(C_{1-6}$ alkyl)$_2$ Sulphamoyl, $(C_{1-6}$ alkyl)$_2$ N—$S(O)_2$—NH—, $(C_{1-6}$ alkyl)NH—S(O)$_2$—NH—, $NH_2$—S(O)$_2$—NH—, $(C_{1-6}$ alkyl)$_2$ N—$S(O)_2$—N($C_{1-6}$ alkyl)—, $(C_{1-6}$ alkyl)NH—S(O)$_2$—N($C_{1-6}$ alkyl)—, $NH_2$—S(O)$_2$—N($C_{1-6}$ alkyl)—, $N$—($C_{1-6}$ alkyl)—N—($C_{1-6}$ alkylsulphonylamino), $C_1$ alkylsulphonylamino, carbocyclyl-$R^9$ — or heterocyclyl-$R^{21}$; wherein $R_2$ and $R_3$ independently of each other may be optionally substituted on carbon by one or more $R^8$; and
wherein if said heterocyclyl contains an \(-\text{NH}\) moiety that nitrogen may be optionally substituted by a group selected from \(R^5\);

\(R^4\) is selected from cyano, carboxy, carbamoyl, \(C_{1-6}\) alkyl, \(C_{2-6}\) alkenyl, \(C_{2-6}\) alkynyl, \(C_{1-6}\) alkanoyl, \(N-(C_{1-6} \text{ alkyl})\text{carbamoyl}, N,N-(C_{1-6} \text{ alkyl})_2\text{carbamoyl}, C_{1-6}\) alkoxy carbonyl, carbocyclyl or heterocycl; wherein \(R^4\) may be optionally substituted on carbon by one or more \(R^{10}\); and wherein if said heterocyclyl contains an \(-\text{NH}\) moiety that nitrogen may be optionally substituted by a group selected from \(R^{11}\);

\(R^5\) is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, \(C_{1-6}\) alkyl, \(C_{2-6}\) alkenyl, \(C_{2-6}\) alkynyl, \(C_{1-6}\) alkoxy, \(C_{1-6}\) alkanoyloxy, \(N-(C_{1-6} \text{ alkyl})\text{amino}, N,N-(C_{1-6} \text{ alkyl})_2\text{amino}, C_{1-6}\) alkanoylamino, \(N-(C_{1-6} \text{ alkyl})\text{carbamoyl}, N,N-(C_{1-6} \text{ alkyl})_2\text{carbamoyl}, C_{1-6}\) alkoxy carbonyl, \(N-(C_{1-6} \text{ alkyl})\text{sulphamoyl}, N,N-(C_{1-6} \text{ alkyl})_2\text{sulphamoyl}, C_{1-6}\) alky sulphonlamino, carbocyclyl or heterocycl; wherein \(R^5\) may be optionally substituted on carbon by one or more \(R^{12}\); and wherein if said heterocyclyl contains an \(-\text{NH}\) moiety that nitrogen may be optionally substituted by a group selected from \(R^{13}\);

\(n=0, 1, 2 \text{ or } 3\); wherein the values of \(R^5\) may be the same or different;

\(R^6, R^8, R^{10}\) and \(R^{12}\) are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, \(C_{1-6}\) alkyl, \(C_{2-6}\) alkenyl, \(C_{2-6}\) alkynyl, \(C_{1-6}\) alkoxy, \(C_{1-6}\) alkanoyl, \(C_{1-6}\) alkanoyloxy, \(N-(C_{1-6} \text{ alkyl})\text{amino}, N,N-(C_{1-6} \text{ alkyl})_2\text{amino}, C_{1-6}\) alkanoylamino, \(N-(C_{1-6} \text{ alkyl})\text{carbamoyl}, N,N-(C_{1-6} \text{ alkyl})_2\text{carbamoyl}, C_{1-6}\) alkoxy carbonyl, \(N-(C_{1-6} \text{ alkyl})\text{sulphamoyl}, N,N-(C_{1-6} \text{ alkyl})_2\text{sulphamoyl}, C_{1-6}\) alky sulphonlamino, carbocyclyl or heterocycl; wherein \(R^6, R^8, R^{10}\) and \(R^{12}\) independently of each other may be optionally substituted on carbon by one or more \(R^{14}\); and wherein if said heterocyclyl contains an \(-\text{NH}\) moiety that nitrogen may be optionally substituted by a group selected from \(R^{15}\);

\(R^7, R^9, R^{11}, R^{13}\) and \(R^{15}\) are independently selected from \(C_{1-6}\) alkyl, \(C_{1-6}\) alkanoyl, \(C_{1-6}\) alky sulphon, \(C_{1-6}\) alkoxy carbonyl, carbamoyl, \(N-(C_{1-6} \text{ alkyl})\text{carbamoyl}, N,N-(C_{1-6} \text{ alkyl})\text{carbamoyl}, C_{1-6}\) alky carbamoyl, benzyl, benzyl oxycarbonyl, benzoyl and phenyl sulphon; wherein \(R^7, R^9,\)
R¹¹, R¹³ and R¹⁵ independently of each other may be optionally substituted on carbon by on or more R¹⁶;

R¹⁴ and R¹⁶ are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ alkoxy, C₁₋₆ alkanoyloxy, N—(C₁₋₆ alkyl)amine, N,N—(C₁₋₆ alkyl)₂ amine, N,N—(C₁₋₆ alkyl)amino, N—(C₁₋₆ alkyl)carbamoyl, N,N—(C₁₋₆ alkyl)₂ carbamoyl, N,N—(C₁₋₆ alkyl)S(O)ₐ wherein a is 0 to 2, C₁₋₆ alkoxy carbonyl, N—(C₁₋₆ alkyl)sulphamoyl, N,N—(C₁₋₆ alkyl) sulphamoyl, C₁₋₆ alkyl sulphonamido, carbo cyclic or heterocyclic; wherein R¹⁴ and R¹⁶ independently of each other may be optionally substituted on carbon by one or more R¹⁷; and wherein if said heterocyclic contains an —NH— moiety that nitrogen may be optionally substituted by a group selected from R¹⁸;

R¹⁷ is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetox y, methylamino, ethylamino, diethylamino, diethy lamino, N-methyl-N-ethylamino, acetylamino, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N,N-diethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, N-methyl sulphamoyl, N-ethyl sulphamoyl, N,N-dimethyl sulphamoyl, N,N-diethyl sulphamoyl or N-methyl-N-ethyl sulphamoyl; and

R¹⁹ and R²¹ are independently selected from a direct bond, —O—, —N(R²²)—, —C(O)—, —N(R²³)C(O)—, —C(O)N(R²⁴)—, —S(O) —, —SO₂ N(R²⁵)— or —N(R²⁶)SO₂—; wherein R²², R²³, R²⁴, R²⁵ and R²⁶ are independently selected from hydrogen or C₁₋₆ alkyl and s is 0-2;

R¹⁸ is selected from C₁₋₆ alkyl, C₁₋₆ alkenyl, C₁₋₆ alkynyl, C₁₋₆ alkoxy, C₁₋₆ alkanoyloxy, N—(C₁₋₆ alkyl)carbamoyl, N,N—(C₁₋₆ alkyl)carbamoyl, benzyl, benzoxycarbonyl, benzoyl and phenylsulphonyl;

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

In another aspect, the invention provides compounds of Formula (LVII), wherein: R¹ is selected from hydrogen, hydroxy, amino, mercapto, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ alkoxy,
C₁₋₆ alkanoyloxy, N—(C₁₋₆ alkyl)amino, N,N—(C₁₋₆ alkyl)₂ amino, C₁₋₆ alkanoylamino, C₁₋₆ alkanoylamino, N—(C₁₋₆ alkyl)sulphonylamino, 3-5-membered carbocyclic or 3-5-membered heterocyclic; wherein R¹ may be optionally substituted on carbon by one or more R⁶; and wherein if said heterocyclic contains an —NH— moiety that nitrogen may be optionally substituted by a group selected from R⁷; 

R² and R³ are independently selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ alkoxy, C₁₋₆ alkanoyl, C₁₋₆ alkanoyloxy, N—(C₁₋₆ alkyl)amino, N,N—(C₁₋₆ alkyl)₂ amino, C₁₋₆ alkanoylamino, N—(C₁₋₆ alkyl)sulphonylamino, 3-5-membered carbocyclic or 3-5-membered heterocyclic; wherein a is 0 to 2, C₁₋₆ alkoxy carbonyl, N—(C₁₋₆ alkyl)sulphamoyl, N,N—(C₁₋₆ alkyl)sulphamoyl, C₁₋₆ alkanoylamino, N—(C₁₋₆ alkyl)carbamoyl, C₁₋₆ alkoxy carbonyl, carbocyclic or heterocyclic; wherein R² and R³ independently of each other may be optionally substituted on carbon by one or more R⁸; and wherein if said heterocyclic contains an —NH— moiety that nitrogen may be optionally substituted by a group selected from R⁹; 

R⁴ is selected from cyano, carboxy, carbamoyl, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ alkanoyl, N—(C₁₋₆ alkyl)carbamoyl, N,N—(C₁₋₆ alkyl)₂ carbamoyl, C₁₋₆ alkoxy carbonyl, carbocyclic or heterocyclic; wherein R⁴ may be optionally substituted on carbon by one or more R¹₀; and wherein if said heterocyclic contains an —NH— moiety that nitrogen may be optionally substituted by a group selected from R¹¹; 

R⁵ is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ alkoxy, C₁₋₆ alkanoyl, C₁₋₆ alkanoyloxy, N—(C₁₋₆ alkyl)amino, N,N—(C₁₋₆ alkyl)₂ amino, C₁₋₆ alkanoylamino, N—(C₁₋₆ alkyl)carbamoyl, N,N—(C₁₋₆ alkyl)₂ carbamoyl, C₁₋₆ alkoxy carbonyl, carbocyclic or heterocyclic; wherein R⁵ may be optionally substituted on carbon by one or more R²; and wherein if said heterocyclic contains an —NH— moiety that nitrogen may be optionally substituted by a group selected from R¹³; 

n=0, 1, 2 or 3; wherein the values of R⁷ may be the same or different;
$R^6$, $R^8$, $R^{10}$ and $R^{12}$ are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C\textsubscript{1-6} alkyl, C\textsubscript{2-6} alkenyl, C\textsubscript{2-6} alkynyl, C\textsubscript{1-6} alkoxy, C\textsubscript{1-6} alkanoyl, C\textsubscript{1-6} alkanoyloxy, N—(C\textsubscript{2-6} alkyl)amino, N,N—(C\textsubscript{1-6} alkyl) amino, C\textsubscript{1-6} alkanoylamino, N—(C\textsubscript{1-6} alkyl)carbamoyl, N,N—(C\textsubscript{1-6} alkyl)carbamoyl, C\textsubscript{1-6} alkyS(O)\textsubscript{2}$

wherein $a$ is 0 to 2, C\textsubscript{1-6} alkoxy carbonyl, N—(C\textsubscript{1-6} alkyl)sulphamoyl, N,N—(C\textsubscript{1-6} alkyl)sulphamoyl, C\textsubscript{1-6} alkylsulphonylamino, carbocycl or heterocycl; wherein $R^6$, $R^8$, $R^{10}$ and $R^{12}$ independently of each other may be optionally substituted on carbon by one or more $R^{14}$; and wherein if said heterocycl contains an —NH— moiety that nitrogen may be optionally substituted by a group selected from $R^{15}$;

$R^7$, $R^9$, $R^{11}$, $R^{13}$ and $R^{15}$ are independently selected from C\textsubscript{1-6} alkyl, C\textsubscript{1-6} alkanoyl, C\textsubscript{1-6} alkylsulphonyl, C\textsubscript{1-6} alkoxy carbonyl, carbamoyl, N—(C\textsubscript{1-6} alkyl)carbamoyl, N,N—(C\textsubscript{1-6} alkyl)carbamoyl, benzyl, benzyloxy carbonyl, benzoyl and phenylsulphonyl; wherein $R^7$, $R^9$, $R^{11}$, $R^{13}$ and $R^{15}$ independently of each other may be optionally substituted on carbon by on or more $R^{16}$;

$R^{14}$ and $R^{16}$ are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C\textsubscript{1-6} alkyl, C\textsubscript{2-6} alkenyl, C\textsubscript{2-6} alkynyl, C\textsubscript{1-6} alkoxy, C\textsubscript{1-6} alkanoyl, C\textsubscript{1-6} alkanoyloxy, N—(C\textsubscript{2-6} alkyl)amino, N,N—(C\textsubscript{1-6} alkyl) amino, C\textsubscript{1-6} alkanoylamino, N—(C\textsubscript{1-6} alkyl)carbamoyl, N,N—(C\textsubscript{1-6} alkyl)carbamoyl, C\textsubscript{1-6} alkyS(O)\textsubscript{2}$

wherein $a$ is 0 to 2, C\textsubscript{1-6} alkoxy carbonyl, N—(C\textsubscript{1-6} alkyl)sulphamoyl, N,N—(C\textsubscript{1-6} alkyl)sulphamoyl, C\textsubscript{1-6} alkylsulphonylamino, carbocycl or heterocycl; wherein $R^{14}$ and $R^{16}$ independently of each other may be optionally substituted on carbon by one or more $R^{17}$; and wherein if said heterocycl contains an —NH— moiety that nitrogen may be optionally substituted by a group selected from $R^{18}$;

$R^{17}$ is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, acetylamino, N-methyl carbamoyl, N-ethyl carbamoyl, N,N-dimethyl carbamoyl, N,N-diethyl carbamoyl, N-methyl-N-ethyl carbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, N-
methylsulphamoyl, N-ethylsulphamoyl, N,Ndimethylsulphamoyl, N,N-diethylsulphamoyl or N-methyl-N-ethylsulphamoyl; and

\[ R^{19} \text{ and } R^{21} \text{ are independently selected from } -O-, -N(R^{22})-, -C(O)-, -N(R^{23})C(O)-, -C(O)N(R^{24})-, -S(O)_, -SO_2N(R^{25})- \text{ or } -N(R^{26})SO_2-; \]
wherein \( R^{22}, R^{23}, R^{24}, R^{25} \) and \( R^{26} \) are independently selected from hydrogen or \( C_{1-6} \) alkyl and \( s \) is 0-2;

\[ R^{18} \text{ is selected from } C_{1-6} \text{alkyl, } C_{1-6} \text{alkanoyl, } C_{1-6} \text{alkylsulphonyl, } C_{1-6} \text{alkoxycarbonyl, } \]
\[ \text{carbamoyl, } N-(C_{1-6} \text{alkyl})\text{carbamoyl, } N,N-(C_{1-6} \text{alkyl})\text{carbamoyl, } \]
\[ \text{benzyl, } \text{benzyloxy} \text{carbonyl, } \text{benzoyl and phenylsulphonyl; } \]
or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

In another aspect, the invention provides compounds of Formula (LVII), wherein: \( R^{1} \) is selected from hydrogen, hydroxy, amino, mercapto, \( C_{1-6} \text{alkyl, } C_{2-6} \text{alkenyl, } C_{2-6} \text{alkynyl, } \]
\[ C_{1-6} \text{alkanoyloxy, } N-(C_{1-6} \text{alkyl})\text{amino, } N,N-(C_{1-6} \text{alkyl})_2\text{amino, } \]
\[ C_{1-6} \text{alkanoylamino, } C_{1-6} \text{alkylsulphonylamino, } 3-5-\text{membered carbocyclyl or } 3-5-\text{membered heterocyclyl; } \]
wherein \( R^{1} \) may be optionally substituted on carbon by one or more \( R^{6} \); and wherein if said heterocyclyl contains an \(-\text{NH}--\) moiety that nitrogen may be optionally substituted by a group selected from \( R^{2} \);

\[ R^{2} \text{ and } R^{3} \text{ are independently selected from hydrogen, halo, nitro, cyano, hydroxy, amino, } \]
\[ \text{carboxy, carbamoyl, mercapto, sulphamoyl, } C_{1-6} \text{alkyl, } C_{2-6} \text{alkenyl, } C_{2-6} \text{alkynyl, } C_{1-6} \text{alkoxy, } \]
\[ C_{1-6} \text{alkanoyl, } C_{1-6} \text{alkanoyloxy, } N-(C_{1-6} \text{alkyl})\text{amino, } N,N-(C_{1-6} \text{alkyl})_2\text{amino, } \]
\[ C_{1-6} \text{alkanoylamino, } N-(C_{1-6} \text{alkyl})\text{carbamoyl, } N,N-(C_{1-6} \text{alkyl})_2\text{carbamoyl, } C_{1-6} \text{alkylS(O)}_2\text{a} \]
wherein \( a \) is 0 to 2. \( C_{1-6} \text{alkoxycarbonyl, } N-(C_{1-6} \text{alkyl})\text{sulphonylamino, } N,N-(C_{1-6} \text{alkylsulphonyl})\text{amino, } \]
\[ C_{1-6} \text{alkylsulphonylamino, carbocyclyl-R^{19}-- or heterocyclyl-R^{21}--; } \]
wherein \( R^{2} \) and \( R^{3} \) independently of each other may be optionally substituted on carbon by one or more \( R^{8} \); and wherein if said heterocyclyl contains an \(-\text{NH}--\) moiety that nitrogen may be optionally substituted by a group selected from \( R^{9} \);

\[ R^{8} \text{ is selected from cyano, carboxy, carbamoyl, } C_{1-6} \text{alkyl, } C_{2-6} \text{alkenyl, } C_{2-6} \text{alkynyl, } C_{1-6} \text{alkanoyl, } \]
\[ N-(C_{1-6} \text{alkyl})\text{carbamoyl, } N,N-(C_{1-6} \text{alkyl})_2\text{carbamoyl, } C_{1-6} \text{alkoxycarbonyl, } \]
\[ \text{carbocyclyl or } \]

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heterocyclyl; wherein \( R^4 \) may be optionally substituted on carbon by one or more \( R^{10} \); and wherein if said heterocyclyl contains an —NH— moiety that nitrogen may be optionally substituted by a group selected from \( R^{11} \);

\( R^5 \) is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, \( C_{1-6} \) alkyl, \( C_{2-6} \) alkenyl, \( C_{2-6} \) alkynyl, \( C_{1-6} \) alkanoyl, \( C_{1-6} \) alkanoyloxy, \( N—(C_{1-6} \) alkyl)amino, \( N,N—(C_{1-6} \) alkyl) amino, \( C_{1-6} \) alkanoylamino, \( N—(C_{1-6} \) alkyl) carbamoyl, \( N,N—(C_{1-6} \) alkyl) carbamoyl, \( C_{1-6} \) alkylS(O)\(_2\), wherein \( a \) is 0 to 2, \( C_{1-6} \) alkoxy carbonyl, \( N—(C_{1-6} \) alkyl)sulphamoyl, \( N,N—(C_{1-6} \) alkyl)sulphamoyl, \( C_{1-6} \) alkylsulphonylamino, carbocyclyl or heterocyclyl; wherein \( R^5 \) may be optionally substituted on carbon by one or more \( R^{12} \), and wherein if said heterocyclyl contains an —NH— moiety that nitrogen may be optionally substituted by a group selected from \( R^{13} \);

\( n=0, 1, 2 \) or 3; wherein the values of \( R^2 \) may be the same or different;

\( R^6, R^8, R^{10} \) and \( R^{12} \) are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, \( C_{1-6} \) alkyl, \( C_{2-6} \) alkenyl, \( C_{2-6} \) alkynyl, \( C_{1-6} \) alkanoyl, \( C_{1-6} \) alkanoyloxy, \( N—(C_{1-6} \) alkyl)amino, \( N,N—(C_{1-6} \) alkyl) amino, \( C_{1-6} \) alkanoylamino, \( N—(C_{1-6} \) alkyl) carbamoyl, \( N,N—(C_{1-6} \) alkyl) carbamoyl, \( C_{1-6} \) alkylS(O)\(_2\), wherein \( a \) is 0 to 2, \( C_{1-6} \) alkoxy carbonyl, \( N—(C_{1-6} \) alkyl)sulphamoyl, \( N,N—(C_{1-6} \) alkyl)sulphamoyl, \( C_{1-6} \) alkylsulphonylamino, carbocyclyl or heterocyclyl; wherein \( R^6, R^8 \), \( R^{10} \) and \( R^{12} \) independently of each other may be optionally substituted on carbon by one or more \( R^{14} \); and wherein if said heterocyclyl contains an —NH— moiety that nitrogen may be optionally substituted by a group selected from \( R^{15} \);

\( R^7, R^9, R^{11}, R^{13} \) and \( R^{15} \) are independently selected from \( C_{1-6} \) alkyl, \( C_{1-6} \) alkanoyl, \( C_{1-6} \) alkylsulphonylamino, \( C_{1-6} \) alkoxy carbonyl, carbamoyl, \( N—(C_{1-6} \) alkyl)sulphamoyl, \( N,N—(C_{1-6} \) alkyl) carbamoyl, \( C_{1-6} \) alkyl carbamoyl, benzyl, benzoxycarbonyl, benzoyl and phenyl sulphphonyl; wherein \( R^7, R^9, R^{11}, R^{13} \) and \( R^{15} \) independently of each other may be optionally substituted on carbon by on or more \( R^{16} \);

\( R^{14} \) and \( R^{16} \) are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, \( C_{1-6} \) alkyl, \( C_{2-6} \) alkenyl, \( C_{2-6} \) alkynyl, \( C_{1-6} \) alkoxy, \( C_{1-6} \) alkanoyl, \( C_{1-6} \) alkanoyloxy, \( N—(C_{1-6} \) alkyl)amino, \( N,N—(C_{1-6} \) alkyl) amino, \( C_{1-6} \) alkanoylamino, \( N—(C_{1-6} \) alkyl) carbamoyl, \( N,N—(C_{1-6} \) alkyl) carbamoyl, \( C_{1-6} \) alkylS(O)\(_2\), wherein \( a \) is 0 to 2, \( C_{1-6} \) alkoxy carbonyl, \( N—(C_{1-6} \) alkyl)sulphamoyl, \( N,N—(C_{1-6} \) alkyl)sulphamoyl, \( C_{1-6} \) alkylsulphonylamino, carbocyclyl or heterocyclyl; wherein \( R^6, R^8 \), \( R^{10} \) and \( R^{12} \) independently of each other may be optionally substituted on carbon by one or more \( R^{14} \); and wherein if said heterocyclyl contains an —NH— moiety that nitrogen may be optionally substituted by a group selected from \( R^{15} \);

\( n=0, 1, 2 \) or 3; wherein the values of \( R^2 \) may be the same or different;
alkanoylamino, N—((C\textsubscript{1-6})alkyl)carbamoyl, N,N—((C\textsubscript{1-6})alkyl)carbamoyl, (C\textsubscript{1-6})alkylS(O)\textsubscript{a}

wherein \( a \) is 0 to 2, (C\textsubscript{1-6})alkoxycarbonyl, N—((C\textsubscript{1-6})alkyl)sulphamoyl, N,N—((C\textsubscript{1-6})alkyl)sulphamoyl, (C\textsubscript{1-6})alkylsulphonylamino, carbocyclyl or heterocyclyl; wherein \( R' \) and \( R'' \) independently of each other may be optionally substituted on carbon by one or more \( R_6 \); and wherein if said heterocyclyl contains an —NH— moiety that nitrogen may be optionally substituted by a group selected from \( R'\textsubscript{18} \);

\( R'\textsubscript{17} \) is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, acetylaminio, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-N-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, N-methylsulphamoyl, N-ethylsulphamoyl, N,N-dimethylsulphamoyl or N,N-diethylsulphamoyl or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

\( R'\textsubscript{18} \) is selected from (C\textsubscript{1-6})alkyl, (C\textsubscript{1-6})alkanoyl, (C\textsubscript{1-6})alkylsulphonyl, (C\textsubscript{1-6})alkoxycarbonyl, carbamoyl, N—((C\textsubscript{1-6})alkyl)carbamoyl, N,N—((C\textsubscript{1-6})alkyl)carbamoyl, benzyl, benzyloxy carbonyl, benzoyl and phenylsulphonyl;

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

Particular values of the variable groups contained in Formula (LVII) are as follows. Such values may be used, where appropriate, with any of the definitions, claims or embodiments defined hereinbefore or hereinafter.

\( R' \) is selected from (C\textsubscript{1-6})alkyl, (C\textsubscript{1-6})alkoxy, 3-5-membered carbocyclyl, and N,N—((C\textsubscript{1-6})alkyl)\textsubscript{2} amino, wherein \( R' \) may be optionally substituted on carbon by one or more \( R_6 \); and wherein \( R' \) is halo,
$R_1$ is (C$_{1-6}$)alkoxy or 3-5-membered carbocyclyl.

$R_1$ is selected from (C$_{1-6}$)alkyl, (C$_{1-6}$)alkoxy or 3-5-membered carbocyclyl.

$R_1$ is (C$_{1-6}$)alkyl or (C$_{1-6}$)alkoxy.

$R_1$ is 3-5 membered carbocyclyl.

$R_1$ is N,N((C$_{1-6}$)alkyl) amino.

$R_1$ is (C$_{1-6}$)alkyl.

$R_1$ is (C$_{1-4}$)alkyl.

$R_1$ is (C$_{1-6}$)alkoxy.

$R_1$ is selected from methyl, methoxy, trifluoroethoxy, isopropoxy, cyclopropyl, and N,N-dimethylamino;

$R_1$ is isopropoxy or cyclopropyl.

$R_1$ is methyl, methoxy, isopropoxy or cyclopropyl.

$R_1$ is selected from methyl, methoxy, isopropoxy, N,N-dimethylamino, and cyclopropyl.

$R_1$ is isopropoxy.

$R_1$ is methyl.

$R_1$ is ethyl.

$R_1$ is selected from methyl, ethyl, propyl, and butyl.

$R_1$ is selected from (C$_{1-4}$)alkyl, (C$_{1-4}$)alkoxy, and cyclopropyl.

$R_1$ is methoxy.

$R_1$ is cyclopropyl. $R_1$ is N,N-dimethylamino.

$R_1$ is selected from hydrogen, halo, nitro, and (C$_{1-6}$)alkyl, wherein $R_2$ may be optionally substituted on carbon by one or more $R_8$; and wherein $R_8$ is halo.
R² is selected from hydrogen, chloro, fluoro, bromo, nitro, and trifluoromethyl.

R² is halo.

R² is (C₁₋₆)alkyl, wherein R² may be optionally substituted on carbon by one or more R³; and wherein R³ is halo.

R² and R³ are independently selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, (C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₂₋₆)alkynyl, (C₁₋₆)alkoxy, (C₁₋₆)alkanoyl, (C₁₋₆)alkanoyloxy, N—((C₁₋₆)alkyl)amino, N,N—((C₁₋₆)alkyl) amino, (C₁₋₆)alkanoylamino, N—((C₁₋₆)alkyl)carbamoyl, N,N—((C₁₋₆)alkyl)carbamoyl, (C₁₋₆)alkyl)sulphamoyl, (C₁₋₆)alkyl)amino, (C₁₋₆)alkyl)sulphamoylamino, carbocyclyl-R¹⁹— or heterocyclyl-R²¹—; wherein R² and R³ independently of each other may be optionally substituted on carbon by one or more R³; and wherein if said heterocyclyl contains an —NH— moiety that nitrogen may be optionally substituted by a group selected from R³.

R² and R³ are independently selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, (C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₂₋₆)alkynyl, (C₁₋₆)alkoxy, (C₁₋₆)alkanoyl, (C₁₋₆)alkanoyloxy, N—((C₁₋₆)alkyl)amino, N,N—((C₁₋₆)alkyl) amino, (C₁₋₆)alkanoylamino, N—((C₁₋₆)alkyl)carbamoyl, N,N—((C₁₋₆)alkyl)carbamoyl, (C₁₋₆)alkyl)sulphamoyl, (C₁₋₆)alkyl)amino, (C₁₋₆)alkyl)sulphamoylamino, carbocyclyl-R¹⁹— or heterocyclyl-R²¹—; wherein R² and R³ independently of each other may be optionally substituted on carbon by one or more R³; and wherein if said heterocyclyl contains an —NH— moiety that nitrogen may be optionally substituted by a group selected from R³.

R² and R³ are independently selected from hydrogen, halo, N—((C₁₋₆)alkyl)-N—((C₁₋₆)alkyl)sulphamoylamino, or heterocyclyl-R²¹--; wherein R²¹ is a direct bond.

R² and R³ are independently selected from hydrogen and halo.

R² and R³ are independently selected from hydrogen and chloro.
R^2 and R^3 are independently selected from hydrogen, fluoro, chloro, bromo, N-methyl-N-mesylamino and morpholino.

R^2 is halo and R^3 is hydrogen.

R^2 is chloro and R^3 is hydrogen.

R^2 is chloro or fluoro and R^3 is hydrogen. R^3 is selected from hydrogen, halo, cyano, N—((C_{1-6})alkyl)-N—((C_{1-6})alkyl)sulphonyl)amino, ((C_{1-6})alkyl)_2N—S(O)_2—N((C_{1-6})alkyl)—, and heterocyclyl-R^{21}, wherein R^3 may be optionally substituted on carbon by one or more R^3; wherein R^2 is halo; and wherein R^{21} is a bond.

R^3 is hydrogen.

R^3 is halo.

R^3 is selected from N—((C_{1-6})alkyl)-N—((C_{1-6})alkyl)sulphonyl)amino and ((C_{1-6})alkyl)_2N—S(O)_2—N((C_{1-6})alkyl)—.

R^3 is selected from heterocyclyl-R^{21}, wherein R^3 may be optionally substituted on carbon by one or more R^3; wherein R^3 is halo; and wherein R^{21} is a bond.

R^3 is selected from hydrogen, chloro, cyano, trifluoromethyl, (CH_3)_2N—S(O)_2—N(CH_3)—, N-methyl-N-mesylamino, and morpholino.

R^3 is (CH_3)_2N—S(O)_2—N(CH_3)—.

R^3 is N-methyl-N-mesylamino,

R^3 is morpholino.

R^3 is (C_{1-6})alkyl.

R^3 is methyl.

R^3 is halo.

R^3 is fluoro.
n=1.

R^{19} and R^{21} are independently selected from —O—, —N(R^{22})—, —C(O)—, —N(l^{23})C(O)—, —C(O)N(R^{24})—, —S(O)_{s}—, —SO_{2}N(R^{25})— or —N(R^{26})SO_{2}—; wherein R^{22}, R^{23}, R^{24}, R^{25} and R^{26} are independently selected from hydrogen or (C_{1-6})alkyl and s is 0-2.

Therefore in a further aspect of the invention there is provided a compound of Formula (LVII) (as depicted herein above) wherein:

R^{1} is selected from (C_{1-6})alkyl, (C_{1-6})alkoxy or 3-5-membered carbocyclicl;

R^{1} and R^{3} are independently selected from hydrogen, halo, N—((C_{1-6})alkyl)-N—((C_{1-6})alkylsulphonyl)amino, or heterocyclyl-R^{2}—;

R^{4} is (C_{1-6})alkyl;

R^{5} is halo;

n=1;

R^{21} is a direct bond;

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

Therefore in a further aspect of the invention there is provided a compound of Formula (LVII) (as depicted herein above) wherein:

R^{1} is (C_{1-6})alkoxy;

R^{3} and R^{3} are independently selected from hydrogen and halo;

R^{4} is (C_{1-6})alkyl;

R^{5} is halo;

n=1;

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.
Therefore in a further aspect of the invention there is provided a compound of Formula (LVII) 
(as depicted herein above) wherein:

\( R^1 \) is methyl, methoxy, isopropoxy or cyclopropyl;

\( R^2 \) and \( R^3 \) are independently selected from hydrogen, fluoro, chloro, bromo, N-methyl-N-
mesylamino and morpholino;

\( R^4 \) is methyl;

\( R^5 \) is fluoro; and 

\( n=1; \)

or a pharmaceutically acceptable salt, solvate, hydrate, cocystal, or prodrug thereof.

Therefore in a further aspect of the invention there is provided a compound of Formula (LVII) 
(as depicted herein above) wherein:

\( R^1 \) is selected from \((C_{1-6})\)alkyl, \((C_{1-6})\)alkoxy, 3-5-membered carbocyclyl, and \(N,N-((C_{1-6})\)alkyl)\(_2\)amino, wherein \( R^1 \) may be optionally substituted on carbon by one or more \( R^6 \);

\( R^2 \) is selected from hydrogen, halo, nitro, and \((C_{1-6})\)alkyl, wherein \( R^2 \) may be optionally 
substituted on carbon by one or more \( R^8 \);

\( R^3 \) is selected from hydrogen, halo, cyano, \(N-((C_{1-6})\)alkyl)-\(N-((C_{1-6})\)alkylsulphonyl)amino, 
\((C_{1-6})\)alkyl, \((C_{1-6})\)alkyl\(_2\)\(S(O)\)_2\(-N((C_{1-6})\)alkyl\), and heterocyclyl-\(R_1\)\(^{21}\), wherein \( R^3 \) 
may be optionally substituted on carbon by one or more \( R^8 \);

\( R^4 \) is \((C_{1-6})\)alkyl;

\( R^5 \) is halo;

\( R^6 \) is halo;

\( R^8 \) is halo;

\( R^{21} \) is a bond; and 

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n=1;
or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

Therefore in a further aspect of the invention there is provided a compound of Formula (LVII) (as depicted herein above) wherein:

R¹ is selected from methyl, methoxy, trifluoroethoxy, isopropoxy, cyclopropyl, and N,N-dimethylamino;

R² is selected from hydrogen, chloro, fluoro, bromo, nitro, and trifluoromethyl;

R³ is selected from hydrogen, chloro, cyano, trifluoromethyl, (CH₃)₂N—S(O)₂—N(CH₃)—, N-methyl-N-mesylamino, and morpholino;

R⁴ is methyl;

R⁵ is fluoro; and

n is 1;
or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

Therefore in a further aspect of the invention there is provided a compound of Formula (LVII) (as depicted herein above) wherein:

R¹ is selected from (C₁₋₆)alkoxy, wherein R¹ may be optionally substituted on carbon by one or more R⁶;

R² is selected from hydrogen and halo;

R³ is selected from hydrogen, halo, and heterocyclyl-R²¹ —;

R⁴ is (C₁₋₆)alkyl;

R⁵ is halo;

R⁶ is halo;

R²¹ is a bond;
n is 1;

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

Therefore in a further aspect of the invention there is provided a compound of Formula (LVII) (as depicted herein above) wherein:

R¹ is selected from \((C_{1-4})\)alkyl, \((C_{1-4})\)alkoxy, and cyclopropyl;

R² is selected from hydrogen, halo, nitro, and \((C_{1-6})\)alkyl, wherein R² may be optionally substituted on carbon by one or more R³;

R³ is selected from hydrogen, halo, cyano, N—((C₁₋₆)alkyl)-N—((C₁₋₆)alkylsulphonyl)amino, (C₁₋₆)alkyl, ((C₁₋₆)alkyl)₂N—S(Ο)₂—N((C₁₋₆)alkyl)—, and heterocyclyl-R²¹—, wherein R³ may be optionally substituted on carbon by one or more R⁸;

R⁴ is \((C_{1-6})\)alkyl;

R⁵ is halo;

R⁶ is halo;

R⁷ is halo;

R²¹ is a bond; and

n=1;

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

[00731] In a preferred embodiment, the JAK-2 inhibitor is AZD-1480. In a preferred embodiment, the JAK-2 inhibitor is \((S)-5\text{-chloro-N}^2-(1\text{-}(5\text{-fluoropyrimidin-2-yl})\text{ethyl})\text{-N}^4-(5\text{-methyl-1}H\text{-pyrazol-3-yl})\text{pyrimidine-2,4-diamine.}\) In a preferred embodiment, the JAK-2 inhibitor has the chemical structure shown in Formula (LVIII):
or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. The preparation of this compound is described in U.S. Patent No. 8,088,784 and U.S. Patent Application Publication Nos. 2008/0287475 A1; 2010/0160325 A1; and, 2012/0071480 A1, the disclosures of which are incorporated by reference herein. In an embodiment, the JAK-2 inhibitor is selected from the compounds described in U.S. Patent No. 8,088,784 and U.S. Patent Application Publication Nos. 2008/0287475 A1; 2010/0160325 A1; and, 2012/0071480 A1, the disclosures of which are incorporated by reference herein.

[00732] In an embodiment, the JAK-2 inhibitor is a compound of Formula (LIX):

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, wherein:

$R^1$ and $R^2$ are independently selected from hydrogen, halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkanoyl, $C_{1-6}$ alkanoyloxy, $N-(C_{1-6} alkyl)amino, N,N-(C_{1-6} alkyl),_2$-amino, $C_{1-6}$ alkanoylamino, $N-(C_{1-6} alkyl)carbamoyl, N,N-(C_{1-6} alkyl),_2$-carbamoyl, $C_{1-6}$ alkyls(O) wherein a is 0 to 2, $C_{1-6}$ alkoxy carbonyl, $N-(C_{1-6} alkyl)sulphamoyl, N,N-(C_{1-6} alkyl),_2$sulphamoyl, $C_{1-6}$ alkysulphonylamino, carbocyclyl or heterocyclyl; wherein $R^1$
and R² independently of each other may be optionally substituted on carbon by one or more R³; and wherein if said heterocyclyl contains an —NH— moiety that nitrogen may be optionally substituted by a group selected from R⁷;

one of X¹, X², X³ and X⁴ is =N—, the other three are independently selected from =CR⁸—,
=CR⁹— and =CR¹⁰—;

R³ is hydrogen or optionally substituted C₁₋₆ alkyl; wherein said optional substituents are selected from one or more R¹¹;

R² and R³₄ are independently selected from hydrogen, halo, nitro, cyano, hydroxy,
trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C₁₋₆ alkyl, C₂₋₆ alkenyl,
C₂₋₆ alkynyl, C₁₋₆ alkoxy, C₁₋₆ alkanoyl, C₁₋₆ alkanoyloxy, N—(C₁₋₆ alkyl)amino, N,N—(C₁₋₆ alkyl) amino, C₁₋₆ alkanoylamino, N—(C₁₋₆ alkyl)carbamoyl, N,N—(C₁₋₆ alkyl)carbamoyl, C₁₋₆ alkylS(O)₃ wherein a is 0 to 2, C₁₋₆ alkoxy carbonyl, N—(C₁₋₆ alkyl)sulphamoyl, N,N—(C₁₋₆ alkyl)₂ sulphamoyl, C₁₋₆ alkyl sulphonlamino, carbocyclyl or heterocyclyl; wherein R² and R³₄ may be independently optionally substituted on carbon by one or more R¹₂; and wherein if said heterocyclyl contains an —NH— moiety that nitrogen may be optionally substituted by a group selected from R¹³;

A is a direct bond or C₁₋₂ alkylene; wherein said C₁₋₂ alkylene may be optionally substituted by one or more R¹⁴;

Ring C is carbocyclyl or heterocyclyl; wherein if said heterocyclyl contains an —NH— moiety that nitrogen may be optionally substituted by a group selected from R¹⁵;

R⁵ is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₁₋₆ alkoxy, C₁₋₆ alkanoyl, C₁₋₆ alkanoyloxy, N—(C₁₋₆ alkyl)amino, N,N—(C₁₋₆ alkyl) amino, C₁₋₆ alkanoylamino, N—(C₁₋₆ alkyl)carbamoyl, N,N—(C₁₋₆ alkyl)carbamoyl, C₁₋₆ alkylS(O)₃ wherein a is 0 to 2, C₁₋₆ alkoxy carbonyl, N—(C₁₋₆ alkyl)sulphamoyl, N,N—(C₁₋₆ alkyl)₂ sulphamoyl, C₁₋₆ alkyl sulphonlamino, carbocyclyl—R³₇ — or heterocyclyl—R³₈ —; wherein R⁵ may be optionally substituted on carbon by one or more R¹₆; and wherein if said heterocyclyl
contains an —NH— moiety that nitrogen may be optionally substituted by a group selected from R³;

n is 0, 1, 2 or 3; wherein the values of R⁵ may be the same or different;

R⁴, R⁹ and R¹⁰ are independently selected from hydrogen, halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ alkoxy, C₁₋₆ alkanoyl, C₁₋₆ alkanoyloxy, N—(C₁₋₆ alkyl)amino, N,N—(C₁₋₆ alkyl)amino, C₁₋₆ alkanoylamino, N—(C₁₋₆ alkyl)carbamoyl, N,N—(C₁₋₆ alkyl)carbamoyl, C₁₋₆ alkylS(O) wherein a is 0 to 2, C₁₋₆ alkoxy carbonyl, N—(C₁₋₆ alkyl)sulphamoyl, N,N—(C₁₋₆ alkyl)sulphamoyl, C₁₋₆ alkylsulphonylamino, carbocycl-R²⁵ — or heterocycl-R²⁶ —; wherein R⁴, R⁹ and R¹⁰ independently of each other may be optionally substituted on carbon by one or more R¹⁸; and wherein if said heterocycl contains an —NH— moiety that nitrogen may be optionally substituted by a group selected from R¹⁹;

R⁷, R¹¹, R¹², R¹⁴, R¹⁶ and R¹⁸ are independently selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ alkoxy, C₁₋₆ alkanoyl, C₁₋₆ alkanoyloxy, N—(C₁₋₆ alkyl)amino, N,N—(C₁₋₆ alkyl)amino, C₁₋₆ alkanoylamino, N—(C₁₋₆ alkyl)carbamoyl, N,N—(C₁₋₆ alkyl)carbamoyl, C₁₋₆ alkylS(O) wherein a is 0 to 2, C₁₋₆ alkoxy carbonyl, N—(C₁₋₆ alkyl)sulphamoyl, N,N—(C₁₋₆ alkyl)sulphamoyl, C₁₋₆ alkylsulphonylamino, carbocycl-R²⁷ — or heterocycl-R²⁸ —; wherein R⁷, R¹¹, R¹², R¹⁴, R¹⁶ and R¹⁸ independently of each other may be optionally substituted on carbon by one or more R²⁰; and wherein if said heterocycl contains an —NH— moiety that nitrogen may be optionally substituted by a group selected from R²¹;

R⁸, R¹³, R¹⁵, R¹⁷, R¹⁹ and R²¹ are independently selected from C₁₋₆ alkyl, C₁₋₆ alkanoyl, C₁₋₆ alkylsulphonyl, C₁₋₆ alkoxy carbonyl, carbamoyl, N—(C₁₋₆ alkyl)carbamoyl, N,N—(C₁₋₆ alkyl)carbamoyl, benzyl, benzyl oxycarbonyl, benzoyl and phenyl sulphonyl; wherein R⁸, R¹³, R¹⁵, R¹⁷, R¹⁹ and R²¹ independently of each other may be optionally substituted on carbon by one or more R²²;

R²⁰ and R²² are independently selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ alkoxy, C₁₋₆ alkanoyl, C₁₋₆ alkanoyloxy, N—(C₁₋₆ alkyl)amino, N,N—(C₁₋₆ alkyl)amino, C₁₋₆ alkanoylamino, N—(C₁₋₆ alkyl)carbamoyl, N,N—(C₁₋₆ alkyl)carbamoyl, C₁₋₆ alkylS(O) wherein a is 0 to 2, C₁₋₆ alkoxy carbonyl, N—(C₁₋₆ alkyl)sulphamoyl, N,N—(C₁₋₆ alkyl)sulphamoyl, C₁₋₆ alkylsulphonylamino, carbocycl-R²⁵ — or heterocycl-R²⁶ —; wherein R⁸, R¹³, R¹⁵, R¹⁷, R¹⁹ and R²¹ independently of each other may be optionally substituted on carbon by one or more R²²;
alkanoylamino, N—(C\textsubscript{1-6} alkyl)carbamoyl, N,N—(C\textsubscript{1-6} alkyl)carbamoyl, C\textsubscript{1-6} alkylS(O)\textsubscript{a}

wherein \textit{a} is 0 to 2, C\textsubscript{1-6} alkoxycarbonyl, N—(C\textsubscript{1-6} alkyl)sulphamoyl, N,N—(C\textsubscript{1-6} alkyl)sulphamoyl, C\textsubscript{1-6} alkylsulphonylamino, C\textsubscript{1-6} alkylsulphonyl-N—(C\textsubscript{1-6} alkyl)amino, carbocycl-R\textsuperscript{35} — or heterocycl-R\textsuperscript{36} —; wherein R\textsuperscript{20} and R\textsuperscript{22} independently of each other may be optionally substituted on carbon by one or more R\textsuperscript{23}; and wherein if said heterocycl contains an —NH— moiety that nitrogen may be optionally substituted by a group selected from R\textsuperscript{34};

R\textsuperscript{25}, R\textsuperscript{26}, R\textsuperscript{27}, R\textsuperscript{28}, R\textsuperscript{35}, R\textsuperscript{36}, R\textsuperscript{37} and R\textsuperscript{38} are independently selected from a direct bond, —O—, —N(R\textsuperscript{29})—, —C(O)—, —N(R\textsuperscript{30})C(O)—, —C(O)N(R\textsuperscript{31})—, —S(O)\textsubscript{2}—, —NH═CH—, —SO\textsubscript{2}N(R\textsuperscript{32})— or —N(R\textsuperscript{33})SO\textsubscript{2}—; wherein R\textsuperscript{29}, R\textsuperscript{30}, R\textsuperscript{31}, R\textsuperscript{32} and R\textsuperscript{33} are independently selected from hydrogen or C\textsubscript{1-6} alkyl and s is 0-2;

R\textsuperscript{23} is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, acetylamino, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-N-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethoxysulphonyl, methoxycarbonyl, ethoxycarbonyl, N-methylsulphamoyl, N-ethylsulphamoyl, N,N-dimethylsulphamoyl, N,N-diethylsulphamoyl, N-methyl-N-ethylsulphamoyl or phenyl; and

R\textsuperscript{24} is selected from C\textsubscript{1-6} alkyl, C\textsubscript{1-6} alkanoyl, C\textsubscript{1-6} alkylsulphonyl, C\textsubscript{1-6} alkoxycarbonyl, carbamoyl, N—(C\textsubscript{1-6} alkyl)carbamoyl, N,N—(C\textsubscript{1-6} alkyl)carbamoyl, benzyl, benzyloxy carbonyl, benzoyl and phenyl sulphonyl;

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

[00733] In a preferred embodiment, the JAK-2 inhibitor is (S)-5-fluoro-2-((1-(4-fluorophenyl)ethyl)amino)-6-((5-methyl-1 H-pyrazol-3-yl)amino)nicotinonitrile. In a preferred embodiment, the JAK-2 inhibitor has the chemical structure shown in Formula (LX):
or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. The preparation of this compound is described in U.S. Patent No. 8,324,252 and U.S. Patent Application Publication Nos. 2008/0139561 A1 and 2013/0090358 A1, the disclosures of which are incorporated by reference herein. In an embodiment, the JAK-2 inhibitor is selected from the compounds described in U.S. Patent No. 8,324,252 and U.S. Patent Application Publication Nos. 2008/0139561 A1 and 2013/0090358 A1, the disclosures of which are incorporated by reference herein.

[00734] In an embodiment, the JAK-2 inhibitor is a compound of Formula (LXII):

\[
(R_3)_n \quad \text{Formula (LXII)}
\]

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, wherein:

- D is CH or N;
- E is CH or N;
- X is CH\(_2\), NR\(_4\), O or S;
- U is CH or N;
- V is CH or N;
Y is CH or N;
Z is CH or N;
R₁ is NR₅R₆, CR₅R₆R₇, SR₅ or OR₅;
R₂ is (C≡O)OH, (C≡O)NH₂, (C≡O)NHR₄ or heterocycll;
R₃ is
(a) hydrogen;
(b) C₁₋₆ alkyl, which is optionally substituted with halo, hydroxyl, amino, phenyl, heterocycll, C₁₋₆ alkyl or R₁₀;
(c) C₂₋₆ alkenyl, which is optionally substituted with halo, hydroxyl, amino, phenyl, heterocycll, C₁₋₆ alkyl or R₄;
(d) C₃₋₁₀ cycloalkyl, which is optionally substituted with C₁₋₆ alkyl, OR₄, NR₅R₆, phenyl (which is optionally substituted with C₁₋₆ alkyl, OR₄ or NR₅R₆), halo, R₁₀ or heterocycll;
(e) —(CO)R₈;
(f) —(CO)—NR₈R₉;
(g) C₄₋₁₀ heterocycll, which is optionally substituted on either the carbon or the heteroatom with C₁₋₆ alkyl, halo, R₁₀, OR₄, NR₅R₆, phenyl (which is optionally substituted with C₁₋₆ alkyl, OR₄ or NR₅R₆), —(CO)R₈ or —(CO)—NR₈R₉;
(h) OR₄;
(i) NR₅R₆;
(j) halo;
(k) Aryl, which is optionally substituted with one or more groups selected from C₁₋₆ alkyl (which is optionally substituted with one to three halo), halo or R₁₀;
(l) Heteroaryl, which is optionally substituted with one or more groups selected from C₁₋₆ alkyl (which is optionally substituted with one to three halo), halo or R₁₀;
(m) O-aryl, which is optionally substituted with one or more groups selected from C₁₋₆ alkyl, halo or R₁₀;
(n) O—C₁₋₆ alkyl, which is optionally substituted with C₁₋₆ alkyl, halo or R₁₀; or
(o) L-A-R₁₀;
R₄ is
(a) hydrogen;
(b) $C_{1-6}$ alkyl, which is optionally substituted with halo, hydroxyl, amino, aryl or heterocyclyl;

(c) $C_{3-10}$ cycloalkyl, which is optionally substituted with $C_{1-6}$ alkyl, OR$_{11}$, NR$_{8}$$R_{11}$, phenyl (which is optionally substituted with $C_{1-6}$ alkyl, OR$_{11}$ or NR$_{8}$$R_{11}$), heterocyclyl, aryl or heteroaryl;

(d) $-(CO)R_{8}$;

(e) $-(CO)NR_{8}$$R_{9}$;

(f) $C_{4-10}$ heterocyclyl, which is optionally substituted on either the carbon or the heteroatom with $C_{1-6}$ alkyl, OR$_{11}$, NR$_{8}$$R_{11}$, phenyl (which is optionally substituted with $C_{1-6}$ alkyl, OR$_{11}$ or NR$_{8}$$R_{11}$), heterocyclyl, $-(CO)R_{8}$ or $-(CO)NR_{8}$$R_{9}$;

(g) OR$_{11}$;

(h) NR$_{8}$$R_{11}$;

(i) Aryl, which is optionally substituted with one to five halo or R$_{10}$;

(j) Heteroaryl (wherein the heteroaryl has 5 or 6 members in which 1, 2, 3, or 4 of the atoms is a heteroatom selected from N, S and O), which is optionally substituted with one to five halo or R$_{10}$;

$R_{5}$ is

(a) hydrogen;

(b) $C_{1-8}$ alkyl, which is optionally substituted with halo, hydroxyl, amino, aryl, cycloalkyl or heterocyclyl;

(c) $C_{3-10}$ cycloalkyl, which is optionally substituted with $C_{1-6}$ alkyl, (C$_{1-6}$ alkyl)aryl, (C$_{1-6}$ alkyl)OR$_{9}$, OR$_{4}$, NR$_{8}$$R_{4}$, phenyl (which is optionally substituted with $C_{1-6}$ alkyl, OR$_{4}$, NR$_{8}$$R_{4}$, heterocyclyl, $-(CO)R_{8}$ or $-(CO)NR_{8}$$R_{9}$);

(d) $-(CO)R_{8}$;

(e) $-(CO)NR_{8}$$R_{9}$;

(f) $C_{1-6}$ alkyl(C=O)NR$_{8}$$C_{9}$ (C=O)NR$_{8}$$R_{9}$;

(g) $C_{4-10}$ heterocyclyl which is optionally substituted on either the carbon or the heteroatom with one to three substituents selected from $C_{1-6}$ alkyl, halo, OR$_{4}$, NR$_{8}$$R_{4}$, $-(CO)R_{8}$, (CO)—NR$_{8}$$R_{9}$ or phenyl (which is optionally substituted with $C_{1-6}$ alkyl, OR$_{4}$, NR$_{8}$$R_{4}$, heterocyclyl, $-(CO)R_{8}$ or $-(CO)NR_{8}$$R_{9}$);

$R_{6}$ is
(a) hydrogen;
(b) C\textsubscript{1-8} alkyl, which is optionally substituted with halo, hydroxyl, amino, aryl, cycloalkyl or heterocycl;
(c) C\textsubscript{3-10} cycloalkyl, which is optionally substituted with C\textsubscript{1-6} alkyl, (C\textsubscript{1-6} alkyl)aryl, (C\textsubscript{1-6} alkyl)OR\textsubscript{8}, OR\textsubscript{4}, NR\textsubscript{8} R\textsubscript{4}, phenyl (which is optionally substituted with C\textsubscript{1-6} alkyl, OR\textsubscript{4}, NR\textsubscript{8} R\textsubscript{4}), heterocycl, —(CO)R\textsubscript{8} or —(CO)—NR\textsubscript{8} R\textsubscript{4};
(d) —(CO)R\textsubscript{8};
(e) —(CO)—NR\textsubscript{8} R\textsubscript{4};
(f) C\textsubscript{1-6} alkyl(C\textsubscript{=O})NR\textsubscript{8} R\textsubscript{4} (C\textsubscript{=O})NR\textsubscript{8} R\textsubscript{4};
(g) C\textsubscript{3-10} heterocycl which is optionally substituted on either the carbon or the heteroatom with one to three substituents selected from C\textsubscript{1-6} alkyl, halo, OR\textsubscript{4}, NR\textsubscript{8} R\textsubscript{4}, —(CO)R\textsubscript{8}, (CO)—NR\textsubscript{8} R\textsubscript{4} or phenyl (which is optionally substituted with C\textsubscript{1-6} alkyl, OR\textsubscript{4}, NR\textsubscript{8} R\textsubscript{4}), heterocycl, —(CO)R\textsubscript{8} or —(CO)—NR\textsubscript{8} R\textsubscript{4};

R\textsubscript{5} is

(a) hydrogen;
(b) C\textsubscript{1-8} alkyl, which is optionally substituted with halo, hydroxyl, amino, phenyl or heterocycl;
(c) C\textsubscript{3-10} cycloalkyl, which is optionally substituted with C\textsubscript{1-6} alkyl, OR\textsubscript{4}, NR\textsubscript{8} R\textsubscript{4}, phenyl (which is optionally substituted with C\textsubscript{1-6} alkyl, OR\textsubscript{4}, NR\textsubscript{8} R\textsubscript{4}, heterocycl, —(CO)R\textsubscript{8} or —(CO)—NR\textsubscript{8} R\textsubscript{4};
(d) C\textsubscript{3-10} heterocycl which is optionally substituted on either the carbon or the heteroatom with C\textsubscript{1-6} alkyl, OR\textsubscript{4}, NR\textsubscript{8} R\textsubscript{4}, phenyl (which is optionally substituted with C\textsubscript{1-6} alkyl, OR\textsubscript{4}, NR\textsubscript{8} R\textsubscript{4}, heterocycl, —(CO)R\textsubscript{8} or —(CO)—NR\textsubscript{8} R\textsubscript{4};

Or R\textsubscript{5} and R\textsubscript{8} together with the atoms between them, can form a three to ten membered heterocyclic or heteroaryl ring which is optionally substituted with C\textsubscript{1-6} alkyl, (C\textsubscript{1-6} alkyl)aryl, (C\textsubscript{1-6} alkenyl)aryl, (C\textsubscript{1-6} alkyl)OR\textsubscript{8}, OR\textsubscript{4}, NR\textsubscript{8} R\textsubscript{4}, phenyl (which is optionally substituted with C\textsubscript{1-6} alkyl, OR\textsubscript{4}, NR\textsubscript{8} R\textsubscript{4}, heterocycl, —(CO)R\textsubscript{8} or —(CO)—NR\textsubscript{8} R\textsubscript{4}, —(CO)R\textsubscript{8}; —(CO)—NR\textsubscript{8} R\textsubscript{9}, or heterocycl;

R\textsubscript{8} is hydrogen or C\textsubscript{1-6} alkyl, —(CO)R\textsubscript{4}, —(CO)N(R\textsubscript{4});
R\textsubscript{9} is hydrogen or C\textsubscript{1-6} alkyl;
R\textsubscript{10} is:
(a) hydrogen;
(b) CO$_2$R$_{11}$;
(c) C(O)R$_{11}$;
(d) NHR$_{11}$;
(e)NR$_{11}$R$_{12}$;
(f) NHS(O)$_2$R$_{11}$;
(g) NHC(O)R$_{11}$;
(h) NHC(O)OR$_{11}$;
(i) NH—C═(NH)NH$_2$;
(j) NHC(O)NH$_2$;
(k) NHC(O)NHR$_{11}$;
(l) NHC(O)NR$_{11}$R$_{12}$;
(m) NC$_3$-6cycloalkyl;
(n) C(O)NHR$_{11}$;
(o) C(O)NR$_{11}$R$_{12}$;
(p) SO$_2$NHR$_{11}$;
(q) SO$_2$NHC(O)R$_{12}$; or
(r) SO$_2$R$_{11}$;

R$_{11}$ is selected from the group consisting of:
(a) hydrogen,
(b) C$_3$-6cycloalkyl, which is optionally substituted with aryl, heteroaryl or one to five halo;
(c) C$_{1-6}$alkyl, which is optionally substituted with aryl, heteroaryl, or one to five halo;
(d) Aryl, which is optionally substituted with one to five halo;
(e) Heteroaryl (wherein the heteroaryl has 5 or 6 members in which 1, 2, 3, or 4 of the atoms is a heteroatom selected from N, S and O), which is optionally substituted with one to five halo;

R$_{12}$ is selected from the group consisting of:
(a) hydrogen,
(b) C$_{1-6}$alkyl, which is optionally substituted with aryl, heteroaryl or one to five halo;
(c) C3-6cycloalkyl, which is optionally substituted with aryl, heteroaryl or one to five halo;
(d) Aryl, which is optionally substituted with one to five halo;
(e) Heteroaryl (wherein the heteroaryl has 5 or 6 members in which 1, 2, 3, or 4 of the atoms is a heteroatom selected from N, S and O), which is optionally substituted with one to five halo;

A is absent or is selected from the group consisting of: aryl or heteroaryl (wherein the heteroaryl is a monocyclic ring of 5 or 6 atoms or a bicyclic ring of 9 or 10 atoms in which 1, 2, 3, or 4 of the atoms is a heteroatom selected from N, S and O), wherein said aryl or heteroaryl is optionally substituted with one or more substituents selected from halo, (C1-3)alkyl, —C(O)OH, CF3, —SO2(C1-3)alkyl, SO2N(C1-3)alkyl, SO2NHC(O)—(C1-3)alkyl or N(CH3)2;

L is absent or is selected from the group consisting of: —(CH2)k—W—, —Z—(CH2)k—, —C≡C—, —C1-6 alkyl—, —C3-6 cycloalkyl— and —C2-5 alkene—, wherein the alkene is optionally substituted with one or more groups selected from C1-6 alkyl or C1-6 cycloalkyl;

W is selected from the group consisting of: O, NH, NC1-6 alkyl and S(O)m, with the proviso that when W is O, S(O)m, NH or NC1-6 alkyl and simultaneously A is absent then R1 is CO2R12, COR11, CONHR11, or CONR11R12;

k=0, 1, 2, 3, 4, or 5;
m=0, 1, or 2;
n=0, 1, 2, or 3;
or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, or stereoisomer thereof.

[00735] In a preferred embodiment, the JAK-2 inhibitor is ((R)-7-(2-amino-4-carboxamide, which is also named 7-(2-amino-4-carboxamide. In a preferred embodiment, the JAK-2 inhibitor has the chemical structure shown in Formula (LXII):
or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. The preparation of this compound is known to those of ordinary skill in the art, and is described in J. Lim, et al., Discovery of 1-amino-5H-pyrido[4,3-b]indol-4-carboxamide inhibitors of Janus kinase-2 (JAK2) for the treatment of myeloproliferative disorders, *J. Med. Chem.* **2011**, *54*, 7334-7349.

[00736] In selected embodiments, the JAK-2 inhibitor is is a compound selected from the JAK-2 inhibitors disclosed in U.S. Patent No. U.S. 8,518,964 or U.S. Patent Application Publication Nos. 2010/0048551 A1, the disclosures of which are incorporated by reference herein.

CDK4/6 Inhibitors

[00737] In some embodiments, the compositions and methods described include one or more cyclin-dependent kinases 4 and/or 6 (CDK4/6) inhibitors. Exemplary CDK4/6 inhibitors suitable for use in the compositions and methods described herein can be found in U.S. Patent No. 6,689,864; U.S. Patent Application Publication No. 2014/0051644; and 2010/0105653; PCT Patent Application Publication Nos. 2001/060801; 20010/60351; 2008/007113; 2005/012256; 2008/007123; 2007/140222; 2006/106046; 2003/062236; 2005/005426; 1999/21845; 2006/097449; 2006/097460; 1999/02162; 2012/129344; 2010/075074; and 1999/50251, all of which publications are incorporated by reference herein in their entireties.
In some embodiments, a CDK4/6 inhibitor of the present invention is a compound of the Formula (100-I):

\[
\begin{align*}
\text{Formula (100-I)}
\end{align*}
\]

or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof, wherein: the dashed line represents an optional bond;

\(X^1, X^2, \text{and } X^3\) are independently hydrogen, halogen, C-C subalkyl, -haloalkyl, d-C alkoxyl, C alkoxyl, CN, NO\(_2\), OR\(^5\), NR\(^5\) R\(^6\), CO\(_2\)R\(^1\), COR\(^5\), S(O)R\(^5\), S(O)R\(^5\), CONR\(^5\)R\(^6\), NR\(^5\) COR\(^6\), NR\(^5\)SO\(_2\)R\(^6\), SO\(_2\)NR\(^5\)R\(^6\), and P(O)(OR\(^5\))(OR\(^6\)); with the proviso that at least one of \(X^1, X^2, \text{and } X^3\) must be hydrogen;

\(n = 0-2;\)

\(R^1\) is, in each instance, independently, hydrogen, halogen, C-C subalkyl, -C\(\beta\) haloalkyl, C-C subhydroxyalkyl, or C\(3-\)-C\(5\) cycloalkyl;

\(R^2\) and \(R^4\) are independently selected from hydrogen, halogen, C-C subalkyl, C\(3-\)-C cycloalkyl, C alkoxyl, C alkoxyl, -C haloalkyl, -C hydroxyalkyl, C\(2-\)-C subalkenyl, C\(2-\)-C\(2\) alkynyl, nitrile, nitro, OR\(^5\), SR\(^5\), NR\(^5\) R\(^6\), N(O)R\(^5\) R\(^6\), P(O)(OR\(^5\))(OR\(^6\)), \(\text{(CR}^5\text{R}^6\text{)}_m\text{NR}^7\text{R}^8\), COR\(^5\), \(\text{(CR}^5\text{R}^6\text{)}_m\text{C(O)R}^7\), CO\(_2\)R\(^5\), CONR\(^5\)R\(^7\), C(O)NR\(^5\)SO\(_2\)R\(^6\), NR\(^5\)SO\(_2\)R\(^6\), C(O)NR\(^5\)OR\(^6\), S(O)\(_2\)NR\(^5\)R\(^6\), P(O)(OR\(^5\))(OR\(^6\)), \(\text{(CR}^5\text{R}^6\text{)}_m\text{P(O)(OR}^7\text{))(OR}^8\text{)}, \(\text{(CR}^5\text{R}^6\text{)}_m\text{-aryl}, \(\text{(CR}^5\text{R}^6\text{)}_m\text{-heteroaryl, -T(CH}_2\text{)}_m\text{QR}^5\), -C(O)T(CH\(_2\))\(_m\)QR\(^5\), NR\(^5\)C(O)T(CH\(_2\))\(_m\)QR\(^5\), and-\(\text{CR}^5=\text{CR}^5\text{C(O)R}^7\); or

\(R^1\) and \(R^2\) may form a carbocyclic group containing 3-7 ring members, preferably 5-6 ring members, up to four of which can optionally be replaced with a heteroatom independently selected from oxygen, sulfur, and nitrogen, and wherein the carbocyclic group is unsubstituted or substituted with one, two, or three groups independently
selected from halogen, hydroxy, hydroxyalkyl, nitrile, lower C₆-alkyl, lower C₆-alkoxy, alkoxycarbonyl, alkylcarbonyl, alkylcarbonylamino, aminoalkyl, trifluoromethyl, N-hydroxyacetamide, trifluoromethylalkyl, amino, and mono or dialkylamino, (CH₂)ₙC(O)NR₇R₈, and O(CH₂)ₙC(O)OR₇, provided, however, that there is at least one carbon atom in the carbocyclic ring and that if there are two or more ring oxygen atoms, the ring oxygen atoms are not adjacent to one another;

T is O, S, NR₇, N(O)R₇, NR₇R₈W, or CR₈R₉;

Q is O, S, NR₇, N(O)R₇, NR₇R₈W, CO₂, O(CH₂)ₘ-heteroaryl, O(CH₂)ₙS(O),Rₗ, (CH₂)ₙ-heteroaryl, or a carbocyclic group containing from 3-7 ring members, up to four of which ring members are optionally heteroatoms independently selected from oxygen, sulfur, and nitrogen, provided, however, that there is at least one carbon atom in the carbocyclic ring and that if there are two or more ring oxygen atoms, the ring oxygen atoms are not adjacent to one another, wherein the carbocyclic group is unsubstituted or substituted with one, two, or three groups independently selected from halogen, hydroxy, hydroxyalkyl, lower alkyl, lower alkoxy, alkoxycarbonyl, alkylcarbonyl, alkylcarbonylamino, aminoalkyl, trifluoromethyl, N-hydroxyacetamide, trifluoromethylalkyl, amino, and mono or dialkylamino;

W is an anion selected from the group consisting of chloride, bromide, trifluoroacetate, and triethylammonium;

m = 0-6; R' and one of X¹, X² and X³ may form an aromatic ring containing up to three heteroatoms independently selected from oxygen, sulfur, and nitrogen, and optionally substituted by up to 4 groups independently selected from halogen, hydroxy, hydroxyalkyl, lower alkyl, lower alkoxy, alkoxycarbonyl, alkylcarbonyl, alkylcarbonylamino, aminoalkyl, aminoalkylcarbonyl, trifluoromethyl, trifluoromethylalkyl, trifluoromethylalkylaminoalkyl, amino, mono-or dialkylamino, N-hydroxyacetamido, aryl, heteroaryl, carboxyalkyl, nitrile, NR₇SO₂R₉, C(O)NR₇R₉, NR₇C(O)R₇, C(O)OR₇, C(O)NR₇SO₂R₉, (CH₂)ₙSO₂Rₗ, (CH₂)ₙ-heteroaryl, O(CH₂)ₙ-heteroaryl, (CH₂)ₙC(O)NR₇R₉, O(CH₂)ₙC(O)OR₇, (CH₂)ₙSO₂NR₇R₉, and C(O)R₉;

R' is hydrogen, aryl, -alkyl, -C₆-alkoxy, C₃-C₇-cycloalkyl, or C₃-C₇-heterocyclyl;
R⁵ and R⁶ independently are hydrogen, -alkyl, C₂-C₈ alkenyl, C₂-alkynyl, arylalkyl, heterocycloalkyl, aryl, heteroaryl, or heterarylalkyl; or R⁵ and R⁶, when attached to the same nitrogen atom, taken together with the nitrogen to which they are attached, form a heterocyclic ring containing from 3-8 ring members, up to four of which members can optionally be replaced with heteroatoms independently selected from oxygen, sulfur, S(O), S(O)₂, and nitrogen, provided, however, that there is at least one carbon atom in the heterocyclic ring and that if there are two or more ring oxygen atoms, the ring oxygen atoms are not adjacent to one another, wherein the heterocyclic group is unsubstituted or substituted with one, two or three groups independently selected from halogen, hydroxy, hydroxylalkyl, lower alkyl, lower alkoxy, alkoxy carbonyl, alkylcarbonyl, alkylcarbonylamino, aminoalkyl, aminoalkylcarbonyl, trifluoromethylalkyl, trifluoromethylalkylaminoalkyl, amino, nitrile, mono- or dialkylamino, N-hydroxy acetamido, aryl, heteroaryl, carboxyalkyl, NR⁷SO₂R⁸, C(O)NR⁷R⁸, NR⁷C(O)R⁸, C(O)OR⁸, C(O)NR⁷SO₂R⁸, (CH₂)ₙS(O)R⁷, (CH₂)ₙ-heteroaryl, O(CH₂)ₙ-heteroaryl, (CH₂)ₙC(O)NR⁷R⁸, O(CH₂)ₙC(O)OR⁸, and (CH₂)ₙSO₂NR⁷R⁸; R⁷ and R⁸ are, independently, hydrogen, -Cs alkyl, C₂-C₈ alkenyl, C -C₈ alkynyl, arylalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, or heterarylalkyl; or

R⁵ and R⁶, when attached to the same nitrogen atom, taken together with the nitrogen to which they are attached, may form a heterocyclic ring containing from 3-8 ring members, up to four of which members are optionally heteroatoms independently selected from oxygen, sulfur, S(O), S(O)₂, and nitrogen, provided, however, that there is at least one carbon atom in the heterocyclic ring and that if there are two or more ring oxygen atoms, the ring oxygen atoms are not adjacent to one another, wherein the heterocyclic group is unsubstituted or substituted with one, two or three groups independently selected from halogen, hydroxy, hydroxylalkyl, lower alkyl, lower alkoxy, alkoxy carbonyl, alkylcarbonyl, alkylcarbonylamino, aminoalkyl, aminoalkylcarbonyl, trifluoromethyl, trifluoromethylalkyl, trifluoromethylalkylaminoalkyl, amino, nitrile, mono- or dialkylamino, N-hydroxy acetamido, aryl, heteroaryl, carboxyalkyl; and the pharmaceutically acceptable salts, esters, amides, and prodrugs thereof.

[00739] Preferred compounds of the present invention are those having the Formula 100-LT:
a pharmaceutically acceptable salt, ester, amide, or prodrug thereof, wherein: the dashed line represents an optional bond;

wherein \( R^1, R^2, R^3, R^4, X^1, X^2, \) and \( X^3 \), are as defined for Formula (100-I).

[00740] In one preferred embodiment of the present invention one of \( X^1, X^2 \) or \( X^3 \) is hydrogen, halogen, or alkyl. In a further preferred embodiment of the present invention one of \( X^1, X^2 \) or \( X^3 \) is OR\(^5\), NR\(^5\)R\(^6\) or COR\(^5\).

[00741] In a most preferred embodiment of the present invention \( X^1=X^2=X^3=H \). In another preferred embodiment of the present invention \( R^1 \) is hydrogen, halogen or alkyl. In a more preferred embodiment of the present invention \( R^1 \) is alkyl.

[00742] In a preferred embodiment of the present invention one of \( R^2 \) and \( R^4 \) is hydrogen, halogen, -alkyl, -Cs alkoxy, nitrile, OR\(^5\), NR\(^5\)R\(^6\), COR\(^5\), (CR\(^5\)R\(^6\))\(_m\)C(O)R\(^7\), CO\(_2\)R\(^5\), CONR\(^5\)R\(^6\), (CR\(^5\)R\(^6\))\(_m\)-aryl, or (CR\(^5\)R\(^6\))\(_m\)-heteroaryl.

[00743] In a more preferred embodiment of the present invention \( R^2 \) is hydrogen, halogen, -alkyl, OR\(^5\), NR\(^5\)R\(^6\), COR\(^5\), (CR\(^5\)R\(^6\))\(_m\)-aryl, or (CR\(^5\)R\(^6\))\(_m\)-heteroaryl.

[00744] In a further preferred embodiment of the present invention \( R^4 \) is hydrogen, OR\(^5\), or NR\(^5\)R\(^6\).

[00745] In another preferred embodiment of the present invention \( R^3 \) is -C\(_8\) alkyl. In yet another preferred embodiment of the present invention R and R are hydrogen, C\(_t\)-C\(_8\) alkyl, C\(_2\)-C\(_8\) alkenyl, C\(_2\)-C\(_8\) alkynyl, arylalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, or heterarylalkyl. In a further preferred embodiment of the present invention \( R^5 \) and \( R^6 \) together with the nitrogen to which they are attached form a carbocyclic ring containing from 3-8 members, up to four of which members are heteroatoms.
In a more preferred embodiment of the present invention R⁵ and R⁶ together with the nitrogen to which they are attached form a carbocyclic ring containing 5 or 6 members, up to two of which members are heteroatoms.

In a most preferred embodiment of the present invention R⁵ and R⁶ together with the nitrogen to which they are attached form a piperazine ring.

Further preferred embodiments of the present invention are compounds according to Formula (100-I) in which R⁴ is a disubstituted amine.

Especially preferred embodiments of the present invention are compounds according to Formula (100-I) in which R¹ is a methyl group and R² is a cyclopentyl group. Preferred embodiments of the present invention include, but are not limited to, the compounds listed below:

- 8-Cyclopentyl-2-(pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one,
- 6-Bromo-8-cyclopentyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one hydrochloride,
- 8-Cyclopentyl-6-ethyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one hydrochloride,
- 8-Cyclopentyl-7-oxo-2-(5-piperazin-1-yl-pyridin-2-ylamino)-7,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester hydrochloride,
- 6-Amino-8-cyclopentyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one hydrochloride,
- 6-Bromo-8-cyclopentyl-2-[5-((R)-1-methyl-1-pyrrolidin-2-yl)-pyridin-2-ylamino]-8H-pyrido[2,3-d]pyrimidin-7-one hydrochloride,
- 6-Bromo-8-cyclohexyl-2-(pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one,
- 6-Acetyl-8-cyclopentyl-2-[5-(3,5-dimethyl-piperazin-1-yl)-pyridin-2-ylamino]-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one,
- 6-Acetyl-8-cyclopentyl-2-[5-(3,3-dimethyl-piperazin-1-yl)-pyridin-2-ylamino]-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one,
- 6-Acetyl-8-cyclopentyl-5-methyl-2-[5-(4-methyl-piperazin-1-yl)-pyridin-2-ylamino]-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Acetyl-2-[5-(3-amino-pyrrolidin-1-yl)-pyridin-2-ylamino]-8-cyclopentyl-5-methyl-
8H-pyrido[2,3-d]pyrimidin-7-one,
6-Bromo-8-cyclopentyl-5-methyl-2-(5-morpholin-4-yl-pyridin-2-ylamino)-8H-
pyrido[2,3-d]pyrimidin-7-one, 2-[5-[Bis-(2-methoxy-ethyl)-amino]-pyridin-2-
ylamino]-6-bromo-8-cyclopentyl-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Acetyl-8-cyclopentyl-5-methyl-2-(5-morpholin-4-yl-pyridin-2-ylamino)-8H-
pyrido[2,3-d]pyrimidin-7-one,
6-Acetyl-2-[5-[bis-(2-methoxy-ethyl)-amino]-pyridin-2-ylamino]-8-cyclopentyl-5-
methyl-8H-pyrido[2,3-d]pyrimidin-7-one,
4-[6-(8-Cyclopentyl-6-iodo-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-
ylamino)-pyridin-3-yl]-piperazine-l-carboxylic acid tert-butyl ester,
8-Cyclopentyl-6-iodo-5-methyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-8H-
pyrido[2,3-d]pyrimidin-7-one, 4-[6-[8-Cyclopentyl-6-(2-ethoxy-ethoxy)-7-oxo-7,8-
dihydro-pyrido[2,3-d]pyrimidin-2-ylamino]-pyridin-3-yl]-piperazine-l-carboxylic
acid tert-butyl ester,
8-Cyclopentyl-6-2-(2-ethoxy-ethoxy)-2-(5-piperazin-1-yl-pyridin-2-ylamino)-8H-
pyrido[2,3-d]pyrimidin-7-one,
2-[5-[Bis-(2-methoxy-ethyl)-amino]-pyridin-2-ylamino]-6-bromo-8-cyclopentyl-5-
methyl-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Acetyl-2-[5-[bis-(2-methoxy-ethyl)-amino]-pyridin-2-ylamino]-8-cyclopentyl-5-
methyl-8H-pyrido[2,3-d]pyrimidin-7-one,
4-[6-(8-isopropyl-7-oxo-7,8-dihydro-pyrido[2,3]pyrimidin-2-ylamino)-pyridin-3-yl]-
piperazine-l-carboxylic acid tert-butyl ester, 8-isopropyl-2-(5-piperazin-1-yl-
pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one,
4-[6-(8-cyclohexyl-7-oxo-7,8-dihydro-pyrido[2,3]pyrimidin-2-ylamino)-pyridin-3-yl]-
piperazine-l-carboxylic acid tert-butyl ester,
8-cyclohexyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-8H-pyrido[2,3-djpyrimidin-7-one,
4-[6-(8-cyclopropyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino)-pyridin-3-yl]-piperazine-1-carboxylic acid tert-butyl ester, 8-cyclopropyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Bromo-8-cyclopentyl-2-(pyridin-2,6-yl-diamino)-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Bromo-8-cyclopentyl-5-methyl-2-(pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Bromo-8-cyclopentyl-5-methyl-2-[5-(4-methyl-piperazin-1-yl)-pyridin-2-ylamino]-8H-pyrido[2,3-d]pyrimidin-7-one,
8-Cyclopentyl-6-(1-ethoxy-vinyl)-5-methyl-2-[5-(4-methyl-piperazin-1-yl)-pyridin-2-ylamino]-8H-pyrido[2,3-d]pyrimidin-7-one, (I-6-[8-Cyclopentyl-6-(1-ethoxy-vinyl)-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino]-pyridin-3-yl]-pynolidin-3-yl) carbamic acid tert-butyl ester,
6-Acetyl-8-cyclopentyl-2-(4-hydroxy-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-6'-ylamino)-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one, 4-[6-(6-Bromo-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino)-pyridin-3-yl]-azepane-1-carboxylic acid tert-butyl ester,
6-Bromo-8-cyclopentyl-2-(5-[1,4]diazepan-1-yl-pyridin-2-ylamino)-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one,
4-[6-(8-Cyclopentyl-6-(1-ethoxy-vinyl)-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino]-pyridin-3-yl]-[1,4]diazepane-1-carboxylic acid tert-butyl ester,
6-Acetyl-8-cyclopentyl-2-(5-[1,4]diazepan-1-yl-pyridin-2-ylamino)-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Acetyl-8-cyclopentyl-5-methyl-2-(pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one,
4-[6-(8-Cyclopentyl-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino)-pyridin-3-yl]-piperazine-1-carboxylic acid tert-butyl ester, 8-Cyclopentyl-5-methyl-2-(5-piperazin-4-yl-pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one,
4-[6-(6-Bromo-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino)-pyridin-3-yl]-2,2-dimethyl-piperazine-1-carboxylic acid tert-butyl ester,
6-Bromo-8-cyclopentyl-2-[5-(3,3-dimethyl-piperazin-1-yl)-pyridin-2-ylamino]-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one,
4-{6-[8-Cyclopentyl-6-(1-ethoxy-vinyl)-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino]-pyridin-3-yl}-2,2-dimethyl-piperazine-1-carboxylic acid tert-butyl ester,
4-{6-[6-Bromo-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino]-pyridin-3-yl}-2,6-dimethyl-piperazine-1-carboxylic acid tert-butyl ester,
6-Bromo-8-cyclopentyl-2-[5-(3,5-dimethyl-piperazin-1-yl)-pyridin-2-ylamino]-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one,
4-{6-[6-Bromo-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino]-pyridin-3-yl]-2,6-dimethyl-piperazine-1-carboxylic acid tert-butyl ester,
6-Bromo-8-cyclopentyl-2-[5-(3,5-dimethyl-piperazin-1-yl)-pyridin-2-ylamino]-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one,
4-{6-[8-Cyclopentyl-6-(1-ethoxy-vinyl)-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino]-pyridin-3-yl]-2,6-dimethyl-piperazine-1-carboxylic acid tert-butyl ester,
8-Cyclopentyl-6-(1-ethoxy-vinyl)-5-methyl-2-(5-morpholin-4-yl-pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Bromo-8-cyclopentyl-5-methyl-2-(3,4,5,6-tetrahydro-[1,3']bipyridinyl-6'-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one,
8-Cyclopentyl-6-(1-ethoxy-vinyl)-5-methyl-2-(3,4,5,6-tetrahydro-[1,3']bipyridinyl-6'-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Acetyl-8-cyclopentyl-5-methyl-2-(3,4,5,6-tetrahydro-[1,3']bipyridinyl-6'-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one,
4-{6-[8-Cyclopentyl-6-(2-ethoxy-ethyl)-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino]-pyridin-3-yl}-piperazine-1-carboxylic acid tert-butyl ester,
8-Cyclopentyl-6-(2-ethoxy-ethyl)-2-(5-piperazin-1-yl-pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one,
4-{6-[8-Cyclopentyl-6-(2-methoxy-ethoxymethyl)-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino]-pyridin-3-yl}-piperazine-1-carboxylic acid tert-butyl ester,
8-Cyclopentyl-6-(2-methoxy-ethoxymethyl)-2-(5-piperazin-1-yl-pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one,
4-{6-[8-Cyclopentyl-6-(2-methoxy-ethoxymethyl)-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino]-pyridin-3-yl]-piperazine-1-carboxylic acid tert-butyl ester, 8-Cyclopentyl-6-
ethoxymethyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one,
4-[6-(8-Cyclopentyl-6-methoxymethyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino)-pyridin-3-yl]-piperazine-1-carboxylic acid tert-butyl ester,
8-Cyclopentyl-6-methoxymethyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Bromo-8-cyclopentyl-2-[5-(2,6-dimethyl-morpholin-4-yl)-pyridin-2-ylamino]-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one,
8-Cyclopentyl-6-ethoxymethyl-2-(3,4,5,6-tetrahydro-2H-[1,3′]bipyridinyl-6′-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one, 8-Cyclopentyl-6-ethoxymethyl-2-(5-morpholin-4-yl-pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one,
[8-Cyclopentyl-7-oxo-2-(3,4,5,6-tetrahydro-2H-[1,3′]bipyridinyl-6′-ylamino)-7,8-dihydro-pyrido[2,3-d]pyrimidin-6-ylmethyl]-carbamic acid benzyl ester,
8-Cyclopentyl-2-[5-(2,6-dimethyl-morpholin-4-yl)-pyridin-2-ylamino]-6-(1-ethoxyvinyl)-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Acetyl-8-cyclopentyl-2-[5-(2,6-dimethyl-morpholin-4-yl)-pyridin-2-ylamino]-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one,
8-Cyclopentyl-5-methyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-6-propionyl-8H-pyrido[2,3-d]pyrimidin-7-one. Other embodiments of the present invention include, but are not limited to the compounds listed below:
6-Bromo-8-cyclopentyl-2-methyl-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Bromo-8-cyclopentyl-5-methyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one, 8-Cyclopentyl-6-fluoro-2-(5-piperazin-1-yl-pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one hydrochloride,
8-Cyclopentyl-6-methyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one hydrochloride, 8-Cyclopentyl-6-isobutoxy-2-(5-piperazin-1-yl-pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one hydrochloride,
6-Benzyl-8-cyclopentyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one hydrochloride, 8-Cyclopentyl-6-hydroxymethyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one hydrochloride,
2-[5-(4-tert-Butoxycarbonyl-piperazin-1-yl)-pyridin-2-ylamino]-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester, 6-Acetyl-8-cyclopentyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Acetyl-8-cyclopentyl-5-methyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (palbociclib; PD-0332991), 6-Bromo-8-cyclopentyl-5-methyl-2-(pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Bromo-8-cyclopentyl-2-(pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Bromo-8-cyclopentyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Bromo-8-cyclopentyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Bromo-8-cyclopentyl-2-(5-3,5-dimethyl-piperazin-1-yl)-pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Bromo-8-cyclopentyl-2-(5-3,3-dimethyl-piperazin-1-yl)-pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Bromo-8-cyclopentyl-2-(5-4-methyl-piperazin-1-yl)-pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Bromo-8-cyclopentyl-2-(5-3-Amino-pyrrolidin-1-yl)-pyridin-2-ylamino)-6-bromo-8-cyclopentyl-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Bromo-8-cyclopentyl-2-(5-3-Amino-pyrrolidin-1-yl)-pyridin-2-ylamino)-6-bromo-8-cyclopentyl-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Bromo-8-cyclopentyl-2-(5-3-Amino-pyrrolidin-1-yl)-pyridin-2-ylamino)-6-bromo-8-cyclopentyl-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Bromo-8-cyclopentyl-2-(5-3-Amino-pyrrolidin-1-yl)-pyridin-2-ylamino)-6-bromo-8-cyclopentyl-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Acetyl-2-{5-[3-(1-amino-1-methyl-ethyl)-pyrrolidin-1-yl]-pyridin-2-ylamino}-8-cyclopentyl-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one,
1-[6-(6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino)-pyridin-3-yl]-pyrrolidine-2-carboxylic acid,
6-Acetyl-8-cyclopentyl-2-[5-(4-diethylamino-butylamino)-pyridin-2-ylamino]-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one,
8-Cyclopentyl-2-[5-(3,5-dimethyl-piperazin-1-yl)-pyridin-2-ylamino]-6-ethyl-8H-pyrido[2,3-d]pyrimidin-7-one,
8-Cyclopentyl-2-[5-(3,3-dimethyl-piperazin-1-yl)-pyridin-2-ylamino]-6-ethyl-8H-pyrido[2,3-d]pyrimidin-7-one,
8-Cyclopentyl-6-ethyl-2-[5-(4-methyl-piperazin-1-yl)-pyridin-2-ylamino]-8H-pyrido[2,3-d]pyrimidin-7-one,
2-[5-(3-Amino-pyrrolidin-1-yl)-pyridin-2-ylamino]-8-cyclopentyl-6-ethyl-8H-pyrido[2,3-d]pyrimidin-7-one,
8-Cyclopentyl-6-ethyl-2-[5-(3-ethylamino-pyrrolidin-1-yl)-pyridin-2-ylamino]-8H-pyrido[2,3-d]pyrimidin-7-one,
8-Cyclopentyl-6-ethyl-2-(5-pyrrolidin-1-yl-pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one,
2-[5-(3-Amino-pyrrolidin-1-yl)-pyridin-2-ylamino]-8-cyclopentyl-6-ethyl-8H-pyrido[2,3-d]pyrimidin-7-one,
8-Cyclopentyl-6-ethyl-2-[5-(3-ethylamino-pyrrolidin-1-yl)-pyridin-2-ylamino]-8H-pyrido[2,3-d]pyrimidin-7-one,
8-Cyclopentyl-6-ethyl-2-[5-(3-ethylamino-pyrrolidin-1-yl)-pyridin-2-ylamino]-8H-pyrido[2,3-d]pyrimidin-7-one,
8-Cyclopentyl-6-ethyl-2-[5-(3,5-dimethyl-piperazin-1-yl)-pyridin-2-ylamino]-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Benzyl-8-cyclopentyl-2-[5-(3,3-dimethyl-piperazin-1-yl)-pyridin-2-ylamino]-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Benzyl-8-cyclopentyl-2-[5-(4-methyl-piperazin-1-yl)-pyridin-2-ylamino]-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Benzyl-8-cyclopentyl-2-[5-(3-Amino-pyrrolidin-1-yl)-pyridin-2-ylamino]-6-benzyl-8-cyclopentyl-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Benzyl-8-cyclopentyl-2-[5-(3-ethylamino-pyrolidin-1-yl)-pyridin-2-ylamino]-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Benzyl-8-cyclopentyl-2-(5-pyrrolidin-1-yl-pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one,
2-{5-[3-(1-Amino-1-methyl-ethyl)-pyrolidin-1-yl]-pyridin-2-ylamino}-6-benzyl-8-cyclopentyl-8H-pyrido[2,3-d]pyrimidin-7-one, l-[6-(6-Benzyl-8-cyclopentyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino)-pyridin-3-yl]-pyrrolidin-2-carboxylic acid, 6-Benzyl-8-cyclopentyl-2-[5-(4-diethylamino-butylamino)-pyridin-2-ylamino]-8H-pyrido[2,3-d]pyrimidin-7-one,
8-Cyclopentyl-2-[5-(3,5-dimethyl-piperazin-1-yl)-pyridin-2-ylamino]-6-hydroxymethyl-8H-pyrido[2,3-d]pyrimidin-7-one,
8-Cyclopentyl-2-[5-(3,3-dimethyl-piperazin-1-yl)-pyridin-2-ylamino]-6-hydroxymethyl-8H-pyrido[2,3-d]pyrimidin-7-one,
8-Cyclopentyl-6-hydroxymethyl-2-[5-(4-methyl-piperazin-1-yl)-pyridin-2-ylamino]-8H-pyrido[2,3-d]pyrimidin-7-one,
2-[5-(3-Amino-pyrolidin-1-yl)-pyridin-2-ylamino]-8-cyclopentyl-6-hydroxymethyl-8H-pyrido[2,3-d]pyrimidin-7-one, 8-Cyclopentyl-2-[5-(3-ethylamino-pyrolidin-1-yl)-pyridin-2-ylamino]-6-hydroxymethyl-8H-pyrido[2,3-d]pyrimidin-7-one, 8-Cyclopentyl-6-hydroxymethyl-2-[5-(pyrrolidin-1-yl)-pyridin-2-ylamino]-8H-pyrido[2,3-d]pyrimidin-7-one,
2-[5-(3-Amino-pyrolidin-1-yl)-pyridin-2-ylamino]-8-cyclopentyl-6-hydroxymethyl-8H-pyrido[2,3-d]pyrimidin-7-one, 8-Cyclopentyl-2-[5-(3-ethylamino-pyrolidin-1-yl)-pyridin-2-ylamino]-6-hydroxymethyl-8H-pyrido[2,3-d]pyrimidin-7-one, 1-[6-(6-Cyclopentyl-6-hydroxymethyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino)-pyridin-3-yl]-pyrrolidin-2-carboxylic acid, 8-Cyclopentyl-2-[5-(4-diethylamino-butylamino)-pyridin-2-ylamino]-6-hydroxymethyl-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Amino-8-cyclopentyl-2-[5-(3,5-dimethyl-piperazin-1-yl)-pyridin-2-ylamino]-8H-pyrido[2,3-d]pyrimidin-7-one, 6-Amino-8-cyclopentyl-2-[5-(3,3-dimethyl-piperazin-1-yl)-pyridin-2-ylamino]-8H-pyrido[2,3-d]pyrimidin-7-one, 6-Amino-8-cyclopentyl-2-[5-(4-methyl-piperazin-1-yl)-pyridin-2-ylamino]-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Amino-2-[5-(3-amino-pyrrolidin-1-yl)-pyridin-2-ylamino]-8-cyclopentyl-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Amino-8-cyclopentyl-2-[5-(3-ethylamino-pyrrolidin-1-yl)-pyridin-2-ylamino]-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Amino-8-cyclopentyl-2-(5-pyrrolidin-1-yl-pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Amino-2-{5-[3-(1-amino-1-methyl-ethyl)-pyrrolidin-1-yl]-pyridin-2-ylamino}-8-cyclopentyl-8H-pyrido[2,3-d]pyrimidin-7-one,
l-[6-(6-Amino-8-cyclopentyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino)-pyridin-3-yl]-pyrrolidine-2-carboxylic acid,
6-Amino-8-cyclopentyl-2-[5-(4-diethylamino-butylamino)-pyridin-2-ylamino]-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Bromo-8-cyclopentyl-2-(3,4,5,6-tetrahydro-2H-[1,3′]bipyridinyl-6′-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Bromo-8-cyclopentyl-2-(5-morphin-4-yl-pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one, 6-Bromo-8-cyclopentyl-2-(5-diethylamino-pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one,
2-{5-[Bis-(2-hydroxy-ethyl)-amino]-pyridin-2-ylamino}-6-bromo-8-cyclopentyl-8H-pyrido[2,3-d]pyrimidin-7-one,
2-{5-[Bis-(2-methoxy-ethyl)-amino]-pyridin-2-ylamino}-6-bromo-8-cyclopentyl-8H-pyrido[2,3-d]pyrimidin-7-one,
2-[5-(2-Amino-ethylamino)-pyridin-2-ylamino]-6-bromo-8-cyclopentyl-8H-pyrido[2,3-d]pyrimidin-7-one, 6-Bromo-8-cyclopentyl-2-(5-dimethylamino-pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one,
N-[6-(6-Bromo-8-cyclopentyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino)-pyridin-3-yl]-N-methyl-acetamide, 6-Bromo-8-cyclopentyl-2-[5-(2-methoxy-ethoxy)-pyridin-2-ylamino]-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Bromo-8-cyclopentyl-2-[5-(2-methoxy-ethoxymethyl)-pyridin-2-ylamino]-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Bromo-8-cyclopentyl-2-[5-(2-diethylamino-ethoxy)-pyridin-2-ylamino]-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Bromo-8-cyclopentyl-2-(5-pyrrolidin-1-yl-pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Bromo-8-cyclopentyl-2-(6-methyl-5-piperazin-1-yl-pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one, 6-Bromo-8-cyclopentyl-5-methyl-2-(3,4,5,6-tetrahydro-2H-[1,3′]bipyridinyl-6′-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Bromo-8-cyclopentyl-2-(5-diethylamino-pyridin-2-ylamino)-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one,
2-{5-[Bis-(2-hydroxy-ethyl)-amino]-pyridin-2-ylamino}-6-bromo-8-cyclopentyl-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Bromo-8-cyclopentyl-2-(5-pyrrolidin-1-yl-pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Bromo-8-cyclopentyl-5-methyl-2-(6-methyl-5-piperazin-1-yl-pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Acetyl-8-cyclopentyl-5-methyl-2-(3,4,5,6-tetrahydro-2H-[1,3′]bipyridinyl-6′-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Bromo-8-cyclopentyl-2-(5-diethylamino-pyridin-2-ylamino)-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one.
6-Acetyl-2-{5-[bis-(2-hydroxy-ethyl)-amino]-pyridin-2-ylamino}-8-cyclopentyl-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Acetyl-2-[5-(2-amino-ethylamino)-pyridin-2-ylamino]-8-cyclopentyl-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Acetyl-8-cyclopentyl-2-(5-dimethylamino-pyridin-2-ylamino)-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one,
N-[6-(6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino)-pyridin-3-yl]-N-methyl-acetamide,
6-Acetyl-8-cyclopentyl-2-[5-(2-methoxy-ethoxy)-pyridin-2-ylamino]-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Acetyl-8-cyclopentyl-2-[5-(2-methoxy-ethoxymethyl)-pyridin-2-ylamino]-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Acetyl-8-cyclopentyl-2-[5-(2-diethylamino-ethoxy)-pyridin-2-ylamino]-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Acetyl-8-cyclopentyl-2-(5-pyrrolidin-1-yl-pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Acetyl-8-cyclopentyl-2-(5-morpholin-4-yl-pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Acetyl-8-cyclopentyl-2-[5-(2-diethylamino-pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Acetyl-2-{5-[bis-(2-hydroxy-ethyl)-amino]-pyridin-2-ylamino}-8-cyclopentyl-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Acetyl-2-{5-[bis-(2-methoxy-ethyl)-amino]-pyridin-2-ylamino}-8-cyclopentyl-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Acetyl-2-[5-(2-amino-ethylamino)-pyridin-2-ylamino]-8-cyclopentyl-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Acetyl-8-cyclopentyl-2-(5-dimethylamino-pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one,
N-[6-(6-Acetyl-8-cyclopentyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino)pyridin-3-yl]-N-methyl-acetamide,
6-Acetyl-8-cyclopentyl-2-[5-(2-methoxy-ethoxy)-pyridin-2-ylamino]-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Acetyl-8-cyclopentyl-2-[5-(2-methoxy-ethoxymethyl)-pyridin-2-ylamino]-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Acetyl-8-cyclopentyl-2-[5-(2-diethylamino-ethoxy)-pyridin-2-ylamino]-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Acetyl-8-cyclopentyl-2-(5-pyrrolidin-1-yl-pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Acetyl-8-cyclopentyl-2-(6-methyl-5-piperazin-1-yl-pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Bromo-8-cyclopentyl-2-[5-(2-methoxy-ethoxy)-pyridin-2-ylamino]-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Bromo-8-cyclopentyl-2-[5-(2-diethylamino-ethoxy)-pyridin-2-ylamino]-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Acetyl-8-cyclopentyl-2-(6-methyl-5-piperazin-1-yl-pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Bromo-8-cyclopentyl-2-[5-(2-methoxy-ethoxy)-pyridin-2-ylamino]-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Bromo-8-cyclopentyl-2-[5-(2-diethylamino-ethoxy)-pyridin-2-ylamino]-8H-pyrido[2,3-d]pyrimidin-7-one,
2-(5-Azetidin-1-yl-pyridin-2-ylamino)-6-bromo-8-cyclopentyl-8H-pyrido[2,3-d]pyrimidin-7-one,
N-[6-(6-Bromo-8-cyclopentyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino)pyridin-3-yl]-acetamide,
6-Bromo-8-cyclopentyl-2-(5-phenylamino-pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one, 6-Bromo-8-cyclopentyl-2-[5-(4-fluoro-benzylamino)-pyridin-2-ylamino]-8H-pyrido[2,3-d]pyrimidin-7-one,
N-[6-(6-Bromo-8-cyclopentyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino)pyridin-3-yl]-methanesulfonamide,
6-Bromo-8-cyclopentyl-2-(5-phenyl-pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Amino-8-cyclopentyl-2-[5-(2-methoxy-ethoxy)-pyridin-2-ylamino]-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Amino-8-cyclopentyl-2-[5-(2-methoxy-ethylamino)-pyridin-2-ylamino]-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Amino-8-cyclopentyl-2-[5-(4-fluoro-benzylamino)-pyridin-2-ylamino]-8H-pyrido[2,3-d]pyrimidin-7-one,
N-[6-(6-Amino-8-cyclopentyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino)-pyridin-3-yl]-acetamide,
6-Amino-8-cyclopentyl-2-(5-phenylamino-pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Amino-8-cyclopentyl-2-[5-(4-fluoro-benzylamino)-pyridin-2-ylamino]-8H-pyrido[2,3-d]pyrimidin-7-one,
N-[6-(6-Amino-8-cyclopentyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino)-pyridin-3-yl]-methanesulfonamide,
6-Amino-8-cyclopentyl-2-[5-(4-fluoro-benzylamino)-pyridin-2-ylamino]-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Amino-8-cyclopentyl-2-(5-methanesulfonyl-pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Amino-8-cyclopentyl-2-(5-phenyl-pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Acetyl-8-cyclopentyl-2-[5-(2-methoxy-ethoxy)-pyridin-2-ylamino]-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Acetyl-8-cyclopentyl-2-[5-(2-methoxy-ethylamino)-pyridin-2-ylamino]-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Acetyl-2-(5-azetidin-l-yl-pyridin-2-ylamino)-8-cyclopentyl-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Acetyl-2-(5-azepan-l-yl-pyridin-2-ylamino)-8-cyclopentyl-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one,
N-[6-(6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino)-pyridin-3-yl]-acetamide,
6-Acetyl-8-cyclopentyl-5-methyl-2-(5-phenylamino-pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Acetyl-8-cyclopentyl-2-[5-(4-fluoro-benzylamino)-pyridin-2-ylamino]-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one,
N-[6-(6-Acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino)-pyridin-3-yl]-methanesulfonamide,
6-Acetyl-8-cyclopentyl-2-(5-methanesulfonyl-pyridin-2-ylamino)-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Acetyl-8-cyclopentyl-5-methyl-2-(5-phenyl-pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Benzyl-8-cyclopentyl-2-[5-(2-methoxy-ethoxy)-pyridin-2-ylamino]-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Benzyl-8-cyclopentyl-2-[5-(2-methoxy-ethylamino)-pyridin-2-ylamino]-8H-pyrido[2,3-d]pyrimidin-7-one,
2-(5-Azetidin-1-yl-pyridin-2-ylamino)-6-benzyl-8-cyclopentyl-8H-pyrido[2,3-d]pyrimidin-7-one,
2-(5-Azepan-1-yl-pyridin-2-ylamino)-6-benzyl-8-cyclopentyl-8H-pyrido[2,3-d]pyrimidin-7-one,
N-[6-(6-Benzyl-8-cyclopentyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino)-pyridin-3-yl]-acetamide,
6-Benzyl-8-cyclopentyl-2-(5-phenylamino-pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Benzyl-8-cyclopentyl-2-[5-(4-fluoro-benzylamino)-pyridin-2-ylamino]-8H-pyrido[2,3-d]pyrimidin-7-one,
N-[6-(6-Benzyl-8-cyclopentyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino)-pyridin-3-yl]-methanesulfonamide,
6-Benzyl-8-cyclopentyl-2-(5-methanesulfonyl-pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Benzyl-8-cyclopentyl-2-(5-phenyl-pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one,
8-Cyclopentyl-6-hydroxymethyl-2-[5-(2-methoxy-ethoxy)-pyridin-2-ylamino]-8H-pyrido[2,3-d]pyrimidin-7-one,
8-Cyclopentyl-6-hydroxymethyl-2-[5-(2-methoxy-ethylamino)-pyridin-2-ylamino]-8H-pyrido[2,3-d]pyrimidin-7-one,
2-(5-Azetidin-l-yl-pyridin-2-ylamino)-8-cyclopentyl-6-hydroxymethyl-8H-pyrido[2,3-d]pyrimidin-7-one,
2-(5-Azepan-l-yl-pyridin-2-ylamino)-8-cyclopentyl-6-hydroxymethyl-8H-pyrido[2,3-d]pyrimidin-7-one,
N-[6-(8-Cyclopentyl-6-hydroxymethyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino)-pyridin-3-yl]-acetamide,
8-Cyclopentyl-6-hydroxymethyl-2-(5-phenylamino-pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one,
8-Cyclopentyl-2-[5-(4-fluoro-benzylamino)-pyridin-2-ylamino]-6-hydroxymethyl-8H-pyrido[2,3-d]pyrimidin-7-one,
N-[6-(8-Cyclopentyl-6-hydroxymethyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino)-pyridin-3-yl]-methanesulfonamide,
8-Cyclopentyl-6-hydroxymethyl-2-(5-methanesulfonyl-pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one,
8-Cyclopentyl-6-ethyl-2-[5-(2-methoxy-ethylamino)-pyridin-2-ylamino]-8H-pyrido[2,3-d]pyrimidin-7-one,
8-Cyclopentyl-6-ethyl-2-[5-(2-methoxy-ethoxy)-pyridin-2-ylamino]-8H-pyrido[2,3-d]pyrimidin-7-one,
8-Cyclopentyl-6-ethyl-2-[5-(2-methoxy-ethamino)-pyridin-2-ylamino]-8H-pyrido[2,3-d]pyrimidin-7-one,
2-(5-Azetidin-l-yl-pyridin-2-ylamino)-8-cyclopentyl-6-ethyl-8H-pyrido[2,3-d]pyrimidin-7-one,
2-(5-Azepan-l-yl-pyridin-2-ylamino)-8-cyclopentyl-6-ethyl-8H-pyrido[2,3-d]pyrimidin-7-one,
N-[6-(8-Cyclopentyl-6-ethyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino)-pyridin-3-yl]-acetamide,
8-Cyclopentyl-6-ethyl-2-(5-phenylamino-pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one,
8-Cyclopentyl-6-ethyl-2-[5-(4-fluoro-benzylamino)-pyridin-2-ylamino]-8H-pyrido[2,3-d]pyrimidin-7-one,
N-[6-(8-Cyclopentyl-6-ethyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino)-pyridin-3-yl]-methanesulfonamide,
8-Cyclopentyl-6-ethyl-2-(5-methanesulfonyl-pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one,
8-Cyclopentyl-6-ethyl-2-(5-phenyl-pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Bromo-8-cyclopentyl-2-[5-(piperazine-1-carbonyl)-pyridin-2-ylamino]-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Bromo-8-cyclopentyl-2-[5-(3,5-dimethyl-piperazine-1-carbonyl)-pyridin-2-ylamino]-8H-pyrido[2,3-d]pyrimidin-7-one,
2-[5-(3-Amino-pyrrolidine-1-carbonyl)-pyridin-2-ylamino]-6-bromo-8-cyclopentyl-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Bromo-8-cyclopentyl-2-[5-(morpholine-4-carbonyl)-pyridin-2-ylamino]-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Bromo-8-cyclopentyl-5-methyl-2-[5-(piperazine-1-carbonyl)-pyridin-2-ylamino]-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Bromo-8-cyclopentyl-2-[5-(3,5-dimethyl-piperazine-1-carbonyl)-pyridin-2-ylamino]-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one,
2-[5-(3-Amino-pyrrolidine-1-carbonyl)-pyridin-2-ylamino]-6-bromo-8-cyclopentyl-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Bromo-8-cyclopentyl-5-methyl-2-[5-(morpholine-4-carbonyl)-pyridin-2-ylamino]-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Acetyl-8-cyclopentyl-5-methyl-2-[5-(piperazine-1-carbonyl)-pyridin-2-ylamino]-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Acetyl-8-cyclopentyl-2-[5-(3,5-dimethyl-piperazine-1-carbonyl)-pyridin-2-ylamino]-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Acetyl-2-[5-(3-amino-pyrrolidine-1-carbonyl)-pyridin-2-ylamino]-8-cyclopentyl-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Acetyl-8-cyclopentyl-5-methyl-2-[5-(morpholine-4-carbonyl)-pyridin-2-ylamino]-8H-pyrido[2,3-d]pyrimidin-7-one,
8-Cyclopentyl-6-ethyl-2-[5-(piperazine-1-carbonyl)-pyridin-2-ylamino]-8H-pyrido[2,3-d]pyrimidin-7-one,
8-Cyclopentyl-2-[5-(3,5-dimethyl-piperazine-1-carbonyl)-pyridin-2-ylamino]-6-ethyl-8H-pyrido[2,3-d]pyrimidin-7-one,
2-[5-(3-Amino-pyrrolidine-1-carbonyl)-pyridin-2-ylamino]-8-cyclopentyl-6-ethyl-8H-pyrido[2,3-d]pyrimidin-7-one,
8-Cyclopentyl-6-ethyl-2-[5-(morpholine-4-carbonyl)-pyridin-2-ylamino]-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Bromo-8-cyclopentyl-2-[5-(piperazine-1-sulfonyl)-pyridin-2-ylamino]-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Bromo-8-cyclopentyl-2-[5-(morpholine-4-sulfonyl)-pyridin-2-ylamino]-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Bromo-8-cyclopentyl-2-[5-(piperazine-1-sulfonyl)-pyridin-2-ylamino]-6-bromo-8-cyclopentyl-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Bromo-8-cyclopentyl-2-[5-(3,5-dimethyl-piperazine-1-sulfonyl)-pyridin-2-ylamino]-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Bromo-8-cyclopentyl-5-methyl-2-[5-(piperazine-1-sulfonyl)-pyridin-2-ylamino]-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Bromo-8-cyclopentyl-5-methyl-2-[5-(morpholine-4-sulfonyl)-pyridin-2-ylamino]-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Bromo-8-cyclopentyl-5-methyl-2-[5-(3,5-dimethyl-piperazine-1-sulfonyl)-pyridin-2-ylamino]-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Bromo-8-cyclopentyl-2-[5-(3,5-dimethyl-piperazine-1-sulfonyl)-pyridin-2-ylamino]-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one,
8-Cyclopentyl-2-[(5-(3,5-dimethyl-piperazine-1-sulfonylethyl)pyridin-2-ylamino)-6-ethyl-8H-pyrido[2,3-d]pyrimidin-7-one,  
6-Acetyl-8-cyclopentyl-5-methyl-2-[(5-(piperazine-1-sulfonylethyl)pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one,  
6-Acetyl-8-cyclopentyl-5-methyl-2-[(5-(morpholine-4-sulfonylethyl)pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one,  
6-Acetyl-2-[(5-(3-amino-pyrrolidine-1-sulfonylethyl)pyridin-2-ylamino)-8-cyclopentyl-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one,  
6-Acetyl-8-cyclopentyl-2-[(5-(3,5-dimethyl-piperazine-1-sulfonylethyl)pyridin-2-ylamino)-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one, and  
6-Acetyl-8-cyclopentyl-5-methyl-2-[(1,6)naphthyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one,  
6-Acetyl-8-cyclopentyl-2-[(5-(1,1-dioxa-116-thiomorpholin-4-yl)pyridin-2-ylamino)-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one,  
8-Cyclopentyl-6-hydroxymethyl-5-methyl-2-[(5-piperazin-1-ylpyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one,  
6-Acetyl-2-[(3-chloro-5-piperazin-1-ylpyridin-2-ylamino)-8-cyclopentyl-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one,  
4-[(6-Acetyl-5-methyl-7-oxo-2-(pyridin-2-ylamino)-7H-pyrido[2,3-d]pyrimidin-8-yl)cyclohexanecarboxylic acid,  
4-[(6-Acetyl-2-(5-dimethylamino-pyridin-2-ylamino)-5-methyl-7-oxo-7H-pyrido[2,3-d]pyrimidin-8-yl)cyclohexanecarboxylic acid,  
6-Bromo-8-cyclopentyl-5-methyl-2-[(5-(piperazine-1-sulfonylethyl)pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one,  
6-[(8-Cyclopentyl-6-ethyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino)-3-piperazin-1-yl-pyridine-2-carboxylic acid,  
2-[(6-Acetyl-5-piperazin-1-ylpyridin-2-ylamino)-8-cyclopentyl-6-ethyl-8H-pyrido[2,3-d]pyrimidin-7-one,  
3-[(2-[(6-(8-Cyclopentyl-6-ethyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino)-pyridin-3-yloxy)ethoxy]-propionic acid,
[6-(8-Cyclopentyl-6-ethyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino)pyridin-3-yloxy]-acetic acid,
8-Cyclopentyl-2-(5-{2-[2-(5-methyl-pyridin-2-yl)-ethoxy]-ethoxy}-pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one,
2-[5-(3-Benzene sulfonyl-propoxy)-pyridin-2-ylamino]-8-cyclopentyl-8H-pyrido[2,3-d]pyrimidin-7-one,
8-Cyclopentyl-6-ethyl-2-{5-[2-(2-methoxy-ethoxy)-ethoxy]-pyridin-2-ylamino}-8H-pyrido[2,3-d]pyrimidin-7-one,
8-Cyclopentyl-2-(5-[[3-(3,5-dimethyl-piperazin-1-yl)-propyl]-methyl-amino]-pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one,
8-Cyclopentyl-2-{5-[(3-imidazol-1-yl-propyl)-methyl-amino]-pyridin-2-ylamino}-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Acetyl-5-methyl-2-(5-methyl-pyridin-2-ylamino)-8-piperidin-4-yl-8H-pyrido[2,3-d]pyrimidin-7-one,
6-Acetyl-2-[5-(3,4-dihydroxy-pyridin-1-yl)-pyridin-2-ylamino]-8-methoxymethyl-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one,
or a pharmaceutically-acceptable salt, cocrystal, hydate, solvate, or prodrug of any of the foregoing compounds.

[00750] In an embodiment, the CDK4/6 inhibitor is palbociclib, or a pharmaceutically-acceptable salt, cocrystal, hydate, solvate, or prodrug thereof. In an embodiment, the CDK4/6 inhibitor is 6-acetyl-8-cyclopentyl-5-methyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one, or a pharmaceutically-acceptable salt, cocrystal, hydate, solvate, or prodrug thereof. In an embodiment, the CDK4/6 inhibitor is PD-0332991, or a pharmaceutically-acceptable salt, cocrystal, hydate, solvate, or prodrug thereof. In an embodiment, the CDK4/6 inhibitor has the structure of Formula (100-AA):
or a pharmaceutically-acceptable salt, cocrystal, hydate, solvate, or prodrug thereof.

[00751] In some preferred embodiments, CDK4/6 inhibitors having Formula (100-I) can be prepared, isolated, or obtained by any method known to one of skill in the art, including, but not limited to, synthesis from a suitable precursors, asymmetric synthesis from an achiral starting material, or resolution of a racemic or enantiomeric mixture, for example, chiral chromatography, recrystallization, resolution, diastereomeric salt formation, or derivatization into diastereomeric adducts followed by separation.

[00752] In some preferred embodiments of the CDK4/6 inhibitors of Formula (100-I), a method of preparing the compound having the structure of Formula (100-AB) is provided:

wherein $R^{1A}$ is hydrogen, $(C_1-6)$-alkyl, $C_1$-$C_6$ haloalkyl, $(C_1-6)$-hydroxyalkyl, or $C_3$-$C_7$ cycloalkyl;

$R^{3A}$ is hydrogen, OH, $-\text{NH}_2$, aryl, $(C_1-8)$-alkyl, $C_3$-$C_7$ cycloalkyl, or $(C_1-8)$-heterocyclyl;
R\(^{5A}\) is \(-(CR\(^7\)R\(^8\))_m\)NR\(^7\) - or \(-(CR\(^7\)R\(^8\))_m\) - (3 to 10 member heterocycle comprising a N ring atom), wherein \(m\) is 0, 1, 2 or 3; and each R\(^7\) and R\(^8\) is independently H or (C\(^1\)\(^{-}\))-alkyl; or a pharmaceutically acceptable salt thereof.

[00753] In some embodiments, CDK4/6 inhibitors of Formula (100-AB) can be prepared by a method by the methods described in PCT Application Publication No. 2008032157, which published March 20, 2008, the content of which is incorporated herein by reference in its entirety. In some embodiments, the method of making CDK4/6 inhibitors of Formula (100-AB) comprises: (a) reacting an intermediary compound having the following Formula (100-AC):

\[
\begin{align*}
\text{HN} & \quad \text{R}^{1A} \quad \text{R}^{2A} \\
\text{N} & \quad \text{R}^{3A} \\
\text{R}^{4A} & \quad \text{O} \\
\end{align*}
\]

wherein

R\(^{1A}\) is hydrogen, (C\(^1\)\(^{-}\))-alkyl, (C\(^1\)\(^{-}\))-haloalkyl, (C\(^1\)\(^{-}\))-hydroxalkyl, or (C\(^3\)\(^{-}\))-cycloalkyl;
R\(^{2A}\) is Br or I;
R\(^{3A}\) is hydrogen, OH, -NH\(_2\), aryl, (C\(^8\)\(^{-}\))-alkyl, (C\(^3\)\(^{-}\))-cycloalkyl, or (C\(^3\)\(^{-}\))-heterocyclyl;
R\(^{4A}\) is -R\(^{5A}\)-PG selected from the group consisting of -\((CR\(^7\)R\(^8\))_m\)N(PG)R\(^7\), and -\((CR\(^7\)R\(^8\))_m\) - (3 to 10 member heterocycle comprising a PG protected N ring atom), and PG is an acid-labile amine protecting group; each R\(^7\) and R\(^8\) is independently H or (C\(^1\)\(^{-}\))-alkyl; with (b) a vinyl ether having the following Formula (100AD) in the presence of a transition metal catalyst, a base and optionally a phosphine agent, and in a suitable solvent:

\[
\text{Formula (100-AD)}
\]

wherein R\(^{6A}\) is (C\(^1\)\(^{-}\))-alkyl; and each R\(^7\) and R\(^8\) is independently H or (C\(^1\)\(^{-}\))-alkyl; to form a compound of Formula (100-AE) or Formula (100-AF):

\[
\text{Formula (100-AE)} \quad \text{Formula (100-AF)}
\]

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In some embodiments, enol of Formula (100-AE) is converted into the keto compound of Formula (100-AF) under any suitable acidic condition. In some embodiments, the compound of Formula (100-AE) is isolated in its base form prior to conversion into any pharmaceutically acceptable salt thereof. In some embodiments, pharmaceutically acceptable salts of the compound of Formula (100-AF) can be prepared in situ during the final isolation and purification of the compounds of Formulas (100-AE) and (100-AF) or by separately reacting the purified compound in its free base form with a suitable organic or inorganic acid and isolating the salt thus formed. In some embodiments, acid addition salts of the basic compound of Formula (100-AF) are prepared by contacting the free base form of Formula (100-AF) with a sufficient amount of the desired acid to produce the salt in the conventional manner. In some embodiments, the free base form of the compound of Formula (100-AF) may be regenerated by contacting the salt form with a base and isolating the free base in the conventional manner.

In some embodiments, the enol of Formula (100-AE) is prepared according to scheme III below:
Scheme III

[00756]
In some embodiments, intermediary compound of Formula (100-AE₁) is reacted with butyl vinyl ether and bis-(diphenylphosphinoferrocene) palladium dichloride dichloromethane complex to produce the compound of Formula (100-AE₂):

**Scheme IV**

In some preferred embodiments of the compound of Formula (100-AE), a salt therof can be prepared by reacting the compound of Formula 100-AE₂ with an inorganic acid, for example hydrochloric acid (or hydrogen chloride gas) to form the compound of Formula 100-AE₃ in scheme III above. In some preferred embodiments, a salt of the compound of Formula (100-AF) can be prepared directly from the compound of Formula (100-AE) by reacting the compound of Formula (100-AE) with a suitable organic acid, for example, isethionic acid, to
form the salt of compound of Formula 100-AE₅ in scheme V below.

Scheme V

[00759] Examplary CDK4/6 inhibitors suitable for use in the compositions and methods described herein include a compound of Formula (200-I):

or pharmaceutically acceptable salts, wherein
X is CR⁹, or N;
R¹ is (C₁⁻₈)-alkyl, CN, C(O)OR⁴ or CONR⁵R⁶, a 5-14 membered heteroaryl group, or a 3-14 membered cycloheteroalkyl group;
R² is (C₁₋₈)-alkyl, (C₃₋₁₄)-cycloalkyl, or a 5-14 membered heteroaryl group, and wherein R² may be substituted with one or more (C₁₋₈)-alkyl, or OH; L is a bond, (C₁₋₈)-alkylene, C(O), or C(O)NR³⁰, and wherein L may be substituted or unsubstituted; Y is H, R¹¹, NR¹²R¹³, OH, or Y is part of the following group

\[
\begin{align*}
R^8 & \leftarrow Y \rightarrow Y \rightarrow R^3,
\end{align*}
\]

where Y is CR⁹ or N; where 0-3 R⁸ may be present, and R⁵ is (C₁₋₈)-alkyl, oxo, halogen, or two or more R⁸ may form a bridged alkyl group; W is CR⁹, or N, or O (where W is O, R₃ is absent); R¹ is H, (C₁₋₈)-alkyl, (C₁₋₈)-alkylR¹⁴, (C₃₋₁₄)-cycloalkyl, C(O)(C₁₋₈)-alkyl, (C₁₋₈)-haloalkyl, (C₁₋₈)-alkylOH, C(O)NR¹⁴R¹⁵, (C₁₋₈)-cyanoalkyl, C(O)R¹⁴, (C₁₋₈)-alkylC(O)(C₁₋₈)-alkylNR¹⁴R¹⁵, (C₁₋₈)-alkylC(O)OR¹⁴, NR¹⁴R¹⁵, SO₂(C₁₋₈)-alkyl, (C₁₋₈)-alkyl(C₃₋₁₄)-cycloalkyl, C(O)(C₁₋₈)-alkyl(C₃₋₁₄)-cycloalkyl, (C₁₋₈)-alkoxy, or OH which may be substituted or unsubstituted when R³ is not H. R⁵ is H or halogen; R⁴, R⁵, R⁶, R⁷, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, and R¹⁵ are each independently selected from H, (C₁₋₈)-alkyl, (C₃₋₁₄)-cycloalkyl, a 3-14 membered cycloheteroalkyl group, a (C₆₋₁₄)-aryl group, a 5-14 membered heteroaryl group, alkoxy, C(O)H, C(N)OH, C(N)OCH₃, C(O)(C₆₋₁₄)-alkyl, (C₁₋₈)-alkynNH₂, (C₁₋₈)-alkynOH, and wherein R⁴, R⁵, R⁶, R⁷, R¹⁰, R¹¹, R¹², and R¹³, R¹⁴, and R¹⁵ when not H may be substituted or unsubstituted; m and n are independently 0-2; and wherein L, R¹, R², R³, R⁶, R⁷, R¹⁰, R¹¹, R¹², and R¹³, R¹⁴, and R¹⁵ may be substituted with one or more of (C₁₋₈)-alkyl, (C₂₋₈)-alkenyl, (C₂₋₈)-alkynyl, (C₃₋₁₄)-cycloalkyl, 5-14 membered heteroaryl group, (C₆₋₁₄)-aryl group, a 3-14 membered cycloheteroalkyl group, OH, (O), CN, alkoxy, halogen, or NH₂.

In one embodiment of the compound of Formula (200-I), Y is H, OH, or Y is part of the following group

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where Y is N and W is CR, or N; and where 0-2 R may be present, and R is (C\(_{1-8}\))-alkyl, oxo, or two or more R may form a bridged alkyl group. In one embodiment of the compound of Formula (200-I), Y is N and W is N. In one embodiment of the compound of Formula (200-I), m is 1 or 2. In another embodiment, n is 1 or 2. In one embodiment of the compound of Formula (200-I), m is 1 and n is 2. In another embodiment, m is 2 and n is 1. In a further embodiment, both m and n are 1.

In one embodiment of the compound of Formula (200-I), there are 0-2 R\(^8\) present in compounds of formula (I). It is understood that when there are zero R\(^8\)s, that H is attached to the carbons of the cyclic structure.

In one embodiment of the compound of Formula (200-I), R\(^8\) is methyl, ethyl, propyl, butyl, oxo, or two R can form a bridged (cycloalkyl) group, such as cyclobutyl, cyclopentyl, or cyclohexyl. In one embodiment of the compound of Formula (200-I), R\(^8\) is methyl. In another embodiment no R\(^8\) is present.

In one embodiment of the compound of Formula (200-I), R\(^3\) is H, (C\(_{1-8}\))-alkyl, such as methyl, ethyl, propyl, isopropyl, butyl, penty1, or hexyl; (C\(_{3-14}\))-cycloalkyl, such as cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl; C(O)(C\(_{1-8}\))-alkyl, such as C(O)CH\(_3\), C(O)CH\(_2\)CH\(_3\), or C(O)CH\(_3\)CH\(_2\)CH\(_3\); (C\(_{1-8}\))-alkyLOH, such as CH\(_2\)OH, CH\(_2\)CH\(_2\)OH, CHOHC\(_2\), CH\(_2\)CH\(_2\)CH\(_2\)OH, CHOHC\(_2\)CH\(_2\), or CH\(_2\)CHOHC\(_2\); (C\(_{1-8}\))-cyanoalkyl, such as CH\(_2\)CN, or CH\(_2\)CH\(_2\)CN; (C\(_{0-8}\))-alkylC(O)(C\(_{0-8}\))-alkylNR\(_4\)R\(_8\), such as CH\(_2\)C(O)CH\(_2\)NR\(_4\)R\(_8\); (C\(_{0-8}\))-alkylC(O)OR\(_4\), NR\(_4\)R\(_8\), (C\(_{1-8}\))-alkyl(C\(_{3-14}\))-cycloalkyl, C(O)(C\(_{1-8}\))-alkyl(C\(_{3-14}\))-cycloalkyl, (C\(_{1-8}\))-alkyloxy, (C\(_{1-8}\))-alkylR\(_1\), (C\(_{1-8}\))-haloalkyl, or C(O)R\(_4\), which may be substituted with one or more of OH, CN, F, or NH\(_2\), and wherein R\(_4\) and R\(_8\) are each independently selected from H, (C\(_{1-8}\))-alkyl, (C\(_{3-14}\))-cycloalkyl, alkoxy, C(O)(C\(_{1-8}\))-alkyl, (C\(_{1-8}\))-alkylNH\(_2\), or (C\(_{1-8}\))-alkyloH.

In one embodiment of the compound of Formula (200-I), R\(^4\) and R\(^5\) are each independently selected from H, (C\(_{1-8}\))-alkyl, such as methyl, ethyl, propyl, butyl, penty1, or hexyl; (C\(_{3-14}\))-cycloalkyl, such as cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl; a 3-14 membered cycloheteroalkyl group, such as morpholine, piperidine, or piperazine; a (C\(_{6-14}\))-aryl group, such
as phenyl; a 5-14 membered heteroaryl group, such as pyridine, pyrimidine, or pyridazine; alkoxy, such as methoxy, ethoxy, or propoxy; C(O)H, C(N)OH, C(N)OCH<sub>3</sub>, C(O)(C<sub>1-8</sub>)-alkyl, such as C(O)CH<sub>3</sub>, C(O)CH<sub>2</sub>CH<sub>3</sub>, or C(O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>; (C<sub>1-8</sub>)-alkylNH<sub>2</sub>, such as methyleneNH<sub>2</sub>, ethyleneNH<sub>2</sub>, or propyleneNH<sub>2</sub>; (C<sub>1-8</sub>)-alkylOH, such as methyleneOH, ethyleneOH, or propyleneOH; and R14 and R15 when not H may be unsubstituted or substituted with one or more of (C<sub>1-8</sub>)-alkyl, (C<sub>2-8</sub>)-alkenyl, (C<sub>2-8</sub>)-alkynyl, (C<sub>3-14</sub>)-cycloalkyl, 5-14 membered heteroaryl group, (C<sub>6-14</sub>)-aryl group, a 3-14 membered cycloheteroalkyl group, OH, (O), CN, alkoxy, halogen, or NH<sub>2</sub>.

In another embodiment, the present invention includes compound of Formula (200-I) wherein R<sup>3</sup> is H, (C<sub>1-8</sub>)-alkyl, such as methyl, ethyl, propyl, or isopropyl; or (C<sub>1-8</sub>)-alkylOH, such as CH<sub>3</sub>OH, or CH<sub>2</sub>CH<sub>2</sub>OH. In another embodiment, R<sup>3</sup> is H, isopropyl, CH<sub>2</sub>OH, or CH<sub>2</sub>CH<sub>2</sub>OH. In another embodiment, R<sup>3</sup> is H.

In another embodiment of the compound of Formula (200-I), L is a bond, (C<sub>1-8</sub>)-alkylene, such as —CH<sub>2</sub>—, —CH<sub>2</sub>CH<sub>2</sub>—, or —CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>—; C(O)NH, or C(O).

In another embodiment of the compound of Formula (200-I), R<sup>2</sup> is (C<sub>5-14</sub>)-cycloalkyl; such as cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

In another embodiment of the compound of Formula (200-I), R<sup>2</sup> is cyclopentyl.

In another embodiment of the compound of Formula (200-I), R<sup>1</sup> is CN, C(O)OR<sup>2</sup>, CONR<sup>5</sup>R<sup>6</sup>, or a 5-14 membered heteroaryl group.

In another embodiment of the compound of Formula (200-I), R<sup>1</sup> is CONR<sup>5</sup>R<sup>6</sup>, and R<sup>5</sup> and R<sup>6</sup> are (C<sub>1-8</sub>)-alkyl. In another embodiment, R<sup>1</sup> is CONR<sup>5</sup>R<sup>6</sup> where R<sup>5</sup> and R<sup>6</sup> are methyl. In another embodiment, R<sup>1</sup> is CN.

In another embodiment of the compound of Formula (200-I), X is CR<sup>9</sup>, and R<sup>9</sup> is H or halogen, such as Cl, F, Br, or I.

In another embodiment of the compound of Formula (200-I), one X is N and the other X is CR<sup>9</sup>.

In another embodiment of the compound of Formula (200-I), such as:
In another embodiment of the compound of Formula (200-I), X is CR\textsuperscript{9} and Y is

\[
\text{\begin{figure}[h]
  \centering
  \includegraphics[width=0.5\textwidth]{formula.png}
  \caption{Diagram of compound structure.}
  \label{fig:compound}
\end{figure}}
\]

where m and n are 1, and Y and W are N.

In another embodiment of the compound of Formula (200-I), L is a bond, (C\textsubscript{1-8})-alkylene, or C(O)NH, or C(O); and Y is H, OH, or Y is part of the following group

\[
\text{\begin{figure}[h]
  \centering
  \includegraphics[width=0.5\textwidth]{formula.png}
  \caption{Diagram of compound structure.}
  \label{fig:compound}
\end{figure}}
\]

where Y is N and W is CR\textsuperscript{9}, or N; where 0-2 R\textsuperscript{8} may be present, and R\textsuperscript{8} is (C\textsubscript{1-8})-alkyl, oxo, or two or more R\textsuperscript{8} may link to form a bridged alkyl group and R\textsuperscript{3} is H, (C\textsubscript{1-8})-alkyl, (C\textsubscript{1-3})-alkylR\textsuperscript{14}, (C\textsubscript{1-8})-haloalkyl, C(O)(C\textsubscript{1-8})-alkyl, (C\textsubscript{0-8})-alkylOH, C(O)R\textsuperscript{14}, or (C\textsubscript{0-8})-alkylC(O)(C\textsubscript{0-8})-alkylNR\textsuperscript{14}R\textsuperscript{15}, (C\textsubscript{0-8})-alkylC(O)OR\textsuperscript{14}, or NR\textsuperscript{14}R\textsuperscript{15}; and R\textsuperscript{14} and R\textsuperscript{15} are each independently selected from H, (C\textsubscript{1-8})-alkyl, (C\textsubscript{3-14})-cycloalkyl, alkoxy, C(O)(C\textsubscript{1-3})-alkyl, (C\textsubscript{1-8})-alkylNH\textsubscript{2}, (C\textsubscript{1-8})-alkyloH.

In another embodiment of the compound of Formula (200-I), R\textsuperscript{3} is H, (C\textsubscript{1-8})-alkyl, (C\textsubscript{3-14})-cycloalkyl, C(O)(C\textsubscript{1-8})-alkyl, (C\textsubscript{0-8})-alkylOH, (C\textsubscript{1-8})-cyanoalkyl, (C\textsubscript{0-8})-alkylC(O)(C\textsubscript{0-8})-alkylNR\textsuperscript{14}R\textsuperscript{15}, (C\textsubscript{0-8})-alkylC(O)OR\textsuperscript{14}, NR\textsuperscript{14}R\textsuperscript{15}, (C\textsubscript{1-8})-alkyl(C\textsubscript{3-14})-cycloalkyl, C(O)(C\textsubscript{1-8})-
alkyl(C\textsubscript{3-14})-cycloalkyl, (C\textsubscript{0-8})-alkoxy, which may be substituted with one or more of OH, CN, F, or NH\textsubscript{2}.

In another embodiment of the compound of Formula (200-I), R\textsubscript{3} is H or (C\textsubscript{1-8})-alkyl.

In another embodiment of the compound of Formula (200-I), R\textsuperscript{1} is C(O)OR\textsubscript{4}, CONR\textsubscript{5}R\textsubscript{6}, or a 5-14 membered heteroaryl group.

In one embodiment of the compound of Formula (200-I), Y is

\begin{equation}
\text{Y} \quad \text{where m and n are 1 or 2, and Y and W are N.}
\end{equation}

In another embodiment of the compound of Formula (200-I), L is a bond.

In another embodiment of the compound of Formula (200-I), L is a bond Y is not H.

In another embodiment, the compound of Formula (200-I) has a structure of Formula (200-Ia):

\begin{equation}
(200-Ia)
\end{equation}

and a pharmaceutically acceptable salt thereof, wherein:

R\textsuperscript{51} is (C\textsubscript{3-14})-cycloalkyl which may be unsubstituted or substituted by (C\textsubscript{1-3})-alkyl, or OH;

Z is CH or N; and

V is NR\textsuperscript{56} or CHR\textsuperscript{57};

R\textsuperscript{54} and R\textsuperscript{55} are independently H, (C\textsubscript{1-3})-alkyl,
R\(^5\), R\(^6\), and R\(^7\) are independently H, (C\(_{1-8}\))-alkyl, (C\(_{3-14}\))-cycloalkyl, (C\(_{1-8}\))-haloalkyl, NR\(^8\), C(O)OR\(^9\), C(O)\((C\(_{1-8}\))\)-alkyl, (C\(_{0-8}\))-alkylC(O)\((C\(_{0-8}\))\)-alkyl-NR\(^6\)R\(^5\), (C\(_{1-8}\))-alkoxy, (C\(_{0-8}\))-alkylC(O)(C\(_{0-8}\))-alkyl-NR\(^6\)R\(^5\), (C\(_{1-8}\))-alkylOR\(^6\), C(O)-5-14cycloheteroalkyl group, (C\(_{3-14}\))-cycloalkyl group, each of which when not H may be substituted by one or more of (C\(_{1-8}\))-alkyl, OH, or CN; R\(^8\), R\(^9\), R\(^6\), R\(^5\), and R\(^7\) are H or (C\(_{1-8}\))-alkyl.

R\(^{50}\) is CONR\(^{53}\)R\(^{55}\), or CN and R\(^{54}\) and R\(^{55}\) are H, methyl, or ethyl. In another embodiment, R\(^{54}\) and R\(^{55}\) are both methyl.

In one embodiment of the compound of Formula (200-Ia), R\(^{51}\) is cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. In one embodiment of the compound of Formula (200-Ia), R\(^{51}\) is cyclopentyl.

In one embodiment of the compound of Formula (200-Ia), Z is N. In one embodiment of the compound of Formula (200-Ia), V is NR\(^{56}\). In one embodiment of the compound of Formula (200-Ia), V is NR\(^{56}\), and R\(^{56}\) is H, methyl, ethyl, propyl which may be substituted by OH. In one embodiment of the compound of Formula (200-Ia), R\(^{56}\) is isopropyl. In one embodiment of the compound of Formula (200-Ia), R\(^{56}\) is H. In yet another embodiment, R\(^{56}\) is —CH\(_2\)CH\(_2\)OH.

[00760] In some embodiments, the compound of Formula (200-I) is selected from the group consisting of:

7-Cyclopentyl-2-[5-(3-methyl-piperazin-1-yl)-pyridin-2-ylamino]-7H-pyrrolo[2,3-d]pyrimidine-6-carbonitrile;
7-Cyclopentyl-2-[5-[4-(2-fluoro-ethyl)-piperazin-1-yl]-pyridin-2-ylamino]-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide;
7-Cyclopentyl-2-(4-dimethylamino-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-6'-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide;
2-[5-(4-Carbamoylmethyl-piperazin-1-yl)-pyridin-2-ylamino]-7-cyclopentyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide;
2-[5-[4-(2-Amino-acetyl)-piperazin-1-yl]-pyridin-2-ylamino]-7-cyclopentyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide;
2-[5-(3-Amino-pyrrolidin-1-yl)-pyridin-2-ylamino]-7-cyclopentyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide;
7-Cyclopentyl-2-{5-[4-(2-methoxy-ethyl)-piperazin-1-yl]-pyridin-2-ylamino}-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide;
7-Cyclopentyl-2-[4-(2-hydroxyethyl)-3,4,5,6-tetrahydro-2H-[1,2]bipyrazinyl-5-ylamino]-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide;
7-Cyclopentyl-2-{5-((R)-3-methyl-piperazin-1-yl)-pyridin-2-ylamino}-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide;
7-Cyclopentyl-2-{5-((S)-3-methylpiperazin-1-yl)-pyridin-2-ylamino}-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide;
7-Cyclopentyl-2-[5-(3-methylpiperazin-1-yl)-pyridin-2-ylamino]-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide;
7-Cyclopentyl-2-{5-[4-(3-hydroxypropyl)-piperazin-1-yl]-pyridin-2-ylamino}-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide;
7-Cyclopentyl-2-{5-[4-(pyrrolidine-1-carbonyl)-piperazin-1-yl]-pyridin-2-ylamino}-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide;
7-Cyclopentyl-2-{5-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-pyridin-2-ylamino}-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide;
7-Cyclopentyl-2-{5-[4-((S)-2,3-dihydroxypropyl)-piperazin-1-yl]-pyridin-2-ylamino}-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide;
7-Cyclopentyl-2-{4-dimethylamino-3,4,5,6-tetrahydro-2H-[1,3]bipyridinyl-6-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide;
7-Cyclopentyl-2-(3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl-5'-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide;
7-Cyclopentyl-2-[5-(piperazine-1-carbonyl)-pyridin-2-ylamino]-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide;
7-Cyclopentyl-2-[5-(4-dimethylaminopiperidine-1-carbonyl)-pyridin-2-ylamino]-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide;
7-Cyclopentyl-2-(1',2',3',4',5',6'-hexahydro-[3,4']bipyridinyl-6-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide;
7-Cyclopentyl-2-[5-((S)-3-methylpiperazin-1-ylmethyl)-pyridin-2-ylamino]-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide;
7-Cyclopentyl-2-[5-((R)-2-hydroxypropyl)-piperazin-1-yl]-pyridin-2-ylamino]-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide;
7-Cyclopentyl-2-[5-(4-isopropyl-piperazin-1-yl)-pyridin-2-ylamino]-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide;
7-Cyclopentyl-2-[5-(4-isopropyl-piperidine-1-carbonyl)-pyridin-2-ylamino]-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide;
7-Cyclopentyl-2-[5-(4-isopropyl-piperazin-1-yl)-pyridin-2-ylamino]-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide;
7-Cyclopentyl-2-[5-(4-isopropyl-piperazin-1-yl)-pyridin-2-ylamino]-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide;
7-Cyclopentyl-2-[5-(4-isopropyl-piperazin-1-yl)-pyridin-2-ylamino]-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide;
7-Cyclopentyl-2-[5-(3,3-dimethyl-piperazin-1-yl)-pyridazin-3-ylamino]-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide;
7-Cyclopentyl-2-[5-(3,8-diaza-bicyclo[3.2.1]oct-3-ylmethyl)-pyridin-2-ylamino]-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide;
7-Cyclopentyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide;
7-Cyclopentyl-2-[5-(4-ethyl-piperazin-1-yl)-pyridin-2-ylamino]-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide;
7-Cyclopentyl-2-[5-(4-cyclopentyl-piperazin-1-yl)-pyridin-2-ylamino]-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide;
7-Cyclopentyl-2-(1'-isopropyl-1',2',3',4',5',6'-hexahydro-[3,4']bipyridinyl-6-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide;
7-Cyclopentyl-2-{5-[(R)-4-(2-hydroxyethyl)-3-methyl-piperazin-1-yl]-pyridin-2-ylamino}-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide;
7-Cyclopentyl-2-{5-[(S)-4-(2-hydroxyethyl)-3-methyl-piperazin-1-yl]-pyridin-2-ylamino}-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide;
7-Cyclopentyl-2-(5-[4-(2-hydroxyethyl)-piperazin-1-ylmethyl]-pyridin-2-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide;
7-Cyclopentyl-2-{5-[4-(2-dimethylaminoacetyl)-piperazin-1-yl]-pyridin-2-ylamino}-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide;
7-Cyclopentyl-2-{5-[4-(2-Cyclohexyl-acetyl)piperazin-1-yl]-pyridin-2-ylamino}-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide;
7-Cyclopentyl-2-{5-[4-(3-cyclopentyl-propionyl)-piperazin-1-yl]-pyridin-2-ylamino]-7-H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide;
7-Cyclopentyl-2-{5-[4-(3-cyclopentyl-propionyl)-piperazin-1-yl]pyridin-2-ylamino}7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide;
7-Cyclopentyl-2-{5-[4-(isobutyl)piperazin-1-yl]-pyridin-2-ylamino]-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide;

{4-[6-(7-Cyclopentyl-6-dimethylcarbamoyl-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)pyridin-3-yl]-piperazin-1-yl}-acetic acid methyl ester;
7-Cyclopentyl-2-{5-[4-(2-isopropoxyethyl)-piperazin-1-yl]-pyridin-2-ylamino}-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide;
{4-[6-(7-Cyclopentyl-6-dimethylcarbamoyl-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)pyridin-3-yl]-piperazin-1-yl}-acetic acid ethyl ester;
4-(6-{7-Cyclopentyl-6-[((2-hydroxy-ethyl)methyl-carbamoyl]-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino}-pyridin-3-yl)piperazine-1-carboxylic acid tert-butyl ester; 
7-Cyclopentyl-2-{5-[4-(2-methyl-butyl)piperazin-1-yl]-pyridin-2-ylamino}-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide; 
7-Cyclopentyl-2-[1'-2-hydroxy-ethyl]-1',2',3',4',5',6'-hexahydro-[3,4']bipyridinyl-6-ylamino]-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide; 
{4-[6-(7-Cyclopentyl-6-dimethylcarbamoyl-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-pyridin-3-yl]piperazin-1-yl}-acetic acid; and 
2-{4-[6-(7-Cyclopentyl-6-dimethylcarbamoyl-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-pyridin-3-yl]-piperazin-1-yl}-propionic acid; or pharmaceutically acceptable salts thereof.

[00761] In some exemplary embodiments CDK4/6 inhibitors suitable for use in the compositions and methods of the present invention include a compound having the Formula (300-I):

![Formula (300-I)](image)

or salts or tautomers or N-oxides or solvates thereof; wherein 
X is a group R^1-A-NR^4— or a 5- or 6-membered carbocyclic or heterocyclic ring; 
A is a bond, SO_2, C=O, NR^6 (C=O) or O(C=O) wherein R^6 is hydrogen or (C_1a)-hydrocarbyl optionally substituted by hydroxy or (C_1a)-alkoxy; 
Y is a bond or an alkenylene chain of 1, 2 or 3 carbon atoms in length; 
R^1 is hydrogen; a carbocyclic or heterocyclic group having from 3 to 12 ring members; or a (C_1a)-hydrocarbyl group optionally substituted by one or more substituents selected from halogen, hydroxy, (C_1a)-hydroxy, amino, mono- or di-(C_1a)-hydroxy, and carbocyclic or heterocyclic groups having from 3 to 12 ring members, and wherein 1 or 2 of the carbon atoms of the hydrocarbyl group may optionally be replaced by an atom or group selected from O, S, NH, SO, SO_2;
R² is hydrogen; halogen; (C₁₋₄)-alkoxy (e.g. methoxy); or a (C₁₋₄)-hydrocarbyl group optionally substituted by halogen, hydroxyl or (C₁₋₄)-alkoxy;
R¹ is selected from hydrogen and carbocyclic and heterocyclic groups having from 3 to 12 ring members; and
R³ is hydrogen or a (C₁₋₄)-hydrocarbyl group optionally substituted by halogen, hydroxyl or (C₁₋₄)-alkoxy.

[00762] In some preferred embodiments of the compound having the Formula (300-I), A is C=O, R⁴ is hydrogen, and Y is a bond.

[00763] In some preferred embodiments of the compound having the Formula (300-I), R² is hydrogen or methyl.

[00764] In some preferred embodiments of the compound having the Formula (300-I), R¹ is a carbocyclic or heterocyclic group having from 3 to 12 ring members.

[00765] In some preferred embodiments of the compound having the Formula (300-I), the carbocyclic and heterocyclic groups are substituted by one or more substituent groups R₁⁰ or Rᵢ⁸; wherein:

R₁⁰ is selected from halogen, hydroxy, trifluoromethyl, cyano, nitro, carboxy, amino, mono- or di-(C₁₋₄)-hydrocarbylamino, carbocyclic and heterocyclic groups having from 3 to 12 ring members;
a group R⁺—R⁻ wherein R⁺ is a bond, O, CO, X¹C(X²¹), C(X²)X¹, X¹C(X²)X¹, S, SO, SO₂, NR¹, SO₂NR¹ or NR¹SO₂⁻; and
R⁻ is selected from hydrogen, carbocyclic and heterocyclic groups having from 3 to 12 ring members, and a (C₁₋₄)-hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, carboxy, amino, mono- or di-(C₁₋₄)-hydrocarbylamino, carbocyclic and heterocyclic groups having from 3 to 12 ring members and wherein one or more carbon atoms of the (C₁₋₄)-hydrocarbyl group may optionally be replaced by O, S, SO, SO₂, NR¹, X¹C(X²¹), C(X²¹)X¹ or X¹C(X²¹)X¹;
R⁻ is selected from hydrogen and (C₁₋₄)-hydrocarbyl; and
X¹ is O, S or NR¹ and X² is =O, =S or =NR¹; and
R\(^{10a}\) is selected from halogen, hydroxy, trifluoromethyl, cyano, nitro, carboxy, a group R\(^{c}\)—R\(^{b}\) wherein R\(^{a}\) is a bond, O, CO, X\(^{\prime}\)C(X\(^{\prime}\)), C(X\(^{\prime}\))X\(^{\prime}\), X\(^{\prime}\)C(X\(^{\prime}\))X\(^{\prime}\), S, SO, or SO\(_2\), and R\(^{b}\) is selected from hydrogen and a (C\(_{1-8}\)) hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, carboxy and monocyclic non-aromatic carbocyclic or heterocyclic groups having from 3 to 6 ring members; wherein one or more carbon atoms of the (C\(_{1-8}\)) hydrocarbyl group may optionally be replaced by O, S, SO, SO\(_2\), X\(^{\prime}\)C(X\(^{\prime}\)), C(X\(^{\prime}\))X\(^{\prime}\) or X\(^{\prime}\)C(X\(^{\prime}\))X\(^{\prime}\); X\(^{\prime}\) is O or S; and X\(^{\prime}\) is =O or =S.

[00766] In some preferred embodiments of the compound having the Formula (300-I), R\(^{1}\) is a phenyl ring having 1, 2 or 3 substituents located at the 2-, 3-, 4-, 5- or 6-positions around the ring.

[00767] In some preferred embodiments of the compound having the Formula (300-I), the phenyl group is 2-monosubstituted, 3-monosubstituted, 2,6-disubstituted, 2,3-disubstituted, 2,4-disubstituted 2,5-disubstituted, 2,3,6-trisubstituted or 2,4,6-trisubstituted.

[00768] In some preferred embodiments of the compound having the Formula (300-I), the phenyl group is monosubstituted at the 2-position, or disubstituted at positions 2- and 3-, or disubstituted at positions 2- and 6-with substituents selected from fluorine, chlorine and R\(^{a}\)—R\(^{b}\), where R\(^{c}\) is O and R\(^{b}\) is (C\(_{1-4}\))-alkyl.

[00769] In some preferred embodiments of the compound having the Formula (300-I), the phenyl group is monosubstituted at the 2-position with a substituent selected from fluorine, chlorine, and (C\(_{1-4}\))-alkoxy optionally substituted by one or more fluorine atoms; or disubstituted at the 2- and 5-positions or at 2- and 6-positions with substituents selected from fluorine, chlorine and methoxy.

[00770] In some preferred embodiments of the compound having the Formula (300-I), R\(^{3}\) is selected from monocyclic carbocyclic and heterocyclic groups having from 3 to 6 ring members.

[00771] In some preferred embodiments of the compound having the Formula (300-I), R\(^{3}\) is a carbocyclic or heterocyclic groups, the carbocyclic and/or the heterocyclic groups are substituted by 1, 2 or 3 substituents selected from: halogen; (C\(_{1-4}\))-alkoxy optionally substituted by one or
substituents selected from halogen, hydroxy, (C\textsubscript{1-2})-alkoxy and five and six membered saturated heterocyclic rings containing 1 or 2 heteroatoms selected from O, N and S, the heterocyclic rings being optionally further substituted by one or more (C\textsubscript{1-4})- groups and wherein the S, when present, may be present as S, SO or SO\textsubscript{2}; (C\textsubscript{1-4})-alkyl optionally substituted by one or substituents selected from halogen, hydroxy, (C\textsubscript{1-4})-alkoxy, amino, (C\textsubscript{1-4})-alkylsulphonylamino, 3 to 6 membered cycloalkyl groups, phenyl (optionally substituted by one or more substituents selected from halogen, methyl, methoxy and amino) and five and six membered saturated heterocyclic rings containing 1 or 2 heteroatoms selected from O, N and S, the heterocyclic rings being optionally further substituted by one or more (C\textsubscript{1-4})- groups and wherein the S, when present, may be present as S, SO or SO\textsubscript{2}; hydroxy; amino, mono-(C\textsubscript{1-4})-alkylamino, di-(C\textsubscript{1-4})-alkylamino, benzyloxycarbonylamino and (C\textsubscript{1-4})-alkoxycarbonylamino; carboxy and (C\textsubscript{1-4})-alkoxy carbonyl; (C\textsubscript{1-4})-alkylaminosulphonyl and (C\textsubscript{1-4})-alkylsulphonylamino; (C\textsubscript{1-4})-alkylsulphonyl; a group O-Het\textsuperscript{' or} N—H-Het\textsuperscript{' where Het\textsuperscript{' is a five or six membered saturated heterocyclic ring containing 1 or 2 heteroatoms selected from O, N and S, the heterocyclic rings being optionally further substituted by one or more (C\textsubscript{1-4})- groups and wherein the S, when present, may be present as S, SO or SO\textsubscript{2}; five and six membered saturated heterocyclic rings containing 1 or 2 heteroatoms selected from O, N and S, the heterocyclic rings being optionally further substituted by one or more (C\textsubscript{1-4})-groups and wherein the S, when present, may be present as S, SO or SO\textsubscript{2}; oxo; and six membered aryl and heteroaryl rings containing up to two nitrogen ring members and being optionally substituted by one or substituents selected from halogen, methyl and methoxy.

[00772] In some preferred embodiments, the compound of Formula (300-I) has the structure of Formula (300-II):

![Formula (300-II)](image)

wherein R\textsubscript{1}, R\textsubscript{2}, R\textsubscript{3} and Y are as defined for the compound of Formula (300-I).
In some preferred embodiments of the compound of Formula (300-II), $R_1$ is phenyl optionally substituted by one or more substituents selected from fluorine; chlorine, hydroxy, $\left(C_{1,3}\right)$-hydrocarbyloxy, and $\left(C_{1,3}\right)$-hydrocarbyl, wherein the $\left(C_{1,3}\right)$-hydrocarbyl group is optionally substituted by one or more substituents chosen from hydroxy, fluorine, $\left(C_{1,2}\right)$-alkoxy, amino, mono and di-$\left(C_{1,4}\right)$-alkylamino, saturated carbocyclic groups having 3 to 7 ring members or saturated heterocyclic groups of 5 or 6 ring members and containing up to 2 heteroatoms selected from O, S and N.

In some preferred embodiments of the compound of Formula (300-II), $R_1$ is an unsubstituted phenyl group or a 2-monosubstituted, 3-monosubstituted, 2,3 disubstituted, 2,5 disubstituted or 2,6 disubstituted phenyl group or 2,3-dihydro-benzo[1,4]dioxine, where the substituents are selected from halogen; hydroxyl; $\left(C_{1,3}\right)$-alkoxy and $\left(C_{1,3}\right)$-alkyl groups wherein the $\left(C_{1,3}\right)$-alkyl group is optionally substituted by hydroxy, fluorine, $\left(C_{1,2}\right)$-alkoxy, amino, mono and di-$\left(C_{1,4}\right)$-alkylamino, or saturated carbocyclic groups having 3 to 6 ring members and/or saturated heterocyclic groups of 5 or 6 ring members and containing 1 or 2 heteroatoms selected from N and O.

In some preferred embodiments of the compound of Formula (300-II), $R_1$ is selected from unsubstituted phenyl, 2-fluorophenyl, 2-hydroxyphenyl, 2-methoxyphenyl, 2-methylphenyl, 2-(2-(pyrrolidin-1-yl)ethoxy)-phenyl, 3-fluorophenyl, 3-methoxyphenyl, 2,6-difluorophenyl, 2-fluoro-6-hydroxyphenyl, 2-fluoro-3-methoxyphenyl, 2-fluoro-5-methoxyphenyl, 2-chloro-6-methoxyphenyl, 2-fluoro-6-methoxyphenyl, 2,6-dichlorophenyl and 2-chloro-6-fluorophenyl; and is optionally further selected from 5-fluoro-2-methoxyphenyl; or (d) $R_1$ is selected from 2,6-difluorophenyl, 2-fluoro-6-methoxyphenyl, 2,6-dichlorophenyl and 2-chloro-6-fluorophenyl.

In some embodiments, the compound of Formula (300-I) has the structure of formula (300-IV):
or salts or tautomers or N-oxides or solvates thereof; wherein

R¹ and R² are as defined for the compound of Formula (300-I);

an optional second bond may be present between carbon atoms numbered 1 and 2;

one of U and T is selected from CH₂, CHR¹, CR¹R¹, NR¹, N(O)R¹, O and S(O); and

the other of U and T is selected from, NR¹, O, CH₂, CHR¹, C(R¹), and C=O; r is 0, 1, 2, 3 or 4; t is 0, 1 or 2;

R¹ is selected from hydrogen, halogen, (C₁₃) alkyl and (C₁₃) alkoxy;

R¹ is selected from hydrogen, NHR¹, NOH, NOR¹ and R—a—R²;

R¹ is selected from hydrogen and R—a—R²;

R¹ is a bond, O, CO, X¹C(X¹), C(X¹)X¹, X¹C(X¹)X¹, S, SO, SO², NR², SO²NR² or NR²SO²;

R² is selected from hydrogen, carbocyclic and heterocyclic groups having from 3 to 12 ring members, and a (C₁₃)-hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, amino, mono- or di-(C₁₃)-hydrocarbylamino, carbocyclic and heterocyclic groups having from 3 to 12 ring members and wherein one or more carbon atoms of the (C₁₃)-hydrocarbyl group may optionally be replaced by O, S, SO, SO², NR², X¹C(X¹), C(X¹)X¹ or X¹C(X¹)X¹;

R² is selected from hydroxy and (C₁₄)-hydrocarbyl;

R² is selected from a bond, CO, C(X¹)X¹, SO and SO²NR²; and

R¹ is selected from (C₁₄)-saturated hydrocarbyl optionally substituted by hydroxy, (C₁₄)-alkoxy, halogen or a monocyclic 5- or 6-membered carbocyclic or heterocyclic group, provided that U and T cannot be O simultaneously.

[00777] In some preferred embodiments, the compound of Formula (300-IV) has the structure of Formula (300-IVa):
or salts or tautomers or N-oxides or solvates thereof; wherein

one of U and T is selected from CH₂, CHR¹³, CR¹¹R¹⁵, NR¹⁴, N(O)R¹⁵, O and S(O); and
the other of U and T is selected from CH₂, CHR¹¹, C(R¹¹)₂, and C=O; r is 0, 1 or 2; t is 0, 1 or 2;

R¹¹ is selected from hydrogen and (C₁₋₄)-alkyl;
R¹³ is selected from hydrogen and R⁺—R⁻;
R¹⁴ is selected from hydrogen and R⁺—R⁻;
R⁴ is selected from a bond, CO, C(X²)X¹, SO₂ and SO₂NR⁻;
R¹⁵ is selected from (C₁₋₄)-saturated hydrocarbyl optionally substituted by hydroxy, (C₁₋₄)-alkoxy, halogen or a monocyclic 5- or 6-membered carbocyclic or heterocyclic group.

[00778] In some preferred embodiments of the compound of Formula (300-IVa), T is selected from CH₂, CHR¹³, CH¹¹R¹³, N¹⁴, N(O)R¹⁵, O and S(O), and U is selected from CH₂, CHR¹¹, C(R¹¹)₂, and C=O; and R¹¹ is selected from hydrogen and methyl.

[00779] In some preferred embodiments of the compound of Formula (300-IVa), R¹⁴ is selected from hydrogen and R⁺—R⁻ where R⁻ is selected from hydrogen; monocyclic carbocyclic and heterocyclic groups having from 3 to 7 ring members; and (C₁₋₄)-hydrocarbyl optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, amino, mono- or di-(C₁₋₄)-hydrocarbylamino, and monocyclic carbocyclic and heterocyclic groups having from 3 to 7 ring members and wherein one or more carbon atoms of the (C₁₋₄)-hydrocarbyl group may optionally be replaced by O, S, SO₂, NR⁻, X¹C(X²), C(X²)X¹; R⁻ is selected from hydrogen and (C₁₋₄)-hydrocarbyl; and X¹ is O, S or NR⁻ and X² is =O, =S or =NR⁻.
[00780] In some preferred embodiments of the compound of Formula (300-IVa), $R^{14}$ is selected from hydrogen, $(C_{1-4})$-alkyl optionally substituted by fluoro or a five or six membered saturated heterocyclic group, cyclopropylmethyl, substituted or unsubstituted pyridyl-$(C_{1-2})$-alkyl, substituted or unsubstituted phenyl-$(C_{1-2})$-alkyl, $(C_{1-4})$-alkoxycarbonyl, substituted and unsubstituted phenyl-$(C_{1-2})$-alkoxycarbonyl, substituted and unsubstituted 5- and 6-membered heteroaryl groups, $(C_{1-2})$-alkoxy-$(C_{1-2})$-alkyl and $(C_{1-4})$-alkylsulphonyl.

[00781] In some preferred embodiments, the compound of Formula (300-IVa) has the structure of Formula (300-Va):

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[Formula (300-Va)]
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or salts or tautomers or N-oxides or solvates thereof; wherein

- $R^{14a}$ is selected from hydrogen, $(C_{1-4})$-alkyl optionally substituted by fluoro, cyclopropylmethyl, phenyl-$(C_{1-2})$-alkyl, $(C_{1-4})$-alkoxycarbonyl, phenyl-$(C_{1-2})$-alkoxycarbonyl, $(C_{1-2})$-alkoxy-$(C_{1-2})$-alkyl, and $(C_{1-4})$-alkylsulphonil, wherein the phenyl moieties when present are optionally substituted by one to three substituents selected from fluorine, chlorine, $(C_{1-4})$-alkoxy optionally substituted by fluoro or $(C_{1-2})$-alkoxy, and $(C_{1-4})$-alkyl optionally substituted by fluoro or $(C_{1-2})$-alkoxy;

- $w$ is 0, 1, 2 or 3;

- $R^2$ is hydrogen or methyl;

- $R^{11}$ and $r$ are as defined in claim 16; and

- $R^{19}$ is selected from fluorine; chlorine; $(C_{1-4})$-alkoxy optionally substituted by fluoro or $(C_{1-2})$-alkoxy; and $(C_{1-4})$-alkyl optionally substituted by fluoro or $(C_{1-2})$-alkoxy.

[00782] In some preferred embodiments of the compound of Formula (300-IVa), $w$ is 0 or $w$ is 1, 2 or 3 and the phenyl ring is 2-monosubstituted, 3-monosubstituted, 2,6-disubstituted, 2,3-
disubstituted, 2,4-disubstituted 2,5-disubstituted, 2,3,6-trisubstituted or 2,4,6-trisubstituted, and 
\( R^{11} \) is hydrogen.

[00783] In some preferred embodiments of the compound of Formula (300-Va), the phenyl ring 
is disubstituted at positions 2- and 6- with substituents selected from fluorine, chlorine and 
methoxy.

[00784] In some preferred embodiments of the compound of Formula (300-Va), \( R^{14a} \) is hydrogen 
or methyl.

[00785] In some preferred embodiments, the compound of Formula (300-Va) has the structure of 
Formula (300-VIb):

\[
\text{Formula (300-Va)}
\]

or salts or tautomers or N-oxides or solvates thereof; 
wherein \( R^{20} \) is selected from hydrogen and methyl; 
\( R^{21a} \) is selected from fluorine and chlorine; and 
\( R^{22a} \) is selected from fluorine, chlorine and methoxy.

[00786] In some preferred embodiments, the compound of Formula (300-VIb) is selected from 
the group consisting of:

4-(2,6-difluoro-benzoylamino)-1H-pyrazole-3-carboxylic acid piperidin-4-ylamide; 
4-(2,6-difluoro-benzoylamino)-1H-pyrazole-3-carboxylic acid (1-methyl-piperidin-4-yl)-amide; 
4-(2,6-dichloro-benzoylamino)-1H-pyrazole-3-carboxylic acid piperidin-4-ylamide; and 
4-(2-fluoro-6-methoxy-benzoylamino)-1H-pyrazole-3-carboxylic acid piperidin-4-ylamide.

[00787] In some exemplary embodiments CDK4/6 inhibitors suitable for use in the compositions 
and methods of the present invention include a compound having the Formula (400-I):
wherein \( n' \) is 2-4; and wherein

when \( R_1 \) is H, \( R_2 \) is H or CO(CH\(_2\))\(_n\)CH\(_3\), where \( n=1\text{-}8 \), \( R_3 \) is H, (CH\(_2\))\(_n\)CH\(_3\), where \( n=0\text{-}1 \) or O(CH\(_2\))\(_n\)CH\(_3\), where \( n=0\text{-}1 \) and \( R_4 \) is H, (CH\(_2\))\(_n\)CH\(_3\), or O(CH\(_2\))\(_n\)CH\(_3\), where \( n=0\text{-}1 \); wherein when \( R_1 \) is O(CH\(_2\))\(_n\)CH\(_3\), where \( n=0\text{-}1 \), and \( R_2 \) is H, \( R_3 \) and \( R_4 \) is H and wherein when \( R_1 \) is O(CH\(_2\))\(_n\)CH\(_3\), where \( n=0\text{-}1 \) and \( R_2 \) is CO(CH\(_2\))\(_n\)CH\(_3\), where \( n=1\text{-}8 \) \( R_3 \) is H, (CH\(_2\))\(_n\)CH\(_3\), where \( n=0\text{-}1 \) or O(CH\(_2\))\(_n\)CH\(_3\), where \( n=0\text{-}1 \), and \( R_4 \) is H, (CH\(_2\))\(_n\)CH\(_3\), or O(CH\(_2\))\(_n\)CH\(_3\), where \( n=0\text{-}1 \) or salts thereof.

[00788] In some preferred embodiments, the compound of Formula (400-I) is selected from the group consisting of

- 9-(2-hydroxyethy lamino)-4-methyl-1-nitroacridine,
- 9-(2-hydroxyethylamino)-7-methoxy-1-nitroacridine,
- 9-(2-hydroxyethy lamino)-7 methoxy-4-methyl 1-1-nitroacridine,
- 9-(2-acetoxyethylamino)-1-nitroacridine,
- 9-(2-propionoxyethylamino)-1-nitroacridine,
- 9-(3-hydroxypropylamino)-7-methoxy-1-nitroacridine,
- 9-(3-hydroxypropylamino)-4-methyl 1-1-nitroacridine,
- 9-(2' -acetoxyethylamino)-4-methyl-1-nitroacridine,
- 9-(2' -propionoxyethy lamino)-4-methyl 1-1-nitroacridine,
- 9-(3'-acetoxypropylamino)-4-methyl-1-nitroacridine,
- 9-(2' -propionoxypropylamino)-4-methyl-1- nitroacridine,
- 9-(2' -hydroxyethylamino)-4-methoxy-1-nitroacridine,
- 9-(3'-hydroxypropylamino)-4-methoxy-1-nitroacridine,
- 9-(4'-hydroxybutylamino)-4-methoxy-1-nitroacridine,
9-(4-hydroxybutylamino)-7-methoxy-1-nitroacridine and
9-(2-acetoxyethylamino)-7-methoxy-4-methyl-1-nitroacridine.

[00789] In some embodiments, exemplary CDK4/6 inhibitors suitable for use in the compositions and methods described herein include a compound of Formula (500-I):

Formula (500-I)

wherein,
R₁ is (C₃₋₅)-alkyl, (C₃₋₅)-cycloalkyl or cyclopropyl-methyl; R² and R³ are H or fluorine, wherein at least one of R² or R³ is fluorine;
R₄ is H or CH₃;
R₅ is (C₁₋₅)-alkyl or -NR₆R₇, wherein R₆ and R₇ are (C₁₋₃)-alkyl; Q is CH₂, O, S or a direct bond; and
W and Y are C or N, wherein at least one of W or Y is N and wherein when Q is O or S, W is C; or a pharmaceutically acceptable salt thereof.

[00790] In some preferred embodiments of the compound of Formula (500-I) or a pharmaceutically acceptable salt thereof, R⁴ is isopropyl, cyclopropyl, cyclopentyl or cyclopropyl- methyl.

[00791] In some preferred embodiments of the compound of Formula (500-I), R⁴ is isopropyl.

In some preferred embodiments of the compound of Formula (500-I) or a pharmaceutically acceptable salt thereof, R² and R³ are each fluorine.

[00792] In some preferred embodiments of the compound of Formula (500-I) or a pharmaceutically acceptable salt thereof, R⁴ is H.
In some preferred embodiments of the compound of Formula (500-I) or a pharmaceutically acceptable salt thereof, R⁵ is (C₁₋₃)-alkyl.

[00793] In some preferred embodiments of the compound of Formula (500-I) or a pharmaceutically acceptable salt thereof, R⁵ is -NR⁶R⁷ and R⁶ and R⁷ are each ethyl.

In some preferred embodiments of the compound of Formula (500-I) or a pharmaceutically acceptable salt thereof, Q is CH₂ or a direct bond.

[00794] In some preferred embodiments of the compound of Formula (500-I) or a pharmaceutically acceptable salt thereof, Q is CH₂.

[00795] In some preferred embodiments of the compound of Formula (500-I) or a pharmaceutically acceptable salt thereof, Y is N.

[00796] In some preferred embodiments of the compound of Formula (500-I) or a pharmaceutically acceptable salt thereof, W is N.

[00797] In some preferred embodiments, the compound of Formula (500-I) or a pharmaceutically acceptable salt thereof is selected from the group consisting of:
and
In an embodiment, the CDK4/6 inhibitor is LY-2835219, which is also known as abemaciclib or bemaciclib, or a pharmaceutically acceptable salt thereof. In an embodiment, the CDK4/6 inhibitor is:

or a pharmaceutically acceptable salt, hydrate, solvate, cocrystal, or prodrug thereof.

In some preferred embodiments, a pharmaceutically acceptable salt of the compound of Formula (500-I) comprises the mesylate salt of the compound of Formula (500-I).

In some preferred embodiments, the compound of Formula (500-I) is [5-(4-Ethylpiperazin-1-ylmethyl)-pyridin-2-yl]-[5-fluoro-4-(7-fluoro-3-isopropyl-2-methyl-3H-benzoimidazol-5-yl)-pyrimidin-2-yl]-amine crystalline form III, characterised by an X-ray powder diffraction pattern (CuKa radiation, \( \lambda = 1.54056 \) A) comprising a peak at 21.29 (2\( \Theta \) \( \pm \) 0.1°) and optionally one or more peaks selected from the group comprising 11.54, 10.91, and 12.13 (2\( \Theta \) \( \pm \) 0.1°).
In some preferred embodiments, the compound of Formula (500-I) is [5-(4-Ethyl-piperazin-1-ylmethyl)-pyridin-2-yl]-[5-fluoro-4-(7-fluoro-3-isopropyl-2-methyl-3 H-benzoimidazol-5-y1)-pyrimidin-2-yl]-amine crystalline form III, which is characterised at least by a $^{13}$C NMR spectrum comprising chemical shift peaks v(Fl) [ppm] at 112.7, 127.3 and 129.4.

In some embodiments CDK4/6 inhibitors suitable for use in the compositions and methods of the present invention include a compound of Formula (600-I):

![Formula (600-I)](image)

or a pharmaceutically acceptable salt thereof, a hydrate thereof, or a mixture thereof, wherein:

$R^1$ is a group of Formula (600-IA), Formula (600-IB), Formula (600-IC), or Formula (600-ID):

![600-IA](image)

![600-IB](image)
wherein the symbol indicates the point of attachment of the group of Formula (600-IA), (600-IB), (600-IC), or (600-ID) to the rest of the molecule;

$R^1$ is a (C$_{5,7}$)-cycloalkyl group, is a 5 to 7-membered heterocycl group that includes 1, 2, or 3 heteroatoms selected from N, O, and S, or is a (C$_{7,10}$)-bicyclic group; wherein the (C$_{5,7}$)-cycloalkyl group, the 5 to 7 membered heterocyclyl group, or the (C$_{7,10}$)-bicyclic group is unsubstituted or is substituted with 1-3 substituents independently selected from unsubstituted -(C$_{1,6}$)-alkyl, -OH, halo, -O-(C$_{1,6}$)-alkyl, -CO$_2$H, -C(=O)-O-(C$_{1,6}$)-alkyl, -C(=O)-NR'R", -NR'R", or a substituted -(C$_{1,6}$)-alkyl, wherein the substituted -(C$_{1,6}$)-alkyl is substituted with 1-3 substituents independently selected from halo, -OH, -OCH$_3$, -S(=O)$_2$CH$_3$, or -C(=O)-CH$_3$;

$R^{1a}$ is selected from -H, -F, or -Cl, -(C$_{1,3}$)-alkyl, or -O-(C$_{1,3}$)-alkyl;

$R^{1b}$ is -H, halo, -OH, -O-(C$_{1,6}$)-alkyl, unsubstituted -(C$_{1,6}$)-alkyl, -NR'R", -C(=O)-(C$_{1,6}$)-alkyl, -(C(=O)-O-(C$_{1,6}$)-alkyl, -(C(=O)-H), -(C(=O)-NR'R", or a substituted -(C$_{1,6}$)-alkyl), wherein the substituted -(C$_{1,6}$)-alkyl is substituted with 1-3 substituents independently selected from halo, -OH, -OCH$_3$, -CN, or -NO$_2$;

$R^{1c}$ is -H, -(C$_{1,3}$)-alkyl, or halo;

$R^1$ is -H;

$R^1$ is -H;

$R^1$ is selected from -H, -(C$_{1,6}$)-alkyl, -(C(=O)-(C$_{1,6}$)-alkyl, -(C(=O)-O-(C$_{1,6}$)-alkyl, -(C(=O)-C(=O)-OH, -(C(=O)-NR'R", or -(S(=O)-NR'R"), wherein the alkyl group of the -(C$_{1,6}$)-alkyl, -C(=O)-(C$_{1,6}$)-alkyl), and -(C(=O)-O-(C$_{1,6}$)-alkyl groups is unsubstituted or is substituted with 1-3 substituents independently selected from -OH, F, -(S(=O)$_2$)-(C$_{1,6}$)-alkyl, -O-(C$_{1,6}$)-alkyl, -NR'R", or -CN;
R^{7a} is -H, -CH_{3}, or halo;
R^{7b} is -H, -(C_{1-6})-alkyl, or halo; or R^{7b} is absent if R^{1} is a group of Formula 1B or Formula ID;
R^{7c} is -H, unsubstituted -(C_{1-6})-alkyl, halo, -O-(C_{1-6})-alkyl, -NO_{2}, -CN, -NR'R'', -CO_{2}H, -
C(=O)-O-(C_{1-6} alkyl), -C(=O)-NR'R'', or a substituted -(C_{1-6})-alkyl, wherein the substituted -(C_{1-6})-alkyl is substituted with 1-3 substituents independently selected from -OH, halo, -O-(C_{1-6})-alkyl, -CN, -NR'R'', or -(=O)_{2} - CH_{3}; or R^{7c} is absent if R^{1} is a group of Formula (600-IA) or Formula (600-IC);
R^{8a} is -H, unsubstituted -(C_{1-6})-alkyl, or a substituted -(C_{1-6})-alkyl, wherein the substituted -(C_{1-6})-alkyl is substituted with 1-3 substituents independently selected from -OH, halo, or -O-(C_{1-6})-alkyl; R is -H, unsubstituted -(C_{1-6})-alkyl, or a substituted -(C_{1-6})-alkyl, wherein the substituted -(C_{1-6})-alkyl is substituted with 1-3 substituents independently selected from -OH, halo, or -O-(C_{1-6})-alkyl; or R^{8a} and R^{8b}, when taken together, can represent =O;
R^{8c} is selected from -H, -OH, unsubstituted -(C_{1-6})-alkyl, or a substituted -(C_{1-6})-alkyl, wherein the substituted -(C_{1-6})-alkyl is substituted with 1-3 substituents independently selected from -OH, halo, or -O-(C_{1-6})-alkyl;
R^{8d} is -H, unsubstituted -(C_{1-6})-alkyl, or a substituted -(C_{1-6})-alkyl, wherein the substituted -(C_{1-6})-alkyl is substituted with 1-3 substituents independently selected from -OH, halo, or -O-(C_{1-6})-alkyl;
R^{8e} is -H, unsubstituted -(C_{1-6})-alkyl, or a substituted -(C_{1-6})-alkyl, wherein the substituted -(C_{1-6})-alkyl is substituted with 1-3 substituents independently selected from -OH, halo, or -O-(C_{1-6})-alkyl;
R^{8f} is -H, unsubstituted -(C_{1-6})-alkyl, or a substituted -(C_{1-6})-alkyl, wherein the substituted -(C_{1-6})-alkyl is substituted with 1-3 substituents independently selected from -OH, halo, or -O-(C_{1-6})-alkyl; or R^{8e} and R^{8f}, when taken together, can represent =O; and
R' and R'' are independently selected from -H, unsubstituted -(C_{1-4})-alkyl, or -(C_{14})-alkyl substituted with 1 to 3 substituents independently selected from -OH or - F.

In some preferred embodiments of the compound of Formula (600-I) or the pharmaceutically acceptable salt thereof, the hydrate thereof, or the mixture thereof, R^{2} is a (C_{3,7})-cycloalkyl group that is unsubstituted or is substituted with 1-3 substituents independently selected from unsubstituted -(C_{1-6})-alkyl, -OH, halo, -O-(C_{1-6})-alkyl, -CO_{2}H, -C(=O)-O-(C_{1-6})-alkyl, -
C(=O)-NR'R", -NR'R", or a substituted -(C\textsubscript{1-4})-alkyl, wherein the substituted -(C\textsubscript{1-4})-alkyl is substituted with 1-3 substituents independently selected from halo, -OH, -OCH\textsubscript{3}, -S(=O)\textsubscript{2}-CH\textsubscript{3}, or -C(=O)-CH\textsubscript{3}; and R' and R" are independently substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl.

[00803] In some preferred embodiments of the compound of Formula (600-I) or the pharmaceutically acceptable salt thereof, the hydrate thereof, or the mixture thereof, R\textsuperscript{2} is a cyclohexyl group substituted with a -(C\textsubscript{1-4})-alkyl group.

[00804] In some preferred embodiments of the compound of Formula (600-I) or the pharmaceutically acceptable salt thereof, the hydrate thereof, or the mixture thereof, R\textsuperscript{2} is a group of formula

\[
\begin{array}{c}
\text{\includegraphics[width=0.2\textwidth]{cyclohexyl.png}} \\
\text{CH}_3
\end{array}
\]

wherein the \(\equiv\equiv\equiv\equiv\) symbol indicates the point of attachment to the rest of the molecule.

[00805] In some preferred embodiments of the compound of Formula (600-I) or the pharmaceutically acceptable salt thereof, the hydrate thereof, or the mixture thereof, R\textsuperscript{1} is a group of Formula (600-IA) or Formula (600-IB).

[00806] In some preferred embodiments of the compound of Formula (600-I) or the pharmaceutically acceptable salt thereof, the hydrate thereof, or the mixture thereof, R\textsuperscript{1} is a group of Formula (600-IA).

[00807] In some preferred embodiments of the compound of Formula (600-I) or the pharmaceutically acceptable salt thereof, the hydrate thereof, or the mixture thereof, R\textsuperscript{2} is a (C\textsubscript{5-7})-cycloalkyl group that is unsubstituted or is substituted with 1-3 -(C\textsubscript{1-6})-alkyl groups; R\textsuperscript{1a} is selected from -H, -(C\textsubscript{1-3})-alkyl, or -O-(C\textsubscript{1-3})-alkyl; R\textsuperscript{3b} is -H; R\textsuperscript{3c} is -H; R\textsuperscript{4} is -H; R\textsuperscript{5} is -H; R\textsuperscript{6} is selected from -H, -(C\textsubscript{1-6})-alkyl, -C(=O)-(C\textsubscript{1-6})-alkyl, or -C(=O)-C(=O)-OH, wherein the alkyl...
group of the -(C\(_{1-6}\))-alkyl and -C(=O)-(C\(_{1-6}\))-alkyl groups is unsubstituted or is substituted with 1-
3 substituents independently selected from -OH, F, -S(=O)\(_2\)-(C\(_{1-6}\))-alkyl, or -O-(C\(_{1-6}\))-alkyl; R\(_7^a\)
is -H;

R\(_7^b\) is -H; or is absent if R\(_1\) is a group of Formula (600-IB) or Formula (600-ID); R\(_7^c\) is -H; or
is absent if R\(_1\) is a group of Formula (600-IA) or Formula (600-IC); R\(_7^a\) is -H; R\(_7^b\) is -H;
R\(_7^c\) is selected from -H, -OH, or unsubstituted -(C\(_{1-6}\))-alkyl; R\(_8^d\) is -H; R\(_8^e\) is -H; and R\(_8^f\) is -H, or the pharmaceutically acceptable salt thereof, the hydrate thereof, mixture thereof.

[00808] In some preferred embodiments, the compound of Formula (600-I) is a compound
having the structure of Formula (600-IIA):

![Formula (600-IIA)](image)

or the pharmaceutically acceptable salt thereof, the hydrate thereof, or the mixture thereof,
wherein:

R\(_8^a\) is selected from -H, -F, or -Cl, -(C\(_{1-3}\))-alkyl, or -O-(C\(_{1-3}\))-alkyl;

R\(_8^b\) is -H, halo, -OH, -O-(C\(_{1-6}\))-alkyl, unsubstituted -(C\(_{1-6}\))-alkyl, -NR'R", -C(=O)-(C\(_{1-6}\))-
alkyl, -C(=O)-O-(C\(_{1-6}\))-alkyl, -C(=O)-NR'R", or a substituted -(C\(_{1-6}\))-alkyl, wherein the
substituted -(C\(_{1-6}\))-alkyl is substituted with 1-3 substituents independently selected from
halo, -OH, -OCH\(_3\), -CN, or -NO\(_2\);

R\(_8^c\) is selected from -H, -(C\(_{1-6}\))-alkyl, -C(=O)-(C\(_{1-6}\))-alkyl, -C(=O)-C(=O)-OH, -C(=O)-NR'R", or
-S(=O)-NR'R", wherein the alkyl group of the -(C\(_{1-6}\))-alkyl and -C(=O)-(C\(_{1-6}\))-alkyl groups is
unsubstituted or is substituted with 1-3 substituents independently selected from -OH, F, -
S(=O)\(_2\)-(C\(_{1-6}\))-alkyl, -O-(C\(_{1-6}\))-alkyl, -NR'R", or -CN; and

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R\textsuperscript{8c} is selected from -H, -OH, unsubstituted -(C\textsubscript{1-6})-alkyl, or a substituted -(Q- C\textsubscript{6} alkyl), wherein the substituted -(C\textsubscript{1-6})-alkyl is substituted with 1-3 substituents independently selected from -OH, halo, or -O-(C\textsubscript{1-6})-alkyl.

[00809] In some preferred embodiments of the compound of Formula (600-IIA), R\textsuperscript{3a} is selected from -H, -(C\textsubscript{1-3})-alkyl, or -O-(C\textsubscript{1-3})-alkyl;

[00810] R\textsuperscript{3b} is -H; R\textsuperscript{6} is selected from -H, -(C\textsubscript{1-6})-alkyl, -C(=O)-(C\textsubscript{1-6})-alkyl, or -C(=O)-C(=O)-OH, wherein the alkyl group of the -(C\textsubscript{1-6})-alkyl and -C(=O)-(C\textsubscript{1-6})-alkyl groups is unsubstituted or is substituted with 1-3 substituents independently selected from -OH, F, -S(=O)\textsubscript{2}-(C\textsubscript{1-6})-alkyl, or -O-(C\textsubscript{1-6})-alkyl; and R\textsuperscript{8c} is selected from -H, unsubstituted -(C\textsubscript{1-6})-alkyl, or -OH, or the pharmaceutically acceptable salt thereof, the hydrate thereof, or the mixture thereof.

[00811] In some preferred embodiments of the compound of Formula (600-IIA), R\textsuperscript{8c} is selected from -H, -CH\textsubscript{3}, or -OH.

[00812] In some preferred embodiments of the compound of Formula (600-IIA), R\textsuperscript{8c} is -H.

[00813] In some preferred embodiments of the compound of Formula (600-IIA), R\textsuperscript{3a} is -H.

[00814] In some preferred embodiments of the compound of Formula (600-IIA), R\textsuperscript{6} is selected from -H, -C(=O)-CH\textsubscript{3}, -CH\textsubscript{2}CH\textsubscript{2}OH, -CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}OH, -C(=O)-CH\textsubscript{2}OH, -C(=O)-C(=O)-OH, -CH\textsubscript{2}CH\textsubscript{2}CF\textsubscript{3}, -CH\textsubscript{2}CH\textsubscript{2}F, -CH\textsubscript{2}CH\textsubscript{2}S(=O)\textsubscript{2}CH\textsubscript{3}, or -CH\textsubscript{2}CH\textsubscript{2}OCH\textsubscript{3}.

[00815] In some preferred embodiments of the compound of Formula (600-IIA), R\textsuperscript{6} is selected from -C(=O)-CH\textsubscript{3} or -C(=O)-CH\textsubscript{2}OH.

[00816] In some preferred embodiments, the compound of Formula (600-I) is selected from the group consisting of:
and
or the pharmaceutically acceptable salt or the hydrate thereof.

[00817] In some preferred embodiments, the compound of Formula (600-I) is:

or a pharmaceutically acceptable salt or hydrate thereof.

[00818] In some preferred embodiments, the compound of Formula (600-I) is:

or a pharmaceutically acceptable salt or hydrate thereof.

[00819] In some preferred embodiments, the compound of Formula (600-I) is:
or a pharmaceutically acceptable salt or hydrate thereof.

[00820] In some preferred embodiments, the compound of Formula (600-I) is selected from the group consisting of:
or a pharmaceutically acceptable salt or hydrate thereof.

In some embodiments, the CDK4/6 inhibitor is selected from the group of compounds disclosed in U.S. Patent Application Publication No. 2012/0100100 A1, 2011/0224227 A1, and 2011/0224221 A1, the disclosures of which are specifically incorporated by reference herein.

Pharmaceutical Compositions

In one embodiment, the invention provides a pharmaceutical composition comprising a combination of a PI3K inhibitor and a BTK inhibitor. In selected embodiments, the PI3K inhibitor is selected from the group consisting of a PI3K-γ inhibitor, a PI3K-δ inhibitor, and a PI3K-γ,δ inhibitor. Said pharmaceutical composition typically also comprises at least one pharmaceutically acceptable excipient.
Said pharmaceutical composition is in one embodiment for use in the treatment of the diseases and conditions described below. In particular, it is for use in the treatment of hyperproliferative disorders.

In selected embodiments, the invention provides a pharmaceutical composition comprising a combination of a PI3K inhibitor and a BTK inhibitor for treating solid tumor cancers, lymphomas and leukemia. In selected embodiments, the PI3K inhibitor is selected from the group consisting of a PI3K-γ inhibitor, a PI3K-δ inhibitor, and a PI3K-γ,δ inhibitor. A kit containing a PI3K inhibitor and a BTK inhibitor formulated into separate preparations for said use in the treatment of treating solid tumor cancers, lymphomas and leukemia is also provided by the invention.

The pharmaceutical compositions are typically formulated to provide a therapeutically effective amount of a combination of a PI3K inhibitor, including a PI3K-γ or PI3K-δ inhibitor, a JAK-2 inhibitor, and/or a BTK inhibitor as the active ingredients, or a pharmaceutically acceptable salt, ester, prodrug, solvate, hydrate or derivative thereof. Where desired, the pharmaceutical compositions contain a pharmaceutically acceptable salt and/or coordination complex thereof, and one or more pharmaceutically acceptable excipients, carriers, including inert solid diluents and fillers, diluents, including sterile aqueous solution and various organic solvents, permeation enhancers, solubilizers and adjuvants.

The pharmaceutical compositions are administered as a combination of a PI3K inhibitor, including a PI3K-γ or a PI3K-δ inhibitor, a JAK-2 inhibitor, and/or a BTK inhibitor. Where desired, other agent(s) may be mixed into a preparation or both components may be formulated into separate preparations for use in combination separately or at the same time.

In selected embodiments, the concentration of each of the PI3K, JAK-2, and BTK inhibitors provided in the pharmaceutical compositions of the invention is independently less than, for example, 100%, 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, 0.4%, 0.3%, 0.2%, 0.1%, 0.09%, 0.08%, 0.07%, 0.06%, 0.05%, 0.04%, 0.03%, 0.02%, 0.01%, 0.009%, 0.008%, 0.007%, 0.006%, 0.005%, 0.004%, 0.003%, 0.002%, 0.001%, 0.0009%, 0.0008%, 0.0007%, 0.0006%, 0.0005%, 0.0004%, 0.0003%, 0.0002% or 0.0001% w/w, w/v or v/v.
In selected embodiments, the concentration of each of the PI3K, JAK-2, and BTK inhibitors provided in the pharmaceutical compositions of the invention is independently greater than 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 19.75%, 19.50%, 19.25% 19%, 18.75%, 18.50%, 18.25% 18%, 17.75%, 17.50%, 17.25% 17%, 16.75%, 16.50%, 16.25% 16%, 15.75%, 15.50%, 15.25% 15%, 14.75%, 14.50%, 14.25% 14%, 13.75%, 13.50%, 13.25% 13%, 12.75%, 12.50%, 12.25% 12%, 11.75%, 11.50%, 11.25% 11%, 10.75%, 10.50%, 10.25% 10%, 9.75%, 9.50%, 9.25% 9%, 8.75%, 8.50%, 8.25% 8%, 7.75%, 7.50%, 7.25% 7%, 6.75%, 6.50%, 6.25% 6%, 5.75%, 5.50%, 5.25% 5%, 4.75%, 4.50%, 4.25%, 4%, 3.75%, 3.50%, 3.25%, 3%, 2.75%, 2.50%, 2.25%, 2%, 1.75%, 1.50%, 125%, 1%, 0.5%, 0.4%, 0.3%, 0.2%, 0.1%, 0.09%, 0.08%, 0.07%, 0.06%, 0.05%, 0.04%, 0.03%, 0.02%, 0.01%, 0.009%, 0.008%, 0.007%, 0.006%, 0.005%, 0.004%, 0.003%, 0.002% or 0.0001% w/w, w/v, or v/v.

In selected embodiments, the concentration of each of the PI3K, JAK-2 and BTK inhibitors of the invention is independently in the range from about 0.0001% to about 50%, about 0.001% to about 40%, about 0.01% to about 30%, about 0.02% to about 29%, about 0.03% to about 28%, about 0.04% to about 27%, about 0.05% to about 26%, about 0.06% to about 25%, about 0.07% to about 24%, about 0.08% to about 23%, about 0.09% to about 22%, about 0.1% to about 21%, about 0.2% to about 20%, about 0.3% to about 19%, about 0.4% to about 18%, about 0.5% to about 17%, about 0.6% to about 16%, about 0.7% to about 15%, about 0.8% to about 14%, about 0.9% to about 12% or about 1% to about 10% w/w, w/v or v/v.

In selected embodiments, the concentration of each of the PI3K, JAK-2, and BTK inhibitors of the invention is independently in the range from about 0.001% to about 10%, about 0.01% to about 5%, about 0.02% to about 4.5%, about 0.03% to about 4%, about 0.04% to about 3.5%, about 0.05% to about 3%, about 0.06% to about 2.5%, about 0.07% to about 2%, about 0.08% to about 1.5%, about 0.09% to about 1%, about 0.1% to about 0.9% w/w, w/v or v/v.

In selected embodiments, the amount of each of the PI3K, JAK-2, and BTK inhibitors of the invention is independently equal to or less than 10 g, 9.5 g, 9.0 g, 8.5 g, 8.0 g, 7.5 g, 7.0 g, 6.5 g, 6.0 g, 5.5 g, 5.0 g, 4.5 g, 4.0 g, 3.5 g, 3.0 g, 2.5 g, 2.0 g, 1.5 g, 1.0 g, 0.95 g, 0.9 g, 0.85 g, 0.8 g, 0.75 g, 0.7 g, 0.65 g, 0.6 g, 0.55 g, 0.5 g, 0.45 g, 0.4 g, 0.35 g, 0.3 g, 0.25 g, 0.2 g, 0.15 g, 0.1 g, 0.09 g, 0.08 g, 0.07 g, 0.06 g, 0.05 g, 0.04 g, 0.03 g, 0.02 g, 0.01 g, 0.009 g, 0.008 g, 0.007
g, 0.006 g, 0.005 g, 0.004 g, 0.003 g, 0.002 g, 0.001 g, 0.0009 g, 0.0008 g, 0.0007 g, 0.0006 g, 0.0005 g, 0.0004 g, 0.0003 g, 0.0002 g or 0.0001 g.

[00832] In selected embodiments, the amount of each of the PI3K, JAK-2, and BTK inhibitors of the invention is independently more than 0.0001 g, 0.0002 g, 0.0003 g, 0.0004 g, 0.0005 g, 0.0006 g, 0.0007 g, 0.0008 g, 0.0009 g, 0.001 g, 0.0015 g, 0.002 g, 0.0025 g, 0.003 g, 0.0035 g, 0.004 g, 0.0045 g, 0.005 g, 0.0055 g, 0.006 g, 0.0065 g, 0.007 g, 0.0075 g, 0.008 g, 0.0085 g, 0.009 g, 0.0095 g, 0.01 g, 0.015 g, 0.02 g, 0.025 g, 0.03 g, 0.035 g, 0.04 g, 0.045 g, 0.05 g, 0.055 g, 0.06 g, 0.065 g, 0.07 g, 0.075 g, 0.08 g, 0.085 g, 0.09 g, 0.095 g, 0.1 g, 0.15 g, 0.2 g, 0.25 g, 0.3 g, 0.35 g, 0.4 g, 0.45 g, 0.5 g, 0.55 g, 0.6 g, 0.65 g, 0.7 g, 0.75 g, 0.8 g, 0.85 g, 0.9 g, 0.95 g, 1 g, 1.5 g, 2 g, 2.5, 3 g, 3.5, 4 g, 4.5 g, 5 g, 5.5 g, 6 g, 6.5 g, 7 g, 7.5 g, 8 g, 8.5 g, 9 g, 9.5 g or 10 g.

[00833] Each of the PI3K, JAK-2, and BTK inhibitors according to the invention is effective over a wide dosage range. For example, in the treatment of adult humans, dosages independently range from 0.01 to 1000 mg, from 0.5 to 100 mg, from 1 to 50 mg per day, and from 5 to 40 mg per day are examples of dosages that may be used. The exact dosage will depend upon the route of administration, the form in which the compound is administered, the gender and age of the subject to be treated, the body weight of the subject to be treated, and the preference and experience of the attending physician.

[00834] Described below are non-limiting exemplary pharmaceutical compositions and methods for preparing the same.

Pharmaceutical Compositions for Oral Administration

[00835] In selected embodiments, the invention provides a pharmaceutical composition for oral administration containing the combination of a PI3K, JAK-2, CDK4/6, and/or BTK inhibitor, and a pharmaceutical excipient suitable for oral administration.

[00836] In selected embodiments, the invention provides a solid pharmaceutical composition for oral administration containing: (i) an effective amount of each of a PI3K, JAK-2, CDK4/6, and/or BTK inhibitor in combination and (ii) a pharmaceutical excipient suitable for oral administration. In selected embodiments, the composition further contains (iii) an effective amount of a fourth compound.
In selected embodiments, the pharmaceutical composition may be a liquid pharmaceutical composition suitable for oral consumption. Pharmaceutical compositions of the invention suitable for oral administration can be presented as discrete dosage forms, such as capsules, sachets, or tablets, or liquids or aerosol sprays each containing a predetermined amount of an active ingredient as a powder or in granules, a solution, or a suspension in an aqueous or non-aqueous liquid, an oil-in-water emulsion, a water-in-oil liquid emulsion, powders for reconstitution, powders for oral consumptions, bottles (including powders or liquids in a bottle), orally dissolving films, lozenges, pastes, tubes, gums, and packs. Such dosage forms can be prepared by any of the methods of pharmacy, but all methods include the step of bringing the active ingredient(s) into association with the carrier, which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient(s) with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation. For example, a tablet can be prepared by compression or molding, optionally with one or more accessory ingredients. Compressed tablets can be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as powder or granules, optionally mixed with an excipient such as, but not limited to, a binder, a lubricant, an inert diluent, and/or a surface active or dispersing agent. Molded tablets can be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

The invention further encompasses anhydrous pharmaceutical compositions and dosage forms since water can facilitate the degradation of some compounds. For example, water may be added (e.g., 5%) in the pharmaceutical arts as a means of simulating long-term storage in order to determine characteristics such as shelf-life or the stability of formulations over time. Anhydrous pharmaceutical compositions and dosage forms of the invention can be prepared using anhydrous or low moisture containing ingredients and low moisture or low humidity conditions. Pharmaceutical compositions and dosage forms of the invention which contain lactose can be made anhydrous if substantial contact with moisture and/or humidity during manufacturing, packaging, and/or storage is expected. An anhydrous pharmaceutical composition may be prepared and stored such that its anhydrous nature is maintained. Accordingly, anhydrous compositions may be packaged using materials known to prevent exposure to water such that they can be included in suitable formulary kits. Examples of suitable
packaging include, but are not limited to, hermetically sealed foils, plastic or the like, unit dose containers, blister packs, and strip packs.

[00839] Each of the PI3K, JAK-2, CDK4/6, and BTK inhibitors as active ingredients can be combined in an intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier can take a wide variety of forms depending on the form of preparation desired for administration. In preparing the compositions for an oral dosage form, any of the usual pharmaceutical media can be employed as carriers, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, and the like in the case of oral liquid preparations (such as suspensions, solutions, and elixirs) or aerosols; or carriers such as starches, sugars, micro-crystalline cellulose, diluents, granulating agents, lubricants, binders, and disintegrating agents can be used in the case of oral solid preparations, in some embodiments without employing the use of lactose. For example, suitable carriers include powders, capsules, and tablets, with the solid oral preparations. If desired, tablets can be coated by standard aqueous or nonaqueous techniques.

[00840] Binders suitable for use in pharmaceutical compositions and dosage forms include, but are not limited to, corn starch, potato starch, or other starches, gelatin, natural and synthetic gums such as acacia, sodium alginate, alginic acid, other alginates, powdered tragacanth, guar gum, cellulose and its derivatives (e.g., ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), polyvinyl pyrrolidone, methyl cellulose, pre-gelatinized starch, hydroxypropyl methyl cellulose, microcrystalline cellulose, and mixtures thereof.

[00841] Examples of suitable fillers for use in the pharmaceutical compositions and dosage forms disclosed herein include, but are not limited to, talc, calcium carbonate (e.g., granules or powder), microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof.

[00842] Disintegrants may be used in the compositions of the invention to provide tablets that disintegrate when exposed to an aqueous environment. Too much of a disintegrant may produce tablets which disintegrate in the bottle. Too little may be insufficient for disintegration to occur, thus altering the rate and extent of release of the active ingredients from the dosage form. Thus,
a sufficient amount of disintegrant that is neither too little nor too much to detrimentally alter the release of the active ingredient(s) may be used to form the dosage forms of the compounds disclosed herein. The amount of disintegrant used may vary based upon the type of formulation and mode of administration, and may be readily discernible to those of ordinary skill in the art. About 0.5 to about 15 weight percent of disintegrant, or about 1 to about 5 weight percent of disintegrant, may be used in the pharmaceutical composition. Disintegrants that can be used to form pharmaceutical compositions and dosage forms of the invention include, but are not limited to, agar-agar, alginic acid, calcium carbonate, microcrystalline cellulose, croscarmellose sodium, crospovidone, polacrilin potassium, sodium starch glycolate, potato or tapioca starch, other starches, pre-gelatinized starch, other starches, clays, other algins, other celluloses, gums or mixtures thereof.

[00843] Lubricants which can be used to form pharmaceutical compositions and dosage forms of the invention include, but are not limited to, calcium stearate, magnesium stearate, sodium stearyl fumarate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil (e.g., peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil), zinc stearate, ethyl oleate, ethyl laureate, agar, or mixtures thereof. Additional lubricants include, for example, a syloid silica gel, a coagulated aerosol of synthetic silica, silicified microcrystalline cellulose, or mixtures thereof. A lubricant can optionally be added in an amount of less than about 0.5% or less than about 1% (by weight) of the pharmaceutical composition.

[00844] When aqueous suspensions and/or elixirs are desired for oral administration, the essential active ingredient therein may be combined with various sweetening or flavoring agents, coloring matter or dyes and, if so desired, emulsifying and/or suspending agents, together with such diluents as water, ethanol, propylene glycol, glycerin and various combinations thereof.

[00845] The tablets can be uncoated or coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glycercyl monostearate or glycercyl distearate can be employed. Formulations for oral use can also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium
carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example, peanut oil, liquid paraffin or olive oil.

[00846] Surfactants which can be used to form pharmaceutical compositions and dosage forms of the invention include, but are not limited to, hydrophilic surfactants, lipophilic surfactants, and mixtures thereof. That is, a mixture of hydrophilic surfactants may be employed, a mixture of lipophilic surfactants may be employed, or a mixture of at least one hydrophilic surfactant and at least one lipophilic surfactant may be employed.

[00847] A suitable hydrophilic surfactant may generally have an HLB value of at least 10, while suitable lipophilic surfactants may generally have an HLB value of or less than about 10. An empirical parameter used to characterize the relative hydrophilicity and hydrophobicity of non-ionic amphiphilic compounds is the hydrophilic-lipophilic balance ("HLB" value). Surfactants with lower HLB values are more lipophilic or hydrophobic, and have greater solubility in oils, while surfactants with higher HLB values are more hydrophilic, and have greater solubility in aqueous solutions. Hydrophilic surfactants are generally considered to be those compounds having an HLB value greater than about 10, as well as anionic, cationic, or zwitterionic compounds for which the HLB scale is not generally applicable. Similarly, lipophilic (i.e., hydrophobic) surfactants are compounds having an HLB value equal to or less than about 10. However, HLB value of a surfactant is merely a rough guide generally used to enable formulation of industrial, pharmaceutical and cosmetic emulsions.

[00848] Hydrophilic surfactants may be either ionic or non-ionic. Suitable ionic surfactants include, but are not limited to, alkylammonium salts; fusidic acid salts; fatty acid derivatives of amino acids, oligopeptides, and polypeptides; glyceride derivatives of amino acids, oligopeptides, and polypeptides; lecithins and hydrogenated lecithins; lysolecithins and hydrogenated lysolecithins; phospholipids and derivatives thereof; lysophospholipids and derivatives thereof; carnitine fatty acid ester salts; salts of alkysulfates; fatty acid salts; sodium docusate; acylactylates; mono- and di-acetylated tartaric acid esters of mono- and di-glycerides; succinylated mono- and di-glycerides; citric acid esters of mono- and di-glycerides; and mixtures thereof.
Within the aforementioned group, ionic surfactants include, by way of example: lecithins, lysolecithin, phospholipids, lysophospholipids and derivatives thereof; carnitine fatty acid ester salts; salts of alkylsulfates; fatty acid salts; sodium docusate; acylactylates; mono- and di-acetylated tartaric acid esters of mono- and di-glycerides; succinylated mono- and di-glycerides; citric acid esters of mono- and di-glycerides; and mixtures thereof.

Ionic surfactants may be the ionized forms of lecithin, lysolecithin, phosphatidylcholine, phosphatidylethanolamine, phosphatidylglycerol, phosphatidic acid, phosphatidylserine, lysophosphatidylcholine, lysophosphatidylethanolamine, lysophosphatidylglycerol, lysophosphatidic acid, lysophosphatidylserine, PEG-phosphatidylethanolamine, PVP-phosphatidylethanolamine, layclic esters of fatty acids, stearoyl-2-lactylate, stearoyl lactylate, succinylated monoglycerides, mono/diacetylated tartaric acid esters of mono/diglycerides, citric acid esters of mono/diglycerides, cholylsarcosine, caproate, caprylate, caprate, laurate, myristate, palmitate, oleate, ricinoleate, linoleate, linolenate, stearate, lauryl sulfate, teracecyl sulfate, docusate, lauroyl carnitines, palmitoyl carnitines, myristoyl carnitines, and salts and mixtures thereof.

Hydrophilic non-ionic surfactants may include, but not limited to, alkylglucosides; alkylmaltosides; alkylthioglucosides; lauryl macrogolglycerides; polyoxyalkylene alkyl ethers such as polyethylene glycol alkyl ethers; polyoxyalkylene alkylphenols such as polyethylene glycol alkyl phenols; polyoxyalkylene alkyl phenol fatty acid esters such as polyethylene glycol fatty acids monoesters and polyethylene glycol fatty acids diesters; polyethylene glycol glycerol fatty acid esters; polyglycerol fatty acid esters; polyoxyalkylene sorbitan fatty acid esters such as polyethylene glycol sorbitan fatty acid esters; hydrophilic transesterification products of a polyol with at least one member of the group consisting of glycerides, vegetable oils, hydrogenated vegetable oils, fatty acids, and sterols; polyoxyethylene sterols, derivatives, and analogues thereof; polyoxyethylated vitamins and derivatives thereof; polyoxyethylene-polyoxypropylene block copolymers; and mixtures thereof; polyethylene glycol sorbitan fatty acid esters and hydrophilic transesterification products of a polyol with at least one member of the group consisting of triglycerides, vegetable oils, and hydrogenated vegetable oils. The polyol may be glycerol, ethylene glycol, polyethylene glycol, sorbitol, propylene glycol, pentaerythritol, or a saccharide.
Other hydrophilic-non-ionic surfactants include, without limitation, PEG-10 laurate, PEG-12 laurate, PEG-20 laurate, PEG-32 laurate, PEG-32 dilaurate, PEG-12 oleate, PEG-15 oleate, PEG-20 oleate, PEG-20 dioleate, PEG-32 oleate, PEG-200 oleate, PEG-400 oleate, PEG-15 stearate, PEG-32 distearate, PEG-40 stearate, PEG-100 stearate, PEG-20 dilaurate, PEG-25 glyceryl trioleate, PEG-32 dioleate, PEG-20 glycercyl laurate, PEG-30 glycercyl laurate, PEG-20 glycercyl stearate, PEG-20 glycercyl oleate, PEG-30 glycercyl oleate, PEG-30 glycercyl laurate, PEG-40 glycercyl laurate, PEG-40 palm kernel oil, PEG-50 hydrogenated castor oil, PEG-40 castor oil, PEG-35 castor oil, PEG-60 castor oil, PEG-40 hydrogenated castor oil, PEG-60 hydrogenated castor oil, PEG-60 corn oil, PEG-6 caprate/caprylate glycerides, PEG-8 caprate/caprylate glycerides, polyglyceryl-10 laurate, PEG-30 cholesterol, PEG-25 phyto sterol, PEG-30 soya sterol, PEG-20 trioleate, PEG-40 sorbitan oleate, PEG-80 sorbitan laurate, polysorbate 20, polysorbate 80, POE-9 lauryl ether, POE-23 lauryl ether, POE-10 oleyl ether, POE-20 oleyl ether, POE-20 stearyl ether, tocopheryl PEG-100 succinate, PEG-24 cholesterol, polyglyceryl-10oleate, Tween 40, Tween 60, sucrose monostearate, sucrose monolaurate, sucrose monopalmitate, PEG 10-100 nonyl phenol series, PEG 15-100 octyl phenol series, and poloxamers.

Suitable lipophilic surfactants include, by way of example only: fatty alcohols; glycerol fatty acid esters; acetylated glycerol fatty acid esters; lower alcohol fatty acids esters; propylene glycol fatty acid esters; sorbitan fatty acid esters; polyethylene glycol sorbitan fatty acid esters; sterols and sterol derivatives; polyoxyethylated sterols and sterol derivatives; polyethylene glycol alkyl ethers; sugar esters; sugar ethers; lactic acid derivatives of mono- and di-glycerides; hydrophobic transterification products of a polyl with at least one member of the group consisting of glycerides, vegetable oils, hydrogenated vegetable oils, fatty acids and sterols; oil-soluble vitamins/vitamin derivatives; and mixtures thereof. Within this group, preferred lipophilic surfactants include glycerol fatty acid esters, propylene glycol fatty acid esters, and mixtures thereof, or are hydrophobic transterification products of a polyl with at least one member of the group consisting of vegetable oils, hydrogenated vegetable oils, and triglycerides.

In an embodiment, the composition may include a solubilizer to ensure good solubilization and/or dissolution of the compound of the present invention and to minimize precipitation of the compound of the present invention. This can be especially important for...
compositions for non-oral use - e.g., compositions for injection. A solubilizer may also be added to increase the solubility of the hydrophilic drug and/or other components, such as surfactants, or to maintain the composition as a stable or homogeneous solution or dispersion.

[00855] Examples of suitable solubilizers include, but are not limited to, the following: alcohols and polyols, such as ethanol, isopropanol, butanol, benzyl alcohol, ethylene glycol, propylene glycol, butanediols and isomers thereof, glycerol, pentaerythritol, sorbitol, mannitol, transcutol, dimethyl isosorbide, polyethylene glycol, polypropylene glycol, polyvinylalcohol, hydroxypropyl methylcellulose and other cellulose derivatives, cyclodextrins and cyclodextrin derivatives; ethers of polyethylene glycols having an average molecular weight of about 200 to about 6000, such as tetrahydrofurfuryl alcohol PEG ether (glycofurol) or methoxy PEG; amides and other nitrogen-containing compounds such as 2-pyrrolidone, 2-piperidone, ε-caprolactam, N-alkylpyrrolidone, N-hydroxyalkylpyrrolidone, N-alkylpiperidone, N-alkylcaprolactam, dimethylacetamide and polyvinylpyrrolidone; esters such as ethyl propionate, tributylcitrate, acetyl triethylcitrate, acetyl tributyl citrate, triethylcitrate, ethyl oleate, ethyl caprylate, ethyl butyrate, triacetin, propylene glycol monoacetate, propylene glycol diacetate, ε-caprolactone and isomers thereof, δ-valerolactone and isomers thereof, β-butyrolactone and isomers thereof; and other solubilizers known in the art, such as dimethyl acetamide, dimethyl isosorbide, N-methyl pyrrolidones, monoacetoin, diethylene glycol monoethyl ether, and water.

[00856] Mixtures of solubilizers may also be used. Examples include, but not limited to, triacetin, triethylcitrate, ethyl oleate, ethyl caprylate, dimethylacetamide, N-methylpyrrolidone, N-hydroxyethylpyrrolidone, polyvinylpyrrolidone, hydroxypropyl methylcellulose, hydroxypropyl cyclodextrins, ethanol, polyethylene glycol 200-100, glycofurol, transcutol, propylene glycol, and dimethyl isosorbide. Particularly preferred solubilizers include sorbitol, glycerol, triacetin, ethyl alcohol, PEG-400, glycofurol and propylene glycol.

[00857] The amount of solubilizer that can be included is not particularly limited. The amount of a given solubilizer may be limited to a bioacceptable amount, which may be readily determined by one of skill in the art. In some circumstances, it may be advantageous to include amounts of solubilizers far in excess of bioacceptable amounts, for example to maximize the concentration of the drug, with excess solubilizer removed prior to providing the composition to a patient using conventional techniques, such as distillation or evaporation. Thus, if present, the
solubilizer can be in a weight ratio of 10%, 25%, 50%, 100%, or up to about 200% by weight, based on the combined weight of the drug, and other excipients. If desired, very small amounts of solubilizer may also be used, such as 5%, 2%, 1% or even less. Typically, the solubilizer may be present in an amount of about 1% to about 100%, more typically about 5% to about 25% by weight.

[00858] The composition can further include one or more pharmaceutically acceptable additives and excipients. Such additives and excipients include, without limitation, detackifiers, anti-foaming agents, buffering agents, polymers, antioxidants, preservatives, chelating agents, viscomodulators, tonicifiers, flavorants, colorants, odorants, opacifiers, suspending agents, binders, fillers, plasticizers, lubricants, and mixtures thereof.

[00859] In addition, an acid or a base may be incorporated into the composition to facilitate processing, to enhance stability, or for other reasons. Examples of pharmaceutically acceptable bases include amino acids, amino acid esters, ammonium hydroxide, potassium hydroxide, sodium hydroxide, sodium hydrogen carbonate, aluminum hydroxide, calcium carbonate, magnesium hydroxide, magnesium aluminum silicate, synthetic aluminum silicate, synthetic hydrocalcite, magnesium aluminum hydroxide, diisopropylethylamine, ethanolamine, ethylenediamine, triethanolamine, triethylamine, triisopropanolamine, trimethylamine, tris(hydroxymethyl)aminomethane (TRIS) and the like. Also suitable are bases that are salts of a pharmaceutically acceptable acid, such as acetic acid, acrylic acid, adipic acid, alginic acid, alkanesulfonic acid, amino acids, ascorbic acid, benzoic acid, boric acid, butyric acid, carbonic acid, citric acid, fatty acids, formic acid, fumaric acid, gluconic acid, hydroquinosulfonic acid, isoascorbic acid, lactic acid, maleic acid, oxalic acid, para-bromophenylsulfonic acid, propionic acid, p-toluensulfonic acid, salicylic acid, stearic acid, succinic acid, tannic acid, tartaric acid, thioglycolic acid, toluenesulfonic acid, uric acid, and the like. Salts of polyprotic acids, such as sodium phosphate, disodium hydrogen phosphate, and sodium dihydrogen phosphate can also be used. When the base is a salt, the cation can be any convenient and pharmaceutically acceptable cation, such as ammonium, alkali metals and alkaline earth metals. Example may include, but not limited to, sodium, potassium, lithium, magnesium, calcium and ammonium.

[00860] Suitable acids are pharmaceutically acceptable organic or inorganic acids. Examples of suitable inorganic acids include hydrochloric acid, hydrobromic acid, hydriodic acid, sulfuric
acid, nitric acid, boric acid, phosphoric acid, and the like. Examples of suitable organic acids include acetic acid, acrylic acid, adipic acid, alginic acid, alkanesulfonic acids, amino acids, ascorbic acid, benzoic acid, boric acid, butyric acid, carbonic acid, citric acid, fatty acids, formic acid, fumaric acid, gluconic acid, hydroquinosulfonic acid, isoascorbic acid, lactic acid, maleic acid, methanesulfonic acid, oxalic acid, para-bromophenylsulfonic acid, propionic acid, p-toluenesulfonic acid, salicylic acid, stearic acid, succinic acid, tannic acid, tartaric acid, thioglycolic acid, toluenesulfonic acid and uric acid.

**Pharmaceutical Compositions for Injection**

[00861] In selected embodiments, the invention provides a pharmaceutical composition for injection containing the combination of the PI3K, JAK-2, CDK4/6, and BTK inhibitors and a pharmaceutical excipient suitable for injection. Components and amounts of agents in the compositions are as described herein.

[00862] The forms in which the compositions of the present invention may be incorporated for administration by injection include aqueous or oil suspensions, or emulsions, with sesame oil, corn oil, cottonseed oil, or peanut oil, as well as elixirs, mannitol, dextrose, or a sterile aqueous solution, and similar pharmaceutical vehicles.

[00863] Aqueous solutions in saline are also conventionally used for injection. Ethanol, glycerol, propylene glycol and liquid polyethylene glycol (and suitable mixtures thereof), cyclodextrin derivatives, and vegetable oils may also be employed. The proper fluidity can be maintained, for example, by the use of a coating, such as lecithin, for the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid and thimerosal.

[00864] Sterile injectable solutions are prepared by incorporating the combination of the PI3K, JAK-2, CDK4/6, and BTK inhibitors in the required amounts in the appropriate solvent with various other ingredients as enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile
injectable solutions, certain desirable methods of preparation are vacuum-drying and freeze-drying techniques which yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

**Pharmaceutical Compositions for Topical Delivery**

[00865] In some embodiments, the invention provides a pharmaceutical composition for transdermal delivery containing the combination of the PI3K, JAK-2, CDK4/6, and BTK inhibitors and a pharmaceutical excipient suitable for transdermal delivery.

[00866] Compositions of the present invention can be formulated into preparations in solid, semi-solid, or liquid forms suitable for local or topical administration, such as gels, water soluble jellies, creams, lotions, suspensions, foams, powders, slurries, ointments, solutions, oils, pastes, suppositories, sprays, emulsions, saline solutions, dimethylsulfoxide (DMSO)-based solutions. In general, carriers with higher densities are capable of providing an area with a prolonged exposure to the active ingredients. In contrast, a solution formulation may provide more immediate exposure of the active ingredient to the chosen area.

[00867] The pharmaceutical compositions also may comprise suitable solid or gel phase carriers or excipients, which are compounds that allow increased penetration of, or assist in the delivery of, therapeutic molecules across the stratum corneum permeability barrier of the skin. There are many of these penetration-enhancing molecules known to those trained in the art of topical formulation. Examples of such carriers and excipients include, but are not limited to, humectants (e.g., urea), glycols (e.g., propylene glycol), alcohols (e.g., ethanol), fatty acids (e.g., oleic acid), surfactants (e.g., isopropyl myristate and sodium lauryl sulfate), pyrrolidones, glycerol monolaurate, sulfoxides, terpenes (e.g., menthol), amines, amides, alkanes, alkanols, water, calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols.

[00868] Another exemplary formulation for use in the methods of the present invention employs transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the combination of the PI3K, JAK-2, CDK4/6, and BTK inhibitors in controlled amounts, either with or without another agent.
[00869] The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art. See, e.g., U.S. Patent Nos. 5,023,252; 4,992,445 and 5,001,139. Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

Other Pharmaceutical Compositions

[00870] Pharmaceutical compositions may also be prepared from compositions described herein and one or more pharmaceutically acceptable excipients suitable for sublingual, buccal, rectal, intraosseous, intraocular, intranasal, epidural, or intraspinal administration. Preparations for such pharmaceutical compositions are well-known in the art. See, e.g., Anderson et al., eds., Handbook of Clinical Drug Data, Tenth Edition, McGraw-Hill, 2002; and Pratt and Taylor, eds., Principles of Drug Action, Third Edition, Churchill Livingston, N.Y., 1990, each of which is incorporated by reference herein in its entirety.

[00871] Administration of the combination of the PI3K, JAK-2, CDK4/6, and BTK inhibitors or pharmaceutical composition of these compounds can be effected by any method that enables delivery of the compounds to the site of action. These methods include oral routes, intraduodenal routes, parenteral injection (including intravenous, intraarterial, subcutaneous, intramuscular, intravascular, intraperitoneal or infusion), topical (e.g., transdermal application), rectal administration, via local delivery by catheter or stent or through inhalation. The combination of compounds can also be administered intraadiposally or intrathecally.

[00872] The compositions of the invention may also be delivered via an impregnated or coated device such as a stent, for example, or an artery-inserted cylindrical polymer. Such a method of administration may, for example, aid in the prevention or amelioration of restenosis following procedures such as balloon angioplasty. Without being bound by theory, compounds of the invention may slow or inhibit the migration and proliferation of smooth muscle cells in the arterial wall which contribute to restenosis. A compound of the invention may be administered, for example, by local delivery from the struts of a stent, from a stent graft, from grafts, or from the cover or sheath of a stent. In some embodiments, a compound of the invention is admixed with a matrix. Such a matrix may be a polymeric matrix, and may serve to bond the compound to the stent. Polymeric matrices suitable for such use, include, for example, lactone-based
polyesters or copolyesters such as polylactide, polycaprolactonglycolide, polyorthoesters, polyanhydrides, polyaminoacids, polysaccharides, polyphosphazenes, poly(ether-ester) copolymers (e.g. PEO-PLLA); polydimethylsiloxane, poly(ethylene-vinylacetate), acrylate-based polymers or copolymers (e.g., polyhydroxyethyl methacrylate, polyvinyl pyrrolidinone), fluorinated polymers such as polytetrafluoroethylene and cellulose esters. Suitable matrices may be nondegrading or may degrade with time, releasing the compound or compounds. The combination of the PI3K, JAK-2, CDK4/6, and BTK inhibitors may be applied to the surface of the stent by various methods such as dip/spin coating, spray coating, dip-coating, and/or brush-coating. The compounds may be applied in a solvent and the solvent may be allowed to evaporate, thus forming a layer of compound onto the stent. Alternatively, the compound may be located in the body of the stent or graft, for example in microchannels or micropores. When implanted, the compound diffuses out of the body of the stent to contact the arterial wall. Such stents may be prepared by dipping a stent manufactured to contain such micropores or microchannels into a solution of the compound of the invention in a suitable solvent, followed by evaporation of the solvent. Excess drug on the surface of the stent may be removed via an additional brief solvent wash. In yet other embodiments, compounds of the invention may be covalently linked to a stent or graft. A covalent linker may be used which degrades in vivo, leading to the release of the compound of the invention. Any bio-labile linkage may be used for such a purpose, such as ester, amide or anhydride linkages. The combination of the PI3K, JAK-2, CDK4/6, and BTK inhibitors may additionally be administered intravascularly from a balloon used during angioplasty. Extravascular administration of the combination of the PI3K, JAK-2, CDK4/6, and BTK inhibitors via the pericard or via advential application of formulations of the invention may also be performed to decrease restenosis.

[00873] Exemplary parenteral administration forms include solutions or suspensions of active compound in sterile aqueous solutions, for example, aqueous propylene glycol or dextrose solutions. Such dosage forms can be suitably buffered, if desired.

[00874] The invention also provides kits. The kits include each of the PI3K, CDK4/6, JAK-2, and BTK inhibitors, either alone or in combination in suitable packaging, and written material that can include instructions for use, discussion of clinical studies and listing of side effects. Such kits may also include information, such as scientific literature references, package insert
materials, clinical trial results, and/or summaries of these and the like, which indicate or establish
the activities and/or advantages of the composition, and/or which describe dosing,
adминистration, side effects, drug interactions, or other information useful to the health care
provider. Such information may be based on the results of various studies, for example, studies
using experimental animals involving in vivo models and studies based on human clinical trials.
The kit may further contain another agent. In selected embodiments, the PI3K, CDK4/6, JAK-2,
and BTK inhibitors and the agent are provided as separate compositions in separate containers
within the kit. In selected embodiments, the PI3K, CDK4/6, JAK-2, and BTK inhibitors and the
agent are provided as a single composition within a container in the kit. Suitable packaging and
additional articles for use (e.g., measuring cup for liquid preparations, foil wrapping to minimize
exposure to air, and the like) are known in the art and may be included in the kit. Kits described
herein can be provided, marketed and/or promoted to health providers, including physicians,
nurses, pharmacists, formulary officials, and the like. Kits may also, in selected embodiments, be
marketed directly to the consumer.

Dosages and Dosing Regimens

[00875] The amounts of the combination of the PI3K, CDK4/6, JAK-2, and BTK inhibitors
administered will be dependent on the mammal being treated, the severity of the disorder or
condition, the rate of administration, the disposition of the compounds and the discretion of the
prescribing physician. However, an effective dosage is in the range of about 0.001 to about 100
mg per kg body weight per day, such as about 1 to about 35 mg/kg/day, in single or divided
doses. For a 70 kg human, this would amount to about 0.05 to 7 g/day, such as about 0.05 to
about 2.5 g/day. In some instances, dosage levels below the lower limit of the aforesaid range
may be more than adequate, while in other cases still larger doses may be employed without
causing any harmful side effect - e.g., by dividing such larger doses into several small doses for
administration throughout the day.

[00876] In selected embodiments, the combination of the PI3K, CDK4/6, JAK-2, and BTK
inhibitors is administered in a single dose. Typically, such administration will be by injection -
e.g., intravenous injection, in order to introduce the agents quickly. However, other routes may
be used as appropriate. A single dose of the combination of the PI3K, CDK4/6, JAK-2, and BTK
inhibitors may also be used for treatment of an acute condition.
In selected embodiments, the combination of the PI3K, CDK4/6, JAK-2, and BTK inhibitors is administered in multiple doses. Dosing may be about once, twice, three times, four times, five times, six times, or more than six times per day. Dosing may be about once a month, once every two weeks, once a week, or once every other day. In other embodiments, the combination of the PI3K, JAK-2, CDK4/6, and BTK inhibitors is administered about once per day to about 6 times per day. In another embodiment the administration of the combination of the PI3K, CDK4/6, JAK-2, and BTK inhibitors continues for less than about 7 days. In yet another embodiment the administration continues for more than about 6, 10, 14, 28 days, two months, six months, or one year. In some cases, continuous dosing is achieved and maintained as long as necessary.

Administration of the agents of the invention may continue as long as necessary. In selected embodiments, the combination of the PI3K, JAK-2, CDK4/6, and BTK inhibitors is administered for more than 1, 2, 3, 4, 5, 6, 7, 14, or 28 days. In some embodiments, the combination of the PI3K, JAK-2, CDK4/6, and BTK inhibitors is administered for less than 28, 14, 7, 6, 5, 4, 3, 2, or 1 day. In selected embodiments, the combination of the PI3K, JAK-2, CDK4/6, and BTK inhibitors is administered chronically on an ongoing basis - e.g., for the treatment of chronic effects.

An effective amount of the combination of the PI3K, JAK-2, CDK4/6, and BTK inhibitors may be administered in either single or multiple doses by any of the accepted modes of administration of agents having similar utilities, including rectal, buccal, intranasal and transdermal routes, by intra-arterial injection, intravenously, intraperitoneally, parenterally, intramuscularly, subcutaneously, orally, topically, or as an inhalant.

Methods of Treatment

In selected embodiments, the invention provides a method of treating a hyperproliferative disorder in a mammal that comprises administering to said mammal a therapeutically effective amount of a CDK4/6 inhibitor and a BTK inhibitor, or a pharmaceutically acceptable salt or ester, prodrug, solvate or hydrate of the BTK inhibitor or CDK4/6 inhibitor. In selected embodiments, the invention provides a method of treating a hyperproliferative disorder in a mammal that comprises administering to said mammal a therapeutically effective amount of a CDK4/6 inhibitor, a BTK inhibitor, and a PI3K inhibitor.
(or a PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor) or a pharmaceutically acceptable salt or ester, prodrug, solvate or hydrate of any of the PI3K inhibitor, CDK4/6 inhibitor, and BTK inhibitor. In selected embodiments, the invention provides a method of treating a hyperproliferative disorder in a mammal that comprises administering to said mammal a therapeutically effective amount of a CDK4/6 inhibitor, a BTK inhibitor, a JAK-2 inhibitor, and a PI3K inhibitor (or a PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor) or a pharmaceutically acceptable salt or ester, prodrug, solvate or hydrate of any of the PI3K inhibitor, CDK4/6 inhibitor, JAK-2 inhibitor, and/or BTK inhibitor.

[00881] In selected embodiments, the invention provides a method of treating, with a combination of a PI3K inhibitor, including a PI3K-γ or PI3K-δ inhibitor, a JAK-2 inhibitor, a BTK inhibitor, and/or a CDK4/6 inhibitor, a hyperproliferative disorder in a mammal selected from the group consisting of bladder cancer, squamous cell carcinoma including head and neck cancer, pancreatic ductal adenocarcinoma (PDA), pancreatic cancer, colon carcinoma, mammmary carcinoma, breast cancer, fibrosarcoma, mesothelioma, renal cell carcinoma, lung carcinoma, thyma, prostate cancer, colorectal cancer, ovarian cancer, acute myeloid leukemia, thymus cancer, brain cancer, squamous cell cancer, skin cancer, eye cancer, retinoblastoma, melanoma, intraocular melanoma, oral cavity and oropharyngeal cancers, gastric cancer, stomach cancer, cervical cancer, head, neck, renal cancer, kidney cancer, liver cancer, ovarian cancer, prostate cancer, colorectal cancer, esophageal cancer, testicular cancer, gynecological cancer, thyroid cancer, acquired immune deficiency syndrome (AIDS)-related cancers (e.g., lymphoma and Kaposi's sarcoma), viral-induced cancers such as cervical carcinoma (human papillomavirus), B-cell lymphoproliferative disease and nasopharyngeal carcinoma (Epstein-Barr virus), Kaposi's Sarcoma and primary effusion lymphomas (Kaposi's sarcoma herpesvirus), hepatocellular carcinoma (hepatitis B and hepatitis C viruses), and T-cell leukemias (Human T-cell leukemia virus-1), glioblastoma, esophageal tumors, hematological neoplasms, non-small-cell lung cancer, chronic myelocytic leukemia, diffuse large B-cell lymphoma (including activated B-cell (ABC) and germinal center B-cell (GCB) subtypes), esophagus tumor, follicle center lymphoma, head and neck tumor, hepatitis C virus infection, hepatocellular carcinoma, Hodgkin’s disease, metastatic colon cancer, multiple myeloma, non-Hodgkin’s lymphoma, indolent non-Hodgkin’s lymphoma, ovary tumor, pancreas tumor, renal cell carcinoma, small-cell lung cancer, stage IV melanoma, chronic lymphocytic leukemia, B-cell acute lymphoblastic leukemia (ALL), mature
B-cell ALL, follicular lymphoma, mantle cell lymphoma, and Burkitt’s lymphoma.

In selected embodiments, the invention provides a method of treating an inflammatory, immune, or autoimmune disorder in a mammal with a combination of a PI3K inhibitor, including a PI3K-γ or PI3K-δ inhibitor, a JAK-2 inhibitor, a BTK inhibitor, and/or a CDK4/6 inhibitor. In selected embodiments, the invention also provides a method of treating a disease with a combination of a PI3K inhibitor, including a PI3K-γ or PI3K-δ inhibitor, a JAK-2 inhibitor, a BTK inhibitor, and/or a CDK4/6 inhibitor, wherein the disease is selected from the group consisting of tumor angiogenesis, chronic inflammatory disease, rheumatoid arthritis, atherosclerosis, inflammatory bowel disease, skin diseases such as psoriasis, eczema, and scleroderma, diabetes, diabetic retinopathy, retinopathy of prematurity, age-related macular degeneration, hemangioma, glioma and melanoma, ulcerative colitis, atopic dermatitis, pouchnitis, spondylarthritis, uveitis, Behcets disease, polymyalgia rheumatica, giant-cell arteritis, sarcoidosis, Kawasaki disease, juvenile idiopathic arthritis, hidradenitis suppurativa, Sjögren’s syndrome, psoriatic arthritis, juvenile rheumatoid arthritis, ankylosing spondylitis, Crohn’s Disease, lupus, and lupus nephritis.

In selected embodiments, the invention provides a method of treating, with a composition including a PI3K inhibitor, including a PI3K-γ or PI3K-δ inhibitor, a JAK-2 inhibitor, a BTK inhibitor, and/or a CDK4/6 inhibitor, disorders such as hyperproliferative disorder, including but not limited to cancer such as acute myeloid leukemia, thymus, brain, lung, squamous cell, skin, eye, retinoblastoma, intraocular melanoma, oral cavity and oropharyngeal, bladder, gastric, stomach, pancreatic, bladder, breast, cervical, head, neck, renal, kidney, liver, ovarian, prostate, colorectal, esophageal, testicular, gynecological, thyroid, CNS, PNS, AIDS-related (e.g., lymphoma and Kaposi’s sarcoma) or viral-induced cancer. In some embodiments, said pharmaceutical composition is for the treatment of a non-cancerous hyperproliferative disorder such as benign hyperplasia of the skin (e.g., psoriasis), restenosis, or prostate (e.g., benign prostatic hypertrophy (BPH)). In some embodiments, the invention provides a method of treating a hyperproliferative disorder selected from the group consisting of myeloproliferative proliferative neoplasm, chronic myelogenous leukemia, chronic neutrophilic leukemia, polycythemia vera, primary myelofibrosis, essential thrombocytemia, chronic eosinophilic leukemia, mastocytosis, and myelodysplastic syndrome. In some embodiments, the invention provides a method of treating a glioma, wherein the glioma is selected from the group
consisting of fibrillary astrocytoma, anaplastic astrocytoma, pilocytic astrocytoma, astrocytoma, pleomorphic xanthoastrocytoma, subependymal giant cell astrocytoma, glioblastoma multiforme, oligodendroglioma, ependymoma, subependymoma, choroid plexus tumor, choroid plexus papilloma, choroid plexus carcinoma, oligoastrocytoma, gliomatosis cerebri, and gliosarcoma. In some embodiments, the invention provides a method of treating a cancer, wherein the cancer is selected from primary central nervous system lymphoma, reticulum cell sarcoma, diffuse histiocytic lymphoma, and microglioma.

[00884] In selected embodiments, the invention provides a method of treating a solid tumor cancer with a composition including a combination of a PI3K inhibitor, including a PI3K-γ or PI3K-δ inhibitor, a JAK-2 inhibitor, a BTK inhibitor, and/or a CDK4/6 inhibitor, wherein the dose is effective to inhibit signaling between the solid tumor cells and at least one microenvironment selected from the group consisting of macrophages, monocytes, mast cells, helper T cells, cytotoxic T cells, regulatory T cells, natural killer cells, myeloid-derived suppressor cells, regulatory B cells, neutrophils, dendritic cells, and fibroblasts. In selected embodiments, the invention provides a method of treating pancreatic cancer, breast cancer, ovarian cancer, melanoma, lung cancer, head and neck cancer, and colorectal cancer using a combination of a BTK inhibitor, a PI3K inhibitor, a JAK-2 inhibitor, and/or a CDK4/6 inhibitor, wherein the dose is effective to inhibit signaling between the solid tumor cells and at least one microenvironment selected from the group consisting of macrophages, monocytes, mast cells, helper T cells, cytotoxic T cells, regulatory T cells, natural killer cells, myeloid-derived suppressor cells, regulatory B cells, neutrophils, dendritic cells, and fibroblasts. In an embodiment, the invention provides a method for treating pancreatic cancer, breast cancer, ovarian cancer, melanoma, lung cancer, head and neck cancer, and colorectal cancer using a combination of a BTK inhibitor and gemcitabine, or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof. In an embodiment, the invention provides a method for treating pancreatic cancer, breast cancer, ovarian cancer, melanoma, lung cancer, head and neck cancer, and colorectal cancer using a combination of a BTK inhibitor and gemcitabine, or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof, wherein the BTK inhibitor is a compound of Formula (XVIII).

[00885] In one embodiment, the invention provides (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof,
and (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, for use in treating a cancer.

[00886] In one embodiment, the invention provides (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (3) a phosphoinositide 3-kinase (PI3K) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, for use in treating a cancer.

[00887] In one embodiment, the invention provides (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (3) a PI3K-δ inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, for use in treating a cancer.

[00888] In one embodiment, the invention provides (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (3) an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof, for use in treating a cancer.

[00889] In one embodiment, the invention provides (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a phosphoinositide 3-kinase (PI3K) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (4) an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof, for use in treating a cancer.

[00890] In one embodiment, the invention provides (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2)
a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a PI3K-δ inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (4) an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof, for use in treating a cancer.

[00891] In one embodiment, the invention provides (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (3) a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, for use in treating a cancer.

[00892] In one embodiment, the invention provides (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a phosphoinositide 3-kinase (PI3K) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (4) a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, for use in treating a cancer.

[00893] In one embodiment, the invention provides (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a PI3K-δ inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (4) a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, for use in treating a cancer.

[00894] In one embodiment, the invention provides (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab,
and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof; and (4) a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, for use in treating a cancer.

[00895] In one embodiment, the invention provides (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a phosphoinositide 3-kinase (PI3K) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (4) an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof; and (5) a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, for use in treating a cancer.

[00896] In one embodiment, the invention provides (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a PI3K-δ inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (4) an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof; and (5) a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, for use in treating a cancer.

[00897] In one embodiment, the invention provides (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (2) a BTK inhibitor having the structure:
or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof, for use in treating a cancer.

[00898] In one embodiment, the invention provides (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a BTK inhibitor having the structure:
or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof; and (3) a 
PI3K inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug 
thereof, for use in treating a cancer.

[00899] In one embodiment, the invention provides (1) a cyclin-dependent kinase-4/6 (CDK4/6) 
inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) 
a BTK inhibitor having the structure:

![Chemical Structure]

or a pharmaceutically-acceptable salt, cocrystal, hydrate, 
solvate, or prodrug thereof; and (3) a PI3K-δ inhibitor or a pharmaceutically acceptable salt, 
solvate, hydrate, cocrystal, or prodrug thereof, for use in treating a cancer.

[00900] In one embodiment, the invention provides (1) a cyclin-dependent kinase-4/6 (CDK4/6) 
inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) 
a BTK inhibitor having the structure:
or a pharmaceutically-acceptable salt, cocystal, hydrate, solvate, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocystal, or prodrug thereof; and (3) an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof, for use in treating a cancer.

[00901] In one embodiment, the invention provides (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocystal, or prodrug thereof; and (2) a BTK inhibitor having the structure:
or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a phosphoinositide 3-kinase (PI3K) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (4) an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof, for use in treating a cancer.

[00902] In one embodiment, the invention provides (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (2) a BTK inhibitor having the structure:
or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a PI3K-δ inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (4) an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof, for use in treating a cancer.

[00903] In one embodiment, the invention provides (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (2) a BTK inhibitor having the structure:
or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (3) a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, for use in treating a cancer.

[00904] In one embodiment, the invention provides (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (2) a BTK inhibitor having the structure:
or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a phosphoinositide 3-kinase (PI3K) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (4) a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, for use in treating a cancer.

[00905] In one embodiment, the invention provides (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (2) a BTK inhibitor having the structure:
(1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a PI3K-δ inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (4) a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, for use in treating a cancer.

[00906] In one embodiment, the invention provides (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (2) a BTK inhibitor having the structure:
or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof; and (4) a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, for use in treating a cancer.

[00907] In one embodiment, the invention provides (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (2) a BTK inhibitor having the structure:
or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a phosphoinositide 3-kinase (PI3K) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (4) an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof; and (5) a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, for use in treating a cancer.

[00908] In one embodiment, the invention provides (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (2) a BTK inhibitor having the structure:
or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a PI3K-δ inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (4) an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof; and (5) a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, for use in treating a cancer.

[00909] In one embodiment, the invention provides (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, and (2) a BTK inhibitor is selected from the group consisting of ibrutinib:
and pharmaceutically-acceptable salts, cocrystals, hydrates, solvates, or prodrugs thereof, for use in treating a cancer.

[00910] In one embodiment, the invention provides (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a BTK inhibitor is selected from the group consisting of ibrutinib:

and pharmaceutically-acceptable salts, cocrystals, hydrates, solvates, or prodrugs thereof; and (3) a phosphoinositol 3-kinase (PI3K) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, for use in treating a cancer.

[00911] In one embodiment, the invention provides (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2)
a BTK inhibitor is selected from the group consisting of ibrutinib:

and pharmaceutically-acceptable salts, cocrystals, hydrates, solvates, or prodrugs thereof; and (3) a PI3K-δ inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, for use in treating a cancer.

[00912] In one embodiment, the invention provides (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a BTK inhibitor is selected from the group consisting of ibrutinib:

and pharmaceutically-acceptable salts, cocrystals, hydrates, solvates, or prodrugs thereof; and (3) an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates,
variants, radioisotope-labeled complexes, and biosimilars thereof, for use in treating a cancer.

[00913] In one embodiment, the invention provides (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a BTK inhibitor is selected from the group consisting of ibrutinib:

[00914] In one embodiment, the invention provides (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a BTK inhibitor is selected from the group consisting of ibrutinib:
and pharmaceutically-acceptable salts, cocrystals, hydrates, solvates, or prodrugs thereof; (3) a PI3K-δ inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (4) an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof, for use in treating a cancer.

[00915] In one embodiment, the invention provides (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a BTK inhibitor is selected from the group consisting of ibrutinib:
a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, for use in treating a cancer.

[00916] In one embodiment, the invention provides (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a BTK inhibitor is selected from the group consisting of ibrutinib:

![Chemical structures](attachment:image)

and pharmaceutically-acceptable salts, cocrystals, hydrates, solvates, or prodrugs thereof; (3) a phosphoinositide 3-kinase (PI3K) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (4) a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, for use in treating a cancer.

[00917] In one embodiment, the invention provides (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a BTK inhibitor is selected from the group consisting of ibrutinib:
and pharmaceutically-acceptable salts, cocrystals, hydrates, solvates, or prodrugs thereof; (3) a PI3K-δ inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (4) a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, for use in treating a cancer.

[00918] In one embodiment, the invention provides (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a BTK inhibitor is selected from the group consisting of ibrutinib:

and pharmaceutically-acceptable salts, cocrystals, hydrates, solvates, or prodrugs thereof; (3) an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates,
variants, radioisotope-labeled complexes, and biosimilars thereof; and (4) a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, for use in treating a cancer.

[00919] In one embodiment, the invention provides (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a BTK inhibitor is selected from the group consisting of ibrutinib:

and pharmaceutically-acceptable salts, cocrystals, hydrates, solvates, or prodrugs thereof; (3) a phosphoinositide 3-kinase (PI3K) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (4) an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof; and (5) a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, for use in treating a cancer.

[00920] In one embodiment, the invention provides (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a BTK inhibitor is selected from the group consisting of ibrutinib:
and pharmaceutically-acceptable salts, cocrystals, hydrates, solvates, or prodrugs thereof; (3) a PI3K-δ inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (4) an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof; and (5) a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, for use in treating a cancer.

[00921] In one embodiment, the invention provides (1) a CDK4/6 inhibitor selected from palbociclib:

or a pharmaceutically-acceptable salt, cocrystal, hydate, solvate, or prodrug thereof; and (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, for use in treating a cancer.
In one embodiment, the invention provides (1) a CDK4/6 inhibitor selected from palbociclib:

or a pharmaceutically-acceptable salt, cocrystal, hydate, solvate, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (3) a phosphoinositide 3-kinase (PI3K) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, for use in treating a cancer.

In one embodiment, the invention provides (1) a CDK4/6 inhibitor selected from palbociclib:

or a pharmaceutically-acceptable salt, cocrystal, hydate, solvate, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (3) a PI3K-δ inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, for use in treating a cancer.
[00924] In one embodiment, the invention provides (1) a CDK4/6 inhibitor selected from palbociclib:

![CDK4/6 Inhibitor Structure]

or a pharmaceutically-acceptable salt, cocrystal, hydate, solvate, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (3) an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof, for use in treating a cancer.

[00925] In one embodiment, the invention provides (1) a CDK4/6 inhibitor selected from palbociclib:

![CDK4/6 Inhibitor Structure]

or a pharmaceutically-acceptable salt, cocrystal, hydate, solvate, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a phosphoinositide 3-kinase (PI3K) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (4) an anti-
CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof, for use in treating a cancer.

[00926] In one embodiment, the invention provides (1) a CDK4/6 inhibitor selected from palbociclib:

![CDK4/6 inhibitor](image)

or a pharmaceutically-acceptable salt, cocrystal, hydate, solvate, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a PI3K-δ inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (4) an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof, for use in treating a cancer.

[00927] In one embodiment, the invention provides (1) a CDK4/6 inhibitor selected from palbociclib:
or a pharmaceutically-acceptable salt, cocrystal, hydate, solvate, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (3) a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, for use in treating a cancer.

[00928] In one embodiment, the invention provides (1) a CDK4/6 inhibitor selected from palbociclib:

![Chemical structure of palbociclib]

or a pharmaceutically-acceptable salt, cocrystal, hydate, solvate, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a phosphoinositide 3-kinase (PI3K) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (4) a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, for use in treating a cancer.

[00929] In one embodiment, the invention provides (1) a CDK4/6 inhibitor selected from palbociclib:
or a pharmaceutically-acceptable salt, cocrystal, hydate, solvate, or prodrug thereof; (2) a 
Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, 
cocrystal, or prodrug thereof; (3) a PI3K-δ inhibitor or a pharmaceutically acceptable salt, 
solvate, hydrate, cocrystal, or prodrug thereof; and (4) a JAK-2 inhibitor or a pharmaceutically 
acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, for use in treating a cancer.

[00930] In one embodiment, the invention provides (1) a CDK4/6 inhibitor selected from 
palbociclib:

![Chemical Structure]

or a pharmaceutically-acceptable salt, cocrystal, hydate, solvate, or prodrug thereof; (2) a 
Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, 
cocrystal, or prodrug thereof; (3) an anti-CD20 antibody selected from the group consisting of 
rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, 
derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof; and 
(4) a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or 
prodrug thereof, for use in treating a cancer.

[00931] In one embodiment, the invention provides (1) a CDK4/6 inhibitor selected from 
palbociclib:
or a pharmaceutically-acceptable salt, cocystal, hydate, solvate, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocystal, or prodrug thereof; (3) a phosphoinositide 3-kinase (PI3K) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocystal, or prodrug thereof; (4) an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibrutinomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof; and (5) a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocystal, or prodrug thereof, for use in treating a cancer.

[00932] In one embodiment, the invention provides (1) a CDK4/6 inhibitor selected from palbociclib:

or a pharmaceutically-acceptable salt, cocystal, hydate, solvate, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocystal, or prodrug thereof; (3) a PI3K-δ inhibitor or a pharmaceutically acceptable salt,
solvate, hydrate, cocrystal, or prodrug thereof; (4) an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibrutinomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof; and (5) a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, for use in treating a cancer.

[00933] In one embodiment, the invention provides (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (3) a PI3K inhibitor selected from the group consisting of:

![Chemical structures](image)

and pharmaceutically acceptable salts, solvates, hydrates, cocrystals, or prodrugs thereof, for use in treating a cancer.

[00934] In one embodiment, the invention provides (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2)
a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (3) a PI3K-δ inhibitor selected from the group consisting of:

and pharmaceutically acceptable salts, solvates, hydrates, cocrystals, or prodrugs thereof, for use in treating a cancer.

[00935] In one embodiment, the invention provides (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a PI3K inhibitor selected from the group consisting of:
and pharmaceutically acceptable salts, solvates, hydrates, cocrystals, or prodrugs thereof; and (4) an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof, for use in treating a cancer.

[00936] In one embodiment, the invention provides (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a PI3K-δ inhibitor selected from the group consisting of:
and pharmaceutically acceptable salts, solvates, hydrates, cocrystals, or prodrugs thereof; and (4) an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof, for use in treating a cancer.

In one embodiment, the invention provides (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate,
hydrate, cocrystal, or prodrug thereof; (3) a PI3K inhibitor selected from the group consisting of:

and pharmaceutically acceptable salts, solvates, hydrates, cocrystals, or prodrugs thereof, for use in treating a cancer.

[00938] In one embodiment, the invention provides (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate,
hydrate, cocrystal, or prodrug thereof; (3) a PI3K inhibitor selected from the group consisting of:

and pharmaceutically acceptable salts, solvates, hydrates, cocrystals, or prodrugs thereof; and (4) a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, for use in treating a cancer.

[00939] In one embodiment, the invention provides (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2)
a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a PI3K inhibitor selected from the group consisting of:

[00940] and pharmaceutically acceptable salts, solvates, hydrates, cocrystals, or prodrugs thereof; (4) an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof; and
(5) a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, for use in treating a cancer.

[00941] In one embodiment, the invention provides (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a PI3K-δ inhibitor selected from the group consisting of:

![Chemical structures](attachment:image.png)

, idelalisib:

, acalisib:
and pharmaceutically acceptable salts, solvates, hydrates, cocrystals, or prodrugs thereof; (4) an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof; and (5) a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, for use in treating a cancer.

[00942] In one embodiment, the invention provides (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (3) an anticoagulent or an antiplatelet active pharmaceutical ingredient, for use in treating a cancer.

[00943] In one embodiment, the invention provides (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (3) a phosphoinositide 3-kinase (PI3K) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, for use in treating a cancer.

[00944] In one embodiment, the invention provides (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a PI3K-δ inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (4) an anticoagulent or an antiplatelet

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active pharmaceutical ingredient, for use in treating a cancer.

[00945] In one embodiment, the invention provides (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof; and (4) an anticoagulant or an antiplatelet active pharmaceutical ingredient., for use in treating a cancer.

[00946] In one embodiment, the invention provides (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a phosphoinositol 3-kinase (PI3K) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (4) an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof; and (5) an anticoagulant or an antiplatelet active pharmaceutical ingredient., for use in treating a cancer.

[00947] In one embodiment, the invention provides (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a PI3K-δ inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (4) an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof; and (5) an anticoagulant or an antiplatelet active pharmaceutical ingredient, for use in treating a cancer.

[00948] In one embodiment, the invention provides (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate,
hydrate, cocrystal, or prodrug thereof; (3) a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (4) an anticoagulant or an antiplatelet active pharmaceutical ingredient, for use in treating a cancer.

[00949] In one embodiment, the invention provides (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a phosphoinositide 3-kinase (PI3K) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (4) a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (5) an anticoagulant or an antiplatelet active pharmaceutical ingredient, for use in treating a cancer.

[00950] In one embodiment, the invention provides (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a PI3K-δ inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (4) a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (5) an anticoagulant or an antiplatelet active pharmaceutical ingredient, for use in treating a cancer.

[00951] In one embodiment, the invention provides (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibrutinomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof; (4) a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (5) an anticoagulant or an antiplatelet active pharmaceutical ingredient, for use in treating a cancer.

[00952] In one embodiment, the invention provides (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate,
hydrate, cocrystal, or prodrug thereof; (3) a phosphoinositide 3-kinase (PI3K) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (4) an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof; and (5) a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (6) an anticoagulant or an antiplatelet active pharmaceutical ingredient, for use in treating a cancer.

[00953] In one embodiment, the invention provides (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a PI3K-δ inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (4) an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof; and (5) a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (6) an anticoagulant or an antiplatelet active pharmaceutical ingredient, for use in treating a cancer.

[00954] In one embodiment, the invention provides (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (3) a JAK-2 inhibitor selected from the group consisting of ruxolitinib:

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\begin{align*}
&\text{N} \\
&\text{\begin{tikzpicture}
&\draw (0,0) circle (1cm);
&\draw (90:1) -- (0:1) -- (210:1) -- (330:1) -- cycle;
&\draw (180:1) -- (90:1);
&\draw (0,0) -- (90:1);
&\draw (0,0) node[above] {\text{NH}};
&\end{tikzpicture}}
\end{align*}
\]

pacritinib:
and pharmaceutically-acceptable salts, cocrystals, hydrates, solvates, or prodrugs thereof, for use in treating a cancer.

[00955] In one embodiment, the invention provides (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a phosphoinositide 3-kinase (PI3K) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (4) a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, for use in treating a cancer.

[00956] In one embodiment, the invention provides (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a PI3K-δ inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (4) a JAK-2 inhibitor selected from the group consisting of ruxolitinib:

 pacritinib:
and pharmaceutically-acceptable salts, cocrystals, hydrates, solvates, or prodrugs thereof, for use in treating a cancer.

[00957] In one embodiment, the invention provides (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a phosphoinositide 3-kinase (PI3K) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (4) an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof; and (5) a JAK-2 inhibitor selected from the group consisting of ruxolitinib:

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\text{pacritinib:}
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and pharmaceutically-acceptable salts, cocrystals, hydrates, solvates, or prodrugs thereof, for use in treating a cancer.

[00958] In one embodiment, the invention provides (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a PI3K-δ inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (4) an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof; and (5) a JAK-2 inhibitor selected from the group consisting of ruxolitinib:

![Chemical structure of ruxolitinib]

and pacritinib:
and pharmaceutically-acceptable salts, cocrystals, hydrates, solvates, or prodrugs thereof, for use in treating a cancer.

[00959] The cancer may be any cancer that may be treated with the compositions disclosed herein. In one preferred embodiment, the cancer is a B cell hematological malignancy selected from the hematological malignancy is selected from the group consisting of chronic lymphocytic leukemia (CLL), small lymphocytic leukemia (SLL), non-Hodgkin’s lymphoma (NHL), diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), Hodgkin’s lymphoma, B cell acute lymphoblastic leukemia (B-ALL), Burkitt’s lymphoma, Waldenström's macroglobulinemia (WM), Burkitt’s lymphoma, multiple myeloma, or myelofibrosis. In one preferred embodiment, the cancer is a solid tumor cancer, and wherein the solid tumor cancer is selected from the group consisting of bladder cancer, non-small cell lung cancer, cervical cancer, anal cancer, pancreatic cancer, squamous cell carcinoma including head and neck cancer, renal cell carcinoma, melanoma, ovarian cancer, small cell lung cancer, glioblastoma, gastrointestinal stromal tumor, breast cancer, lung cancer, colorectal cancer, thyroid cancer, bone sarcoma, stomach cancer, oral cavity cancer, oropharyngeal cancer, gastric cancer, kidney cancer, liver cancer, prostate cancer, colorectal cancer, esophageal cancer, testicular cancer, gynecological cancer, thyroid cancer, colon cancer, and brain cancer. In one preferred embodiment, the cancer is in a human sensitive to bleeding events. Preferably, the bleeding event is selected from the group consisting of subdural hematoma, gastrointestinal bleeding, hematuria, post-procedural hemorrhage, bruising, and petechiae. In one preferred embodiment, the cancer is selected from the group consisting of bladder cancer, squamous cell carcinoma including head and neck cancer, pancreatic ductal adenocarcinoma (PDA), pancreatic cancer, colon carcinoma, mammary carcinoma, breast cancer, fibrosarcoma, mesothelioma, renal

Efficacy of the compounds and combinations of compounds described herein in treating, preventing and/or managing the indicated diseases or disorders can be tested using various models known in the art. For example, models for determining efficacy of treatments for pancreatic cancer are described in Herreros-Villanueva, et al. World J. Gastroenterol. 2012, 18, 1286-1294. Models for determining efficacy of treatments for breast cancer are described e.g. in A. Fantozzi, Breast Cancer Res. 2006, 8, 212. Models for determining efficacy of treatments for ovarian cancer are described e.g. in Mullany et al., Endocrinology 2012, 153, 1585-92; and Fong et al., J. Ovarian Res. 2009, 2, 12. Models for determining efficacy of treatments for melanoma are described e.g. in Damsky et al., Pigment Cell & Melanoma Res. 2010, 23, 853–859. Models for determining efficacy of treatments for lung cancer are described e.g. in Meuwissen et al., Genes & Development, 2005, 19, 643-664. Models for determining efficacy of treatments for lung cancer are described e.g. in Kim, Clin. Exp. Otorhinolaryngol. 2009, 2, 55-60; and Sano, Head Neck Oncol. 2009, 1, 32. Models for determining efficacy of treatments for colorectal cancer, including the CT26 model, are described below in the examples.

Efficacy of the compounds and combinations of compounds described herein in treating, preventing and/or managing other indicated diseases or disorders described here can also be tested using various models known in the art. Efficacy in treating, preventing and/or
managing asthma can be assessed using the ova induced asthma model described, for example, in Lee et al., *J. Allergy Clin. Immunol*. 2006, 118, 403-9. Efficacy in treating, preventing and/or managing arthritis (e.g., rheumatoid or psoriatic arthritis) can be assessed using the autoimmune animal models described in, for example, Williams et al., *Chem. Biol*. 2010, 17, 123-34, WO 2009/088986, WO 2009/088880, and WO 2011/008302. Efficacy in treating, preventing and/or managing psoriasis can be assessed using transgenic or knockout mouse model with targeted mutations in epidermis, vasculature or immune cells, mouse model resulting from spontaneous mutations, and immuno-deficient mouse model with xenotransplantation of human skin or immune cells, all of which are described, for example, in Boehncke et al., *Clinics in Dermatology*, 2007, 25, 596-605. Efficacy in treating, preventing and/or managing fibrosis or fibrotic conditions can be assessed using the unilateral ureteral obstruction model of renal fibrosis, which is described, for example, in Chevalier et al., *Kidney International* 2009, 75, 1145-1152; the bleomycin induced model of pulmonary fibrosis described in, for example, Moore et al., *Am. J. Physiol. Lung. Cell. Mol. Physiol*. 2008, 294, L152-L160; a variety of liver/biliary fibrosis models described in, for example, Chuang et al., *Clin. Liver Dis*. 2008, 12, 333-347 and Omenetti et al., *Laboratory Investigation*, 2007, 87, 499-514 (biliary duct-ligated model); or any of a number of myelofibrosis mouse models such as described in Varicchio et al., *Expert Rev. Hematol*. 2009, 2, 315-334. Efficacy in treating, preventing and/or managing scleroderma can be assessed using a mouse model induced by repeated local injections of bleomycin described, for example, in Yamamoto et al., *J. Invest. Dermatol*. 1999, 112, 456-462. Efficacy in treating, preventing and/or managing dermatomyositis can be assessed using a myositis mouse model induced by immunization with rabbit myosin as described, for example, in Phyanagi et al., *Arthritis & Rheumatism*, 2009, 60(10), 3118-3127. Efficacy in treating, preventing and/or managing lupus can be assessed using various animal models described, for example, in Ghoreishi et al., *Lupus*, 2009, 19, 1029-1035; Ohl et al., *J. Biomed. & Biotechnol.*, Article ID 432595 (2011); Xia et al., *Rheumatology*, 2011, 50, 2187-2196; Pau et al., *PLoS ONE*, 2012, 7(5), e36761; Mustafa et al., *Toxicology*, 2011, 90, 156-168; Ichikawa et al., *Arthritis & Rheumatism*, 2012, 62(2), 493-503; Rankin et al., *J. Immunology*, 2012, 188, 1656-1667. Efficacy in treating, preventing and/or managing Sjögren’s syndrome can be assessed using various mouse models described, for example, in Chiorini et al., *J. Autoimmunity*, 2009, 33, 190-196.
Methods of Treating Patients Sensitive to Bleeding Events

In selected embodiments, the invention provides a method of treating a cancer in a human sensitive to bleeding events, comprising the step of administering a therapeutically effective dose of a BTK inhibitor, or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof, and a CDK-4/6 inhibitor, or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof. In a preferred embodiment, the invention provides a method of treating a cancer in a human sensitive to bleeding events, comprising the step of administering a therapeutically effective dose of a BTK inhibitor, wherein the BTK inhibitor is Formula (XVIII), or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof. In some embodiments, the invention provides a method of treating a hyperproliferative disorder, such as a cancer or an inflammatory, immune, or autoimmune disease, in a human intolerant to ibrutinib.

In an embodiment, the invention provides a method of treating a cancer in a human sensitive to bleeding events, comprising the step of administering a therapeutically effective dose of a BTK inhibitor, wherein the BTK inhibitor is Formula (XVIII), or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof, and a CDK-4/6 inhibitor, or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof, further comprising the step of administering a therapeutically effective dose of an anticoagulant or antiplatelet active pharmaceutical ingredient.

In selected embodiments, the invention provides a method of treating a cancer in a human sensitive to bleeding events, comprising the step of administering a therapeutically effective dose of a BTK inhibitor, wherein the BTK inhibitor is Formula (XVIII), and wherein the cancer is selected from the group consisting of bladder cancer, squamous cell carcinoma including head and neck cancer, pancreatic ductal adenocarcinoma (PDA), pancreatic cancer, colon carcinoma, mammary carcinoma, breast cancer, fibrosarcoma, mesothelioma, renal cell carcinoma, lung carcinoma, thyroma, prostate cancer, colorectal cancer, ovarian cancer, acute myeloid leukemia, thymus cancer, brain cancer, squamous cell cancer, skin cancer, eye cancer, retinoblastoma, melanoma, intraocular melanoma, oral cavity and oropharyngeal cancers, gastric cancer, stomach cancer, cervical cancer, head, neck, renal cancer, kidney cancer, liver cancer, ovarian cancer, prostate cancer, colorectal cancer, esophageal cancer, testicular cancer, gynecological cancer, thyroid cancer, aquired immune deficiency syndrome (AIDS)-related

[00965] In selected embodiments, the invention provides a method of treating a cancer in a human sensitive to platelet-mediated thrombosis comprising the step of administering a therapeutically effective dose of a BTK inhibitor, wherein the BTK inhibitor is Formula (XVIII), or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof, and a CDK-4/6 inhibitor, or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof.

[00966] In selected embodiments, the BTK inhibitor and the anticoagulant or the antiplatelet active pharmaceutical ingredient are administered sequentially. In selected embodiments, the BTK inhibitor and the anticoagulant or the antiplatelet active pharmaceutical ingredient are administered concomittently. In selected embodiments, the BTK inhibitor is administered before the anticoagulant or the antiplatelet active pharmaceutical ingredient. In selected embodiments, the BTK inhibitor is administered after the anticoagulant or the antiplatelet active pharmaceutical ingredient. In selected embodiments, a CDK-4/6 inhibitor is co-administered with the BTK inhibitor and the anticoagulant or the antiplatelet active pharmaceutical ingredient at the same time or at different times.

[00967] Selected anti-platelet and anticoagulant active pharmaceutical ingredients for use in the methods of the present invention include, but are not limited to, cyclooxygenase inhibitors (e.g., aspirin), adenosine diphosphate (ADP) receptor inhibitors (e.g., clopidogrel and ticlopidine), phosphodiesterase inhibitors (e.g., cilostazol), glycoprotein IIb/IIIa inhibitors (e.g., abciximab, eptifibatide, and tirofiban), adenosine reuptake inhibitors (e.g., dipyridamole), and acetylsalicylic acid (aspirin). In other embodiments, examples of anti-platelet active pharmaceutical ingredients for use in the methods of the present invention include anagrelide, aspirin/extended-release
dipyridamole, cilostazol, clopidogrel, dipyridamole, prasugrel, ticagrelor, ticlopidine, vorapaxar, tirofiban HCl, eptifibatide, abciximab, argatroban, bivalirudin, dalteparin, desirudin, enoxaparin, fondaparinux, heparin, lepirudin, apixaban, dabigatran etexilate mesylate, rivaroxaban, and warfarin.

[00968] In an embodiment, the invention includes a method of treating a cancer, comprising the step of orally administering, to a human in need thereof, a Bruton’s tyrosine kinase (BTK) inhibitor, wherein the BTK inhibitor is (S)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, and a PD-1 inhibitor or a PD-L1 inhibitor, or antigen-binding fragments, variants, or conjugates thereof, further comprising the step of administering a therapeutically effective dose of an anticoagulant or antiplatelet active pharmaceutical ingredient, wherein the anticoagulant or antiplatelet active pharmaceutical ingredient is selected from the group consisting of acenocoumarol, anagrelide, anagrelide hydrochloride, abciximab, aloxiprin, antithrombin, apixaban, argatroban, aspirin, aspirin with extended-release dipyridamole, beraprost, betrixaban, bivalirudin, carbasalate calcium, cilostazol, clopidogrel, clopidogrel bisulfate, cloricromen, dabigatran etexilate, darexaban, dalteparin, dalteparin sodium, desirudin, edoxaban, enoxaparin, enoxaparin sodium, eptifibatide, fondaparinux, fondaparinux sodium, heparin, heparin sodium, heparin calcium, idraparinux, idraparinux sodium, iloprost, indobufen, lepirudin, low molecular weight heparin, melagatran, nadroparin, otamixaban, parnaparin, phenindione, phenprocoumon, prasugrel, picotamide, prostacyclin, ramatroban, reviparin, rivaroxaban, sulodexide, terutroban, terutroban sodium, ticagrelor, ticlopidine, ticlopidine hydrochloride, tinzaparin, tinzaparin sodium, tirofiban, tirofiban hydrochloride, treprostinil, treprostinil sodium, triflusal, vorapaxar, warfarin, warfarin sodium, ximelagatran, salts thereof, solvates thereof, hydrates thereof, and combinations thereof.

[00969] In selected embodiments, the invention provides a method of treating a cancer in a human sensitive to platelet-mediated thrombosis, comprising the step of administering a therapeutically effective dose of a BTK inhibitor, or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof. In a preferred embodiment, the invention
provides a method of treating a cancer in a human sensitive to platelet-mediated thrombosis, comprising the step of administering a therapeutically effective dose of a BTK inhibitor, wherein the BTK inhibitor is Formula (XVIII), or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof. In a preferred embodiment, the invention provides a method of treating a cancer in a human sensitive to platelet-mediated thrombosis, comprising the step of administering a therapeutically effective dose of a BTK inhibitor, wherein the BTK inhibitor is Formula (XVIII), or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof, further comprising the step of administering a therapeutically effective dose of an anticoagulant or antiplatelet agent.

[00970] In selected embodiments, the invention provides a method of treating a cancer in a human with a history of thrombosis, comprising the step of administering a therapeutically effective dose of a BTK inhibitor, wherein the BTK inhibitor is Formula (XVIII), or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof, further comprising the step of administering a therapeutically effective dose of an anticoagulant or antiplatelet agent, wherein the anticoagulant or antiplatelet agent is selected from the group consisting of clopidogrel, prasugrel, ticagrelor, ticlopidine, warfarin, acenocoumarol, dicumarol, phenprocoumon, heparin, low molecular weight heparin, fondaparinux, and idraparinux.

[00971] In selected embodiments, the invention provides a method of treating a cancer in a human sensitive to platelet-mediated thrombosis, comprising the step of administering a therapeutically effective dose of a BTK inhibitor, wherein the BTK inhibitor is Formula (XVIII), and wherein the cancer is selected from the group consisting of bladder cancer, squamous cell carcinoma including head and neck cancer, pancreatic ductal adenocarcinoma (PDA), pancreatic cancer, colon carcinoma, mammary carcinoma, breast cancer, fibrosarcoma, mesothelioma, renal cell carcinoma, lung carcinoma, thyoma, prostate cancer, colorectal cancer, ovarian cancer, acute myeloid leukemia, thymus cancer, brain cancer, squamous cell cancer, skin cancer, eye cancer, retinoblastoma, melanoma, intraocular melanoma, oral cavity and oropharyngeal cancers, gastric cancer, stomach cancer, cervical cancer, head, neck, renal cancer, kidney cancer, liver cancer, ovarian cancer, prostate cancer, colorectal cancer, esophageal cancer, testicular cancer, gynecological cancer, thyroid cancer, acquired immune deficiency syndrome (AIDS)-related cancers (e.g., lymphoma and Kaposi’s sarcoma), viral-induced cancer, glioblastoma, esophageal tumors, hematological neoplasms, non-small-cell lung cancer, chronic myelocytic leukemia,

[00972] In selected embodiments, the invention provides a method of treating a cancer in a human sensitive to platelet-mediated thrombosis comprising the step of administering a therapeutically effective dose of a BTK inhibitor, or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof. In selected embodiments, the invention provides a method of treating a cancer in a human sensitive to platelet-mediated thrombosis, method of treating a cancer in a human with a history of thrombosis, comprising the step of administering a therapeutically effective dose of a BTK inhibitor, wherein the BTK inhibitor is a compound of Formula (XVIII) or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof.

[00973] In selected embodiments, the BTK inhibitor and the anticoagulant or the antiplatelet agent are administered sequentially. In selected embodiments, the BTK inhibitor and the anticoagulant or the antiplatelet agent are administered concomittently. In selected embodiments, the BTK inhibitor is administered before the anticoagulant or the antiplatelet agent. In selected embodiments, the BTK inhibitor is administered after the anticoagulant or the antiplatelet agent.

[00974] Preferred anti-platelet and anticoagulant agents for use in the methods of the present invention include, but are not limited to, cyclooxygenase inhibitors (e.g., aspirin), adenosine diphosphate (ADP) receptor inhibitors (e.g., clopidogrel and ticlopidine), phosphodiesterase inhibitors (e.g., cilostazol), glycoprotein IIb/IIIa inhibitors (e.g., abciximab, eptifibatide, and tirofiban), adenosine reuptake inhibitors (e.g., dipyridamole), and acetylsalicylic acid (aspirin). In other embodiments, examples of anti-platelet agents for use in the methods of the present invention include anagrelide, aspirin/extended-release dipyridamole, cilostazol, clopidogrel, dipyridamole, prasugrel, ticagrelor, ticlopidine, vorapaxar, tirofiban HCl, eptifibatide, abciximab, argatroban, bivalirudin, dalteparin, desirudin, enoxaparin, fondaparinux, heparin, lepirudin,
apixaban, dabigatran etexilate mesylate, rivaroxaban, and warfarin.

Combinations of BTK Inhibitors, PI3K Inhibitors, JAK-2 Inhibitors, and/or CDK4/6 Inhibitors with Anti-CD20 Antibodies

[00975] The BTK inhibitors of the present invention and combinations of the BTK inhibitors with PI3K inhibitors, JAK-2 inhibitors, PD-1 inhibitors, and/or CDK4/6 inhibitors may also be safely co-administered with immunotherapeutic antibodies such as the anti-CD20 antibodies rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, and ibritumomab, and or antigen-binding fragments, derivatives, conjugates, variants, and radioisotope-labeled complexes thereof, which may be given alone or with conventional chemotherapeutic active pharmaceutical ingredients such as those described herein. The CD20 antigen also called human B-lymphocyte-restricted differentiation antigen, Bp35, or B1) is found on the surface of normal “pre-B” and mature B lymphocytes, including malignant B lymphocytes. Nadler, et al., J. Clin. Invest. 1981, 67, 134-40; Stashenko, et al., J. Immunol. 1980, 139, 3260-85. The CD20 antigen is a glycosylated integral membrane protein with a molecular weight of approximately 35 kD. Tedder, et al., Proc. Natl. Acad. Sci. USA, 1988, 85, 208-12. CD20 is also expressed on most B cell non-Hodgkin's lymphoma cells, but is not found on hematopoietic stem cells, pro-B cells, normal plasma cells, or other normal tissues. Anti-CD20 antibodies are currently used as therapies for many hematological malignancies, including indolent NHL, aggressive NHL, and CLL/SLL. Lim, et. al., Haematologica 2010, 95, 135-43; Beers, et. al., Sem. Hematol. 2010, 47, 107-14; and Klein, et al., mAbs 2013, 5, 22-33.

[00976] In an embodiment, the invention provides a method of treating a hematological malignancy or a solid tumor cancer in a human comprising the step of administering to said human a BTK inhibitor of Formula (XVIII), or a pharmacologically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, and further comprising the step of administering an anti-CD20 antibody, wherein the anti-CD20 antibody is a monoclonal antibody or an antigen-binding fragment, derivative, conjugate, variant, or radioisotope-labeled complex thereof. In an embodiment, the invention provides a method of treating a hematological malignancy or a solid tumor cancer in a human comprising the step of administering to said human a BTK inhibitor of Formula (XVIII), or a pharmacologically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, and further comprising the step of administering an anti-CD20 antibody, wherein the anti-CD20 antibody is an anti-CD20 monoclonal antibody or an antigen-binding
fragment, derivative, conjugate, variant, or radioisotope-labeled complex thereof, and wherein the anti-CD20 antibody specifically binds to human CD20 with a $K_d$ selected from the group consisting of $1 \times 10^{-7}$ M or less, $5 \times 10^{-8}$ M or less, $1 \times 10^{-8}$ M or less, and $5 \times 10^{-9}$ M or less. Anti-CD20 monoclonal antibodies are classified as Type I or Type II, as described in Klein, et al., mAbs 2013, 5, 22-33. Type I anti-CD20 monoclonal antibodies are characterized by binding to the Class I epitope, localization of CD20 to lipid rafts, high complement-dependent cytotoxicity, full binding capacity, weak homotypic aggregation, and moderate cell death induction. Type II anti-CD20 monoclonal antibodies are characterized by binding to the Class I epitope, a lack of localization of CD20 to lipid rafts, low complement-dependent cytotoxicity, half binding capacity, homotypic aggregation, and strong cell death induction. Both Type I and Type II anti-CD20 monoclonal antibodies exhibit antibody-dependent cytotoxicity (ADCC) and are thus useful with BTK inhibitors described herein. Type I anti-CD20 monoclonal antibodies include but are not limited to rituximab, ocrelizumab, and ofatumumab. Type II anti-CD20 monoclonal antibodies include but are not limited to obinutuzumab and tositumomab.

[00977] In an embodiment, the invention provides a method of treating a hematological malignancy or a solid tumor cancer in a human comprising the step of administering to said human a BTK inhibitor of Formula (XVIII), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, and further comprising the step of administering an anti-CD20 antibody, wherein the anti-CD20 antibody is a monoclonal antibody or an antigen-binding fragment, derivative, conjugate, variant, or radioisotope-labeled complex thereof. In an embodiment, the invention provides a method of treating a hematological malignancy or a solid tumor cancer in a human comprising the step of administering to said human a BTK inhibitor of Formula (XVIII), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, and further comprising the step of administering an anti-CD20 antibody, wherein the anti-CD20 antibody is an anti-CD20 monoclonal antibody or an antigen-binding fragment, derivative, conjugate, variant, or radioisotope-labeled complex thereof, and wherein the anti-CD20 antibody specifically binds to human CD20 with a $K_d$ selected from the group consisting of $1 \times 10^{-7}$ M or less, $5 \times 10^{-8}$ M or less, $1 \times 10^{-8}$ M or less, and $5 \times 10^{-9}$ M or less.

[00978] In an embodiment, the invention provides a method of treating a hematological malignancy or a solid tumor cancer in a human comprising the step of administering to said human a BTK inhibitor of Formula (XVIII), or a pharmaceutically acceptable salt or ester,
prodrug, cocrystal, solvate or hydrate thereof, and further comprising the step of administering an Type I anti-CD20 antibody, or an antigen-binding fragment, derivative, conjugate, variant, or radioisotope-labeled complex thereof. In an embodiment, the invention provides a method of treating a hematological malignancy or a solid tumor cancer in a human comprising the step of administering to said human a BTK inhibitor of Formula (XVIII), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, and further comprising the step of administering an Type II anti-CD20 antibody, or an antigen-binding fragment, derivative, conjugate, variant, or radioisotope-labeled complex thereof. In an embodiment, the invention provides a method of treating a hematological malignancy or a solid tumor cancer in a human comprising the step of administering to said human a BTK inhibitor of Formula (XVIII), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, and a CDK4/6 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, and further comprising the step of administering an Type I anti-CD20 antibody, or an antigen-binding fragment, derivative, conjugate, variant, or radioisotope-labeled complex thereof. In an embodiment, the invention provides a method of treating a hematological malignancy or a solid tumor cancer in a human comprising the step of administering to said human a BTK inhibitor of Formula (XVIII), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, and a CDK4/6 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, and further comprising the step of administering an Type II anti-CD20 antibody, or an antigen-binding fragment, derivative, conjugate, variant, or radioisotope-labeled complex thereof.

[00979] In selected embodiments, the BTK inhibitors of the present invention and combinations of the BTK inhibitors with PI3K inhibitors, JAK-2 inhibitors, and/or CDK4/6 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof and the anti-CD20 monoclonal antibody are administered sequentially. In selected embodiments, the BTK inhibitors of the present invention and combinations of the BTK inhibitors with PI3K inhibitors, JAK-2 inhibitors, and/or CDK4/6 inhibitors and the anti-CD20 monoclonal antibody are administered concomitantly. In selected embodiments, the BTK inhibitors of the present invention and combinations of the BTK inhibitors with PI3K inhibitors, JAK-2 inhibitors, and/or CDK4/6 inhibitors is administered before the anti-CD20 monoclonal antibody. In selected embodiments, the BTK inhibitors of the present invention and combinations of the BTK
inhibitors with PI3K inhibitors, JAK-2 inhibitors, and/or CDK4/6 inhibitors is administered after the anticoagulant or the antiplatelet active pharmaceutical ingredient. In selected embodiments, the BTK inhibitors of the present invention and combinations of the BTK inhibitors with PI3K inhibitors, JAK-2 inhibitors, and/or CDK4/6 inhibitors and the anti-CD20 monoclonal antibody are administered over the same time period, and the BTK inhibitor administration continues after the anti-CD20 monoclonal antibody administration is completed.

[00980] In an embodiment, the anti-CD20 monoclonal antibody is rituximab, or an antigen-binding fragment, derivative, conjugate, variant, or radioisotope-labeled complex thereof. Rituximab is a chimeric murine-human monoclonal antibody directed against CD20, and its structure comprises an IgG1 kappa immunoglobulin containing murine light- and heavy-chain variable region sequences and human constant region sequences. Rituximab is composed of two heavy chains of 451 amino acids and two light chains of 213 amino acids. The amino acid sequence for the heavy chains of rituximab is set forth in SEQ ID NO:1. The amino acid sequence for the light chains of rituximab is set forth in SEQ ID NO:2. Rituximab is commercially available, and its properties and use in cancer and other diseases is described in more detail in Rastetter, et al., Ann. Rev. Med. 2004, 55, 477-503, and in Plosker and Figgett, Drugs, 2003, 63, 803-43. In an embodiment, the anti-CD20 monoclonal antibody is an anti-CD20 biosimilar monoclonal antibody approved by drug regulatory authorities with reference to rituximab. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 90% to SEQ ID NO:1. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 90% to SEQ ID NO:2. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 95% to SEQ ID NO:1. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 95% to SEQ ID NO:2. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 98% to SEQ ID NO:1. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 98% to SEQ ID NO:2. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 99% to SEQ ID NO:1. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 99% to SEQ ID NO:2.

[00981] In an embodiment, the anti-CD20 monoclonal antibody is obinutuzumab, or an antigen-
binding fragment, derivative, conjugate, variant, or radioisotope-labeled complex thereof. Obinutuzumab is also known as afutuzumab or GA-101. Obinutuzumab is a humanized monoclonal antibody directed against CD20. The amino acid sequence for the heavy chains of obinutuzumab is set forth in SEQ ID NO:3. The amino acid sequence for the light chains of obinutuzumab is set forth in SEQ ID NO:4. Obinutuzumab is commercially available, and its properties and use in cancer and other diseases is described in more detail in Robak, Cur. Opin. Investig. Drugs 2009, 10, 588-96. In an embodiment, the anti-CD20 monoclonal antibody is an anti-CD20 biosimilar monoclonal antibody approved by drug regulatory authorities with reference to obinutuzumab. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 90% to SEQ ID NO:3. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 90% to SEQ ID NO:4. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 95% to SEQ ID NO:3. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 95% to SEQ ID NO:4. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 98% to SEQ ID NO:3. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 98% to SEQ ID NO:4. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 99% to SEQ ID NO:3. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 99% to SEQ ID NO:4. In an embodiment, the anti-CD20 monoclonal antibody obinutuzumab is an immunoglobulin G1, anti-(human B-lymphocyte antigen CD20 (membrane-spanning 4-domains subfamily A member 1, B-lymphocyte surface antigen B1, Leu-16 or Bp35)), humanized mouse monoclonal obinutuzumab des-CH3107-K-γ1 heavy chain (222-219’)-disulfide with humanized mouse monoclonal obinutuzumab κ light chain dimer (228-228”:231-231")-bisdisulfide antibody.

[00982] In an embodiment, the anti-CD20 monoclonal antibody is ofatumumab, or an antigen-binding fragment, derivative, conjugate, variant, or radioisotope-labeled complex thereof. Ofatumumab is described in Cheson, J. Clin. Oncol. 2010, 28, 3525-30. The crystal structure of the Fab fragment of ofatumumab has been reported in Protein Data Bank reference 3GIZ and in Du, et al., Mol. Immunol. 2009, 46, 2419-2423. Ofatumumab is commercially available, and its preparation, properties, and use in cancer and other diseases are described in more detail in U.S.
Patent No. 8,529,202 B2, the disclosure of which is incorporated herein by reference. In an embodiment, the anti-CD20 monoclonal antibody is an anti-CD20 biosimilar monoclonal antibody approved by drug regulatory authorities with reference to ofatumumab. In an embodiment, the anti-CD20 monoclonal antibody has a variable heavy chain sequence identity of greater than 90% to SEQ ID NO:5. In an embodiment, the anti-CD20 monoclonal antibody has a variable light chain sequence identity of greater than 90% to SEQ ID NO:6. In an embodiment, the anti-CD20 monoclonal antibody has a variable heavy chain sequence identity of greater than 95% to SEQ ID NO:5. In an embodiment, the anti-CD20 monoclonal antibody has a variable light chain sequence identity of greater than 95% to SEQ ID NO:6. In an embodiment, the anti-CD20 monoclonal antibody has a variable heavy chain sequence identity of greater than 98% to SEQ ID NO:5. In an embodiment, the anti-CD20 monoclonal antibody has a variable light chain sequence identity of greater than 98% to SEQ ID NO:6. In an embodiment, the anti-CD20 monoclonal antibody has a Fab fragment heavy chain sequence identity of greater than 90% to SEQ ID NO:7. In an embodiment, the anti-CD20 monoclonal antibody has a Fab fragment light chain sequence identity of greater than 90% to SEQ ID NO:8. In an embodiment, the anti-CD20 monoclonal antibody has a Fab fragment heavy chain sequence identity of greater than 95% to SEQ ID NO:7. In an embodiment, the anti-CD20 monoclonal antibody has a Fab fragment light chain sequence identity of greater than 95% to SEQ ID NO:8. In an embodiment, the anti-CD20 monoclonal antibody has a Fab fragment heavy chain sequence identity of greater than 98% to SEQ ID NO:7. In an embodiment, the anti-CD20 monoclonal antibody has a Fab fragment light chain sequence identity of greater than 98% to SEQ ID NO:8. In an embodiment, the anti-CD20 monoclonal antibody has a Fab fragment heavy chain sequence identity of greater than 99% to SEQ ID NO:7. In an embodiment, the anti-CD20 monoclonal antibody has a Fab fragment light chain sequence identity of greater than 99% to SEQ ID NO:8. In an embodiment, the anti-CD20 monoclonal antibody ofatumumab is an immunoglobulin G1, anti-(human B-lymphocyte antigen CD20 (membrane-spanning 4-domains subfamily A member 1, B-lymphocyte surface antigen B1, Leu-16 or Bp35)); human monoclonal ofatumumab-CD20 γ1 heavy chain (225-214')-disulfide with human monoclonal ofatumumab-
CD20 κ light chain, dimer (231-231''-234-234'')-bisdisulfide antibody.

[00983] In an embodiment, the anti-CD20 monoclonal antibody is veltuzumab, or an antigen-binding fragment, derivative, conjugate, variant, or radioisotope-labeled complex thereof. Veltuzumab is also known as hA20. Veltuzumab is described in Goldenberg, et al., Leuk. Lymphoma 2010, 51, 747-55. In an embodiment, the anti-CD20 monoclonal antibody is an anti-CD20 biosimilar monoclonal antibody approved by drug regulatory authorities with reference to veltuzumab. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 90% to SEQ ID NO:9. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 90% to SEQ ID NO:10. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 95% to SEQ ID NO:9. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 95% to SEQ ID NO:10. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 98% to SEQ ID NO:9. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 98% to SEQ ID NO:10. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 99% to SEQ ID NO:9. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 99% to SEQ ID NO:10. In an embodiment, the anti-CD20 monoclonal antibody ofatumumab is an immunoglobulin G1, anti-(human B-lymphocyte antigen CD20 (membrane-spanning 4-domains subfamily A member 1, Leu-16, Bp35)); [218- arginine,360-glutamic acid,362-methionine]humanized mouse monoclonal hA20 γl heavy chain (224-213'')-disulfide with humanized mouse monoclonal hA20 κ light chain (230-230''-233-233'')-bisdisulfide dimer.

[00984] In an embodiment, the anti-CD20 monoclonal antibody is tositumomab, or an antigen-binding fragment, derivative, conjugate, variant, or radioisotope-labeled complex thereof. In an embodiment, the anti-CD20 monoclonal antibody is $^{131}$I-labeled tositumomab. In an embodiment, the anti-CD20 monoclonal antibody is an anti-CD20 biosimilar monoclonal antibody approved by drug regulatory authorities with reference to tositumomab. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 90% to SEQ ID NO:11. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 90% to SEQ ID NO:12. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 95% to SEQ ID
NO:11. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 95% to SEQ ID NO:12. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 98% to SEQ ID NO:11. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 98% to SEQ ID NO:12. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 99% to SEQ ID NO:11. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 99% to SEQ ID NO:12.

[00985] In an embodiment, the anti-CD20 monoclonal antibody is ibritumomab, or an antigen-binding fragment, derivative, conjugate, variant, or radioisotope-labeled complex thereof. The active form of ibritumomab used in therapy is ibritumomab tiuxetan. When used with ibritumomab, the chelator tiuxetan (diethylene triamine pentaacetic acid) is complexed with a radioactive isotope such as ⁹⁰⁸ Y or ¹¹¹ In. In an embodiment, the anti-CD20 monoclonal antibody is ibritumomab tiuxetan, or radioisotope-labeled complex thereof. In an embodiment, the anti-CD20 monoclonal antibody is an anti-CD20 biosimilar monoclonal antibody approved by drug regulatory authorities with reference to tositumomab. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 90% to SEQ ID NO:13. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 90% to SEQ ID NO:14. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 95% to SEQ ID NO:13. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 95% to SEQ ID NO:14. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 98% to SEQ ID NO:13. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 98% to SEQ ID NO:14. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 99% to SEQ ID NO:13. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 99% to SEQ ID NO:14.

[00986] In an embodiment, an anti-CD20 antibody selected from the group consisting of obinutuzumab, ofatumumab, veltuzumab, tositumomab, and ibritumomab, and or antigen-binding fragments, derivatives, conjugates, variants, and radioisotope-labeled complexes thereof, is administered to a subject by infusion in a dose selected from the group consisting of about 10
mg, about 20 mg, about 25 mg, about 50 mg, about 75 mg, 100 mg, about 200 mg, about 300 mg, about 400 mg, about 500 mg, about 600 mg, about 700 mg, about 800 mg, about 900 mg, about 1000 mg, about 1100 mg, about 1200 mg, about 1300 mg, about 1400 mg, about 1500 mg, about 1600 mg, about 1700 mg, about 1800 mg, about 1900 mg, and about 2000 mg. In an embodiment, the anti-CD20 antibody is admininstered weekly. In an embodiment, the anti-CD20 antibody is admininstered every two weeks. In an embodiment, the anti-CD20 antibody is admininstered every three weeks. In an embodiment, the anti-CD20 antibody is admininstered monthly. In an embodiment, the anti-CD20 antibody is administered at a lower initial dose, which is escalated when administered at subsequent intervals admininstered monthly. For example, the first infusion can deliver 300 mg of anti-CD20 antibody, and subsequent weekly doses could deliver 2,000 mg of anti-CD20 antibody for eight weeks, followed by monthly doses of 2,000 mg of anti-CD20 antibody. During any of the foregoing embodiments, the BTK inhibitors of the present invention and combinations of the BTK inhibitors with PI3K inhibitors, JAK-2 inhibitors, PD-1 inhibitors, and/or PD-L1 inhibitors may be administered daily, twice daily, or at different intervals as described above, at the dosages described above.

[00987] In an embodiment, the invention provides a kit comprising a composition comprising a BTK inhibitors of the present invention and combinations of the BTK inhibitors with PI3K inhibitors, JAK-2 inhibitors, PD-1 inhibitors, and/or PD-L1 inhibitors and a composition comprising an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, and ibritumomab, or an antigen-binding fragment, derivative, conjugate, variant, or radioisotope-labeled complex thereof, for use in the treatment of CLL or SLL, hematological malignancies, B cell malignancies, or any of the other diseases described herein. The compositions are typically both pharmaceutical compositions. The kit is for use in co-administration of the anti-CD20 antibody and the BTK inhibitor, either simultaneously or separately, in the treatment of CLL or SLL, hematological malignancies, B cell malignancies, or any of the other diseases described herein.

[00988] The anti-CD20 antibody sequences referenced in the foregoing are summarized in Table 2.

TABLE 2. Anti-CD20 antibody sequences.
<table>
<thead>
<tr>
<th>Identifier</th>
<th>Sequence (One-Letter Amino Acid Symbols)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEQ ID NO:1</td>
<td>GQVGLQGEGAE LVKFGSVKVM SCKASGTFF STHNNWVQKQ PGRCELWNIGA IYPGNDTYS 69</td>
</tr>
<tr>
<td>rituximab</td>
<td>NQKPKRATL TAGHESSAAH MSLYSEIY LGYCEKTVTVS 128</td>
</tr>
<tr>
<td>heavy chain</td>
<td>AASTKPSVPL APAAKSSTSS GQTAALICLV KDYPFPFTVS SWNSSGALIGS VHTFPFVLRQ 189</td>
</tr>
<tr>
<td>SEQ ID NO:2</td>
<td>QVQLVQGSEGAE RIMPSNVKMEV MLYSEIY LGYCEKTVTVS 69</td>
</tr>
<tr>
<td>rituximab</td>
<td>FGSGSSGHTD SLTIIRVEEA DAATYYQCGW TSNPYTFGGQ TKELEIKRTVA APADVFFPFP 129</td>
</tr>
<tr>
<td>light chain</td>
<td>DEQKSSGATAS VYCLLANTFY REARYQKVRGD NALQSGNSQEV SVTEEQKSDS TYSLSLSTTI 180</td>
</tr>
<tr>
<td>SKKYEDKKEVK YACETIVQGQL SPVTSKSNR GC 213</td>
<td></td>
</tr>
<tr>
<td>SEQ ID NO:3</td>
<td>GQVGLQGEGAE LVKFGSVKVM SCKASGTFF STHNNWVQKQ PGRCELWNIGA IYPGNDTYS 69</td>
</tr>
<tr>
<td>obinutuzumab</td>
<td>NQKPKRATL TAGHESSAAH MSLYSEIY LGYCEKTVTVS 128</td>
</tr>
<tr>
<td>heavy chain</td>
<td>AASTKPSVPL APAAKSSTSS GQTAALICLV KDYPFPFTVS SWNSSGALIGS VHTFPFVLRQ 189</td>
</tr>
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<td>SEQ ID NO:4</td>
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</tr>
<tr>
<td>obinutuzumab</td>
<td>FGSGSSGHTD SLTIIRVEEA DAATYYQCGW TSNPYTFGGQ TKELEIKRTVA APADVFFPFP 129</td>
</tr>
<tr>
<td>variable chain</td>
<td>DEQKSSGATAS VYCLLANTFY REARYQKVRGD NALQSGNSQEV SVTEEQKSDS TYSLSLSTTI 180</td>
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<td>SKKYEDKKEVK YACETIVQGQL SPVTSKSNR GC 213</td>
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</tr>
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<td>ofatumumab</td>
<td>NQKPKRATL TAGHESSAAH MSLYSEIY LGYCEKTVTVS 128</td>
</tr>
<tr>
<td>heavy chain</td>
<td>AASTKPSVPL APAAKSSTSS GQTAALICLV KDYPFPFTVS SWNSSGALIGS VHTFPFVLRQ 189</td>
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<td>SEQ ID NO:6</td>
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<td>ofatumumab</td>
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</tr>
<tr>
<td>Fab fragment</td>
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</tr>
<tr>
<td>SKKYEDKKEVK YACETIVQGQL SPVTSKSNR GC 213</td>
<td></td>
</tr>
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<td>SEQ ID NO:7</td>
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<td>ofatumumab</td>
<td>NQKPKRATL TAGHESSAAH MSLYSEIY LGYCEKTVTVS 128</td>
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<tr>
<td>variable chain</td>
<td>AASTKPSVPL APAAKSSTSS GQTAALICLV KDYPFPFTVS SWNSSGALIGS VHTFPFVLRQ 189</td>
</tr>
<tr>
<td>SEQ ID NO:8</td>
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<tr>
<td>ofatumumab</td>
<td>FGSGSSGHTD SLTIIRVEEA DAATYYQCGW TSNPYTFGGQ TKELEIKRTVA APADVFFPFP 129</td>
</tr>
<tr>
<td>Fab fragment</td>
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<tr>
<td>SKKYEDKKEVK YACETIVQGQL SPVTSKSNR GC 213</td>
<td></td>
</tr>
<tr>
<td>SEQ ID NO:9</td>
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<tr>
<td>veltuzumab</td>
<td>NQKPKRATL TAGHESSAAH MSLYSEIY LGYCEKTVTVS 128</td>
</tr>
<tr>
<td>heavy chain</td>
<td>AASTKPSVPL APAAKSSTSS GQTAALICLV KDYPFPFTVS SWNSSGALIGS VHTFPFVLRQ 189</td>
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<tr>
<td>veltuzumab</td>
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</tr>
<tr>
<td>Fab fragment</td>
<td>DEQKSSGATAS VYCLLANTFY REARYQKVRGD NALQSGNSQEV SVTEEQKSDS TYSLSLSTTI 180</td>
</tr>
<tr>
<td>SKKYEDKKEVK YACETIVQGQL SPVTSKSNR GC 213</td>
<td></td>
</tr>
<tr>
<td>SEQ ID NO:11</td>
<td>QVQLVQGSEGAE RIMPSNVKMEV MLYSEIY LGYCEKTVTVS 69</td>
</tr>
<tr>
<td>tositumomab</td>
<td>NQKPKRATL TAGHESSAAH MSLYSEIY LGYCEKTVTVS 128</td>
</tr>
<tr>
<td>heavy chain</td>
<td>AASTKPSVPL APAAKSSTSS GQTAALICLV KDYPFPFTVS SWNSSGALIGS VHTFPFVLRQ 189</td>
</tr>
<tr>
<td>SEQ ID NO:12</td>
<td>QVQLVQGSEGAE RIMPSNVKMEV MLYSEIY LGYCEKTVTVS 69</td>
</tr>
<tr>
<td>tositumomab</td>
<td>FGSGSSGHTD SLTIIRVEEA DAATYYQCGW TSNPYTFGGQ TKELEIKRTVA APADVFFPFP 129</td>
</tr>
<tr>
<td>Fab fragment</td>
<td>DEQKSSGATAS VYCLLANTFY REARYQKVRGD NALQSGNSQEV SVTEEQKSDS TYSLSLSTTI 180</td>
</tr>
<tr>
<td>SKKYEDKKEVK YACETIVQGQL SPVTSKSNR GC 213</td>
<td></td>
</tr>
<tr>
<td>SEQ ID NO:13</td>
<td>QYQLVQGSEGAE RIMPSNVKMEV MLYSEIY LGYCEKTVTVS 69</td>
</tr>
<tr>
<td>ibritumomab</td>
<td>NQKPKRATL TAGHESSAAH MSLYSEIY LGYCEKTVTVS 128</td>
</tr>
<tr>
<td>heavy chain</td>
<td>AASTKPSVPL APAAKSSTSS GQTAALICLV KDYPFPFTVS SWNSSGALIGS VHTFPFVLRQ 189</td>
</tr>
</tbody>
</table>

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Combinations of BTK Inhibitors, PI3K Inhibitors, JAK-2 Inhibitors, PD-1 Inhibitors, and/or PD-L1 and PD-L2 Inhibitors with Chemotherapeutic Active Pharmaceutical Ingredients

The combinations of the BTK inhibitors with PI3K inhibitors, JAK-2 inhibitors, and/or CDK4/6 inhibitors may also be safely co-administered with chemotherapeutic active pharmaceutical ingredients such as gemcitabine and albumin-bound paclitaxel (nab-paclitaxel).

In an embodiment, the invention provides a method of treating a hematological malignancy or a solid tumor cancer in a human comprising the step of administering to said human a BTK inhibitors, a PI3K inhibitor, a JAK-2 inhibitor, and/or a CDK4/6 inhibitor, and further comprising the step of administering a therapeutically-effective amount of gemcitabine, or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof. In an embodiment, the invention provides a method of treating a hematological malignancy or a solid tumor cancer in a human comprising the step of administering to said human a BTK inhibitor of Formula (XVIII), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, and further comprising the step of administering a therapeutically-effective amount of gemcitabine, or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof. In an embodiment, the solid tumor cancer in any of the foregoing embodiments is pancreatic cancer.

In an embodiment, the invention provides a method of treating a hematological malignancy or a solid tumor cancer in a human comprising the step of administering to said human a BTK inhibitor, a PI3K inhibitor, and/or CDK4/6 inhibitor, and further comprising the step of administering a therapeutically-effective amount of a combination of fludarabine, cyclophosphamide, and rituximab (which collectively may be referred to as “FCR” or “FCR chemotherapy”). In an embodiment, the invention provides a method of treating a hematological malignancy or a solid tumor cancer in a human comprising the step of administering to said human BTK inhibitors, a PI3K inhibitor, and/or CDK4/6 inhibitors may also be safely co-administered with chemotherapeutic active pharmaceutical ingredients such as gemcitabine and albumin-bound paclitaxel (nab-paclitaxel).
human a BTK inhibitor of Formula (XVIII), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, and further comprising the step of administering a therapeutically-effective amount of FCR chemotherapy. In an embodiment, the invention provides a hematological malignancy or a solid tumor cancer comprising the step of administering to said human a BTK inhibitor and a CDK4/6 inhibitor, and further comprising the step of administering a therapeutically-effective amount of FCR chemotherapy. FCR chemotherapy has been shown to improve survival in patients with cancer, as described in Hallek, et al., Lancet. 2010, 376, 1164-1174.

[00991] In an embodiment, the invention provides a method of treating a hematological malignancy or a solid tumor cancer in a human comprising the step of administering to said human a BTK inhibitor, a PI3K inhibitor, and/or a CDK4/6 inhibitor, and further comprising the step of administering a therapeutically-effective amount of a combination of rituximab, cyclophosphamide, doxorubicin hydrochloride (also referred to as hydroxydaunomycin), vincristine sulfate (also referred to as oncovin), and prednisone (which collectively may be referred to as “R-CHOP” or “R-CHOP chemotherapy”). In an embodiment, the invention provides a method of treating a hematological malignancy or a solid tumor cancer in a human comprising the step of administering to said human a BTK inhibitor of Formula (XVIII), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, and further comprising the step of administering a therapeutically-effective amount of R-CHOP chemotherapy. In an embodiment, the invention provides a hematological malignancy or a solid tumor cancer comprising the step of administering to said human a BTK inhibitor and/or a CDK4/6 inhibitor, and further comprising the step of administering a therapeutically-effective amount of R-CHOP therapy. R-CHOP chemotherapy has been shown to improve the 10-year progression-free and overall survival rates for patients with cancer, as described in Sehn, Blood, 2010, 116, 2000-2001.

[00992] In an embodiment, the invention provides a method of treating a hematological malignancy or a solid tumor cancer in a human comprising the step of administering to said human a BTK inhibitors, a PI3K inhibitor, a JAK-2 inhibitor, and/or a CDK4/6 inhibitor, and further comprising the step of administering a therapeutically-effective amount of nab-paclitaxel. In an embodiment, the invention provides a method of treating a hematological malignancy or a solid tumor cancer in a human comprising the step of administering to said human a BTK
inhibitor of Formula (XVIII), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, and further comprising the step of administering a therapeutically-effective amount of nab-paclitaxel. In an embodiment, the solid tumor cancer in any of the foregoing embodiments is pancreatic cancer.

EXAMPLES

[00993] The embodiments encompassed herein are now described with reference to the following examples. These examples are provided for the purpose of illustration only and the disclosure encompassed herein should in no way be construed as being limited to these examples, but rather should be construed to encompass any and all variations which become evident as a result of the teachings provided herein.

Example 1 – Synergistic Combination of a BTK inhibitor and a PI3K-δ inhibitor

[00994] Ficoll purified mantle cell lymphoma (MCL) cells (2x10⁵) isolated from bone marrow or peripheral blood were treated with each drug alone and with six equimolar concentrations of a BTK inhibitor (Formula (XVIII)) and a PI3K-δ inhibitor (Formula (IX)) ranging from 0.01 nM to 10 μM on 96-well plates in triplicate. Plated cells were then cultured in HS-5 conditioned media at 37°C with 5% CO₂. After 72 hours of culture, cell viability was determined using an (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium) (MTS) assay (Cell Titer 96, Promega). Viability data were used to generate cell viability curves for each drug alone and in combination for each sample. The potential synergy of the combination of the BTK inhibitor of Formula (XVIII) and the PI3K-δ inhibitor of Formula (IX) at a given equimolar concentration was determined using the median effect model as described in Chou TC, Talalay P. Quantitative analysis of dose-effect relationships: the combined effects of multiple drugs or enzyme inhibitors. Adv Enzyme Regul. 1984; 22: 27-55. The statistical modeling was run in R using a script that utilizes the median effect model as described in Lee JJ, Kong M, Ayers GD, Lotan R, Interaction index and different methods for determining drug interaction in combination therapy. J Biopharm Stat. 2007; 17(3): 461-80. A value of 1, less than 1, and greater than 1 using R defines an additive interaction, a synergistic interaction, and an antagonistic interaction, respectively. The Lee et al. method calculates a 95% confidence interval for each data point. For each viability curve, to be considered synergistic, a data point
must have an interaction index below 1 and the upper confidence interval must also be below 1.

In order to summarize and demonstrate collective synergy results, an interaction dot blot was generated for the primary patient samples.

[00995] A similar approach was utilized to study diffuse large B cell lymphoma (DLBCL) (TMD8) and MCL (MINO) cell lines. Cells were treated with each drug alone and with six equimolar concentrations of the BTK inhibitor of Formula (XVIII) and the PI3K-δ inhibitor of Formula (IX) ranging from 0.003 nM to 1.0 µM (for TMD8) or 0.03 nM to 10 µM (for MINO) on 96-well plates in triplicate. Plated cells were then cultured in standard conditioned media plus FBS at 37°C with 5% CO₂. After 72 hours of culture, viability was determined using an MTS assay (Cell Titer 96, Promega). Viability data were used to generate cell viability curves for each drug alone and in combination for each sample. The results of the experiments described in this example are shown in FIGS 1, 2, 3, and 4.
Example 2 – Synergistic Combination of a BTK inhibitor and a PI3K-δ inhibitor

Combination experiments were performed to determine the synergistic, additive, or antagonistic behavior of drug combinations using the Chou/Talalay method/algorithim by defining combination indexes for drug combinations. Information about experimental design for evaluation of synergy is described in e.g. Chou TC, Talalay P. Quantitative analysis of dose-effect relationships: the combined effects of multiple drugs or enzyme inhibitors. Adv. Enzyme Regul. 1984, 22, 27-55 and more generally in e.g.: Greco, W. R., Bravo, G., Parsons, J. C. The search for synergy: a critical review from a response surface perspective. Pharmacol. Rev. 1995, 47, 331-385. The study was performed using the BTK inhibitor of Formula (XVIII) and the PI3K-δ inhibitor of Formula (IX). Single agent activities were first determined in the various cell lines and subsequently, the combination indexes were established using equimolar ratios taking the single agent drug EC50s into consideration. For individual agents that displayed no single agent activity, equimolar ratios were used at fixed concentrations to establish combination indexes. The readout from 72 hour proliferation assays using Cell TiterGlo (ATP content of remaining cells) determined the fraction of cells that were effected as compared to untreated cells (Fa = fraction affected = (1- ((cells + inhibitor) – background signal) / ((cells + DMSO) – background signal)).

The combination index obtained was ranked according to Table 3.
TABLE 3. Combination Index (CI) Ranking Scheme

<table>
<thead>
<tr>
<th>Range of CI</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.1</td>
<td>Very strong synergism</td>
</tr>
<tr>
<td>0.1-0.3</td>
<td>Strong synergism</td>
</tr>
<tr>
<td>0.3-0.7</td>
<td>Synergism</td>
</tr>
<tr>
<td>0.7-0.85</td>
<td>Moderate synergism</td>
</tr>
<tr>
<td>0.85-0.9</td>
<td>Slight synergism</td>
</tr>
<tr>
<td>0.9-1.1</td>
<td>Nearly additive</td>
</tr>
<tr>
<td>1.1-1.2</td>
<td>Slight antagonism</td>
</tr>
<tr>
<td>1.2-1.45</td>
<td>Moderate antagonism</td>
</tr>
<tr>
<td>1.45-3.3</td>
<td>Antagonism</td>
</tr>
<tr>
<td>3.3-10</td>
<td>Strong antagonism</td>
</tr>
<tr>
<td>&gt;10</td>
<td>Very strong antagonism</td>
</tr>
</tbody>
</table>

[00998] The detailed results of the cell line studies for the BTK inhibitor of Formula (XVIII) and the PI3K-δ inhibitor of Formula (IX) are given in FIG. 5 to FIG. 37. The results of the cell line studies are summarized in Table 4.

TABLE 4. Summary of results of the combination of a BTK inhibitor with a PI3K-δ inhibitor (S = synergistic, A = additive, X = no effect).

<table>
<thead>
<tr>
<th>Cell Line</th>
<th>Indication</th>
<th>ED25</th>
<th>ED50</th>
<th>ED75</th>
<th>ED90</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ramos</td>
<td>Burkitt’s</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>Daudi</td>
<td>Burkitt’s</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>Mino</td>
<td>MCL</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>Pfeiffer</td>
<td>iNHL</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
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<tr>
<td>DOHH</td>
<td>iNHL</td>
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<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>REC-1</td>
<td>iNHL</td>
<td>S</td>
<td>S</td>
<td>A</td>
<td>A</td>
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<tr>
<td>U937</td>
<td>Myeloid</td>
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<td>S</td>
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<td>K562</td>
<td>CML</td>
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<td>ABC</td>
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<td>S</td>
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<td>B-ALL</td>
<td>S</td>
<td>A/S</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>
Example 3 – Synergistic Combination of a BTK inhibitor and the JAK-2 Inhibitor Ruxolitinib

[00999] Combination experiments were performed to determine the synergistic, additive, or antagonistic behavior of drug combinations using the methods described above in Example 2. The study was performed using the BTK inhibitor of Formula (XVIII) and the JAK-2 inhibitor of Formula XXX (ruxolitinib).

[001000] The detailed results of the cell line studies for the BTK inhibitor of Formula (XVIII) and the JAK-2 inhibitor of Formula XXX (ruxolitinib) are given in FIG. 38 to FIG. 65. The results of the cell line studies are summarized in Table 5.

TABLE 5. Summary of results of the combination of a BTK inhibitor with a JAK-2 inhibitor (S = synergistic, A = additive, X = no effect).

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</table>

Example 4 – Synergistic Combination of a BTK Inhibitor and a CDK4/6 Inhibitor

[001001] Following a similar protocol detailed in Examples 1-3, combination experiments involving the BTK inhibitor of Formula (XVIII) and the CDK4/6 inhibitor of Formula (100-I) were performed to determine the synergistic, additive, or antagonistic behavior of drug
combinations using the Chou/Talalay method and algorithm by defining combination indexes for drug combinations. In particular, each of the cell lines: Jeko (B cell lymphoma, mantle), Maver-1 (B cell lymphoma, mantle), Pfeiffer (Follicular lymphoma), SU-DHL-1 (DLBCL-ABC), SU-DHL-2 (DLBCL-ABC), TMD-8 (DLBCL-ABC), HBL-1 (DLBCL-ABC), and Raji (B lymphocyte, Burkitt's lymphoma) was treated with each of BTK inhibitor of Formula (XVIII) and 6-Acetyl-8-cyclopentyl-5-methyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (palbociclib; PD-0332991) alone and in combination with each other. Various concentrations of the BTK inhibitor of Formula (XVIII) and 6-Acetyl-8-cyclopentyl-5-methyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (palbociclib; PD-0332991) were used. The treated cells were cultured and their viability was determined using an MTS assay (Cell Titer 96, Promega). Viability data were used to generate cell viability curves for each drug alone and in combination for each sample. The results of the experiments described in this example are shown in FIG. 66 to FIG. 74.

Example 5 – BTK Inhibitory Effects on a Solid Tumor Microenvironment in an Orthotopic Pancreatic Cancer Model

[001002] An orthotopic pancreatic cancer model was used to investigate the therapeutic efficacy of the combination of the BTK inhibitor of Formula (XVIII) and the PI3K-δ inhibitor of Formula (IX) through treatment of the solid tumor microenvironment. Mice were dosed orally with 15 mg/kg of Formula (XVIII), 15 mg/kg of Formula (IX), or a combination of 15 mg/kg of both drugs.

[001003] Cell line derived from KrasG12D;Trp53R172H;Pdx1-Cre (KPC) mice were orthotopically implanted into the head of the pancreas after 35 passages. Based on the mice background from where the cell lines were generated, 1×10⁶ cells were injected in C57BL/6 mice. Throughout the experiment, animals were provided with food and water ad libitum and subjected to a 12-h dark/light cycle. Animal studies were performed in accordance with the U.S. Public Health Service "Guidelines for the Care and Use of Laboratory Animals" (IACUC). After euthanization, pancreatic tumors were dissected out, weighed and single cell suspensions were prepared for flow cytometry analysis.

[001004] Results of the experiments are shown in FIG. 75, which illustrates tumor growth suppression in the orthotopic pancreatic cancer model. The statistical p-value (presumption
against null hypothesis) is shown for each tested single agent and for the combination against the vehicle. The results show that all three treatments provide statistically significant reductions in tumor volume in the pancreatic cancer model.

[001005] Additional results of the experiments relating to treatment of the tumor microenvironment are shown in FIG. 76 to FIG. 78. FIG. 76 shows the effects of oral dosing with 15 mg/kg of the BTK inhibitor of Formula (XVIII), 15 mg/kg of the PI3K inhibitor of Formula (IX), or a combination of both drugs on myeloid tumor-associated macrophages (TAMs) in pancreatic tumor-bearing mice. FIG. 77 illustrates the effects of oral dosing with 15 mg/kg of the BTK inhibitor of Formula (XVIII), 15 mg/kg of the PI3K inhibitor of Formula (IX), or a combination of both inhibitors on myeloid-derived suppressor cells (MDSCs) in pancreatic tumor-bearing mice. FIG. 78 illustrates the effects of oral dosing with 15 mg/kg of the BTK inhibitor of Formula (XVIII), 15 mg/kg of the PI3K inhibitor of Formula (IX), or a combination of both inhibitors on regulatory T cells (Tregs) in pancreatic tumor-bearing mice. The results shown in FIG. 76 to FIG. 78 demonstrate that of the BTK inhibitor of Formula (XVIII) and the combination of the BTK inhibitor of Formula (XVIII) and the PI3K inhibitor of Formula (IX) reduce immunosuppressive tumor associated myeloid cells and Tregs in pancreatic tumor-bearing mice. Overall, BTK inhibition with Formula (XVIII) or a combination of Formula (XVIII) and Formula (IX) significantly reduced tumor burden in an aggressive orthotopic PDA model, decreased immature myeloid infiltrate, reduced the number of tumor associated macrophages, and reduced the number of immunosuppressive Tregs, demonstrating a strong effect on the tumor microenvironment.

Example 6—Synergistic Combination of a BTK inhibitor and the JAK-2 Inhibitor Pacritinib
[001006] Combination experiments were performed to determine the synergistic, additive, or antagonistic behavior of drug combinations using the methods described above in Example 2. The study was performed using the BTK inhibitor of Formula (XVIII) and the JAK-2 inhibitor of Formula LIV (pacritinib).

[001007] The detailed results of the cell line studies for the BTK inhibitor of Formula (XVIII) and the JAK-2 inhibitor of Formula LIV (pacritinib) are given in FIG. 79 to FIG. 107. The results of the cell line studies are summarized in Table 6.
TABLE 6. Summary of results of the combination of a BTK inhibitor with the JAK-2 inhibitor of Formula LIV (pacritinib) (S = synergistic, A = additive, X = no effect).

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Example 7 – BTK Inhibitory Effects on Solid Tumor Microenvironment in an Ovarian Cancer Model

[001008] The ID8 syngeneic orthotropic ovarian cancer murine model was used to investigate the therapeutic efficacy of the BTK inhibitor of Formula (XVIII) through treatment of the solid tumor microenvironment. Human ovarian cancer models, including the ID8 syngeneic orthotropic ovarian cancer model and other animal models, are described in Fong and Kakar, J. Ovarian Res. 2009, 2, 12; Greenaway et al., Gynecol. Oncol. 2008, 108, 385-94; Urzua et al., Tumour Biol. 2005, 26, 236-44; Janat-Amsbury et al., Anticancer Res. 2006, 26, 3223-28; Janat-Amsbury et al., Anticancer Res. 2006, 26, 2785-89. Animals were treated with vehicle or Formula (XVIII), 15 mg/kg/BID given orally. The results of the study are shown in FIG. 108,
FIG. 108 and FIG. 109 demonstrate that the BTK inhibitor of Formula (XVIII) impairs ID8 ovarian cancer growth in the ID8 syngeneic murine model. FIG. 110 shows that tumor response to treatment with the BTK inhibitor of Formula (XVIII) correlates with a significant reduction in immunosuppressive tumor-associated lymphocytes in tumor-bearing mice. FIG. 111 shows treatment with the BTK inhibitor of Formula (XVIII) impairs ID8 ovarian cancer growth (through reduction in tumor volume) in the syngeneic murine model. FIG. 112 and FIG. 113 show that the tumor response induced by treatment with the BTK inhibitor of Formula (XVIII) correlates with a significant reduction in immunosuppressive B cells in tumor-bearing mice. FIG. 114 and FIG. 115 show that the tumor response induced by treatment with the BTK inhibitor of Formula (XVIII) correlates with a significant reduction in immunosuppressive tumor associated Tregs and an increase in CD8+ T cells.

The results shown in FIG. 108 to FIG. 115 illustrate the surprising efficacy of the BTK inhibitor of Formula (XVIII) in modulating tumor microenvironment in a model predictive of efficacy as a treatment for ovarian cancer in humans.

Example 8 – BTK Inhibitory Effects on Solid Tumor Microenvironment Through Modulation of Tumor-Infiltrating MDSCs and TAMs

A study was performed to observe potential reduction in tumor burden through modulation of tumor infiltrating MDSCs and TAMs using the BTK inhibitor of Formula (XVIII) and/or gemcitabine (“Gem”). In this study, KPC derived mouse pancreatic cancer cells (KrasG12D;Trp53R172H;Pdx1-Cre) were injected into the pancreases. Animals were treated with (1) vehicle; (2) Formula (XVIII), 15 mg/kg/BID given orally; (3) gemcitabine 15 mg/kg intravenous (IV) administered every 4 days for 3 injections; or (4) Formula (XVIII), 15 mg/kg/BID given orally with together with gemcitabine, 15 mg/kg IV administered every 4 days for 3 injections.

Single cell suspensions from tumor samples. Mouse tumor tissue was collected and stored in PBS/0.1% soybean trypsin inhibitor prior to enzymatic dissociation. Samples were finely minced with a scissors and mouse tissue was transferred into DMEM containing 1.0 mg/ml collagenase IV (Gibco), 0.1% soybean trypsin inhibitor, and 50 U/ml DNase (Roche) and incubated at 37 °C for 30 minutes with constant stirring while human tissue was digested in 2.0
mg/ml collagenase IV, 1.0 mg/ml hyluronidase, 0.1% soybean trypsin inhibitor, and 50 U/ml DNase for 45 minutes. Suspensions were filtered through a 100 micron filter and washed with FACS buffer (PBS/0.5% BSA/2.0 mM EDTA) prior to staining. Two million total cells were stained with antibodies as indicated. Intracellular detection of FoxP3 was achieved following permeabilization with BD Perm Buffer III (BD Biosciences) and eBioscience Fix/Perm respectively. Following surface staining, samples were acquired on a BD Fortessa and analyzed using FlowJo (Treestar) software.

[001013] In FIG. 116, the reduction in tumor size upon treatment is shown. The effects on particular cell subsets are shown in the flow cytometry data presented in FIG. 117, FIG. 118, FIG. 119, and FIG. 120.

[001014] The results shown in FIG. 116 to FIG. 120 illustrate reduction in tumor burden by modulating the tumor infiltrating MDSCs and TAMs, which affects Treg and CD8+ T cell levels, through inhibition of BTK using Formula (XVIII).

Example 9 – Effects of BTK Inhibitors on Thrombosis

[001015] Clinical studies have shown that targeting the BCR signaling pathway by inhibiting BTK produces significant clinical benefit (Byrd, et al., N. Engl. J. Med. 2013, 369(1), 32-42, Wang, et al., N. Engl. J. Med. 2013, 369(6), 507-16). However, in these studies, bleeding has been reported in up to 50% of ibrutinib-treated patients. Most bleeding events were of grade 1-2 (spontaneous bruising or petechiae) but, in 5% of patients, they were of grade 3 or higher after trauma. These results are reflected in the prescribing information for ibrutinib, where bleeding events of any grade, including bruising and petechiae, were reported in approximately half of patients treated with ibrutinib (IMBRUVICA package insert and prescribing information, revised July 2014, U.S. Food and Drug Administration).

[001016] Constitutive or aberrant activation of the BCR signaling cascade has been implicated in the propagation and maintenance of a variety of B cell malignancies. Small molecule inhibitors of BTK, a protein early in this cascade and specifically expressed in B cells, have emerged as a new class of targeted agents. There are several BTK inhibitors, including Formula XXVII (CC-292), and Formula XX-A (PCI-32765, ibrutinib), in clinical development. Importantly, early stage clinical trials have found ibrutinib to be particularly active in chronic lymphocytic leukemia (CLL) and mantle cell lymphoma (MCL), suggesting that this class of inhibitors may
play a significant role in various types of cancers (Aalipour and Advani, *Br. J. Haematol.* 2013, 163, 436-43). However, their effects are not limited to leukemia or lymphomas as platelets also rely on the Tec kinases family members BTK and Tec for signal transduction in response to various thrombogenic stimuli (Oda, et al., *Blood* 2000, 95(5), 1663-70; Atkinson, et al. *Blood* 2003, 102(10), 3592-99). In fact, both Tec and BTK play an important role in the regulation of phospholipase Cγ2 (PLCγ2) downstream of the collagen receptor glycoprotein VI (GPVI) in human platelets. In addition, BTK is activated and undergoes tyrosine phosphorylation upon challenge of the platelet thrombin receptor, which requires the engagement of αIIbβ3 integrin and PI3K activity (Laffargue, et al., *FEBS Lett.* 1999, 443(1), 66-70). It has also been implicated in GPIbα-dependent thrombus stability at sites of vascular injury (Liu, et al., *Blood* 2006, 108(8), 2596-603). Thus, BTK and Tec are involved in several processes important in supporting the formation of a stable hemostatic plug, which is critical for preventing significant blood loss in response to vascular injury. Hence, the effects of the BTK inhibitor of Formula (XVIII) and ibrutinib were evaluated on human platelet-mediated thrombosis by utilizing the in vivo human thrombus formation in the VWF HA1 mice model described in Chen, et al. *Nat. Biotechnol.* 2008, 26(1), 114-19.

**[001017] Administration of anesthesia, insertion of venous and arterial catheters, fluorescent labeling and administration of human platelets (5 × 10⁸/ml), and surgical preparation of the cremaster muscle in mice have been previously described (Chen, et al. *Nat Biotechnol.* 2008, 26(1), 114-19). Injury to the vessel wall of arterioles (~40–65 mm diameter) was performed using a pulsed nitrogen dye laser (440 nm, Photonic Instruments) applied through a 20× water-immersion Olympus objective (LUMPlanFl, 0.5 numerical aperture (NA)) of a Zeiss Axio tech vario microscope. Human platelet and wall interactions were visualized by fluorescence microscopy using a system equipped with a Yokogawa CSU-22 spinning disk confocal scanner, iXON EM camera, and 488 nm and 561 nm laser lines to detect BCECF-labeled and rhodamine-labeled platelets, respectively (Revolution XD, Andor Technology). The extent of thrombus formation was assessed for 2 minutes after injury and the area (μm²) of coverage determined (Image IQ, Andor Technology). For the Formula (XVIII), Formula (XXVII) (CC-292), and Formula (XX-A) (ibrutinib) inhibition studies, the BTK inhibitors were were added to purified human platelets for 30 minutes before administration.

**[001018] The in vivo thrombus effects of the BTK inhibitors, Formula (XVIII), Formula (XXVII)
(CC-292), and Formula (XX-A) (ibrutinib), were evaluated on human platelet-mediated thrombosis by utilizing the in vivo human thrombus formation in the VWF HA1 mice model, which has been previously described (Chen, et al. Nat Biotechnol. 2008, 26(1), 114-19). Purified human platelets were preincubated with various concentrations of the BTK inhibitors (0.1 μM, 0.5 μM, or 1 μM) or DMSO and then administered to VWF HA1 mice, followed by laser-induced thrombus formation. The BTK inhibitor-treated human platelets were fluorescently labeled and infused continuously through a catheter inserted into the femoral artery. Their behavior in response to laser-induced vascular injury was monitored in real time using two-channel confocal intravital microscopy (Furie and Furie, J. Clin. Invest. 2005, 115(12), 2255-62). Upon induction of arteriole injury untreated platelets rapidly formed thrombi with an average thrombus size of 6,450 ± 292 mm² (mean ± s.e.m.), as shown in FIG. 121 and FIG. 122. Similarly, Formula (XVIII) (1 μM) treated platelets formed a slightly smaller but not significantly different thrombi with an average thrombus size of 5733 ± 393 mm² (mean ± s.e.m.). In contrast, a dramatic reduction in thrombus size occurred in platelets pretreated with 1 μM of Formula XX-A (ibrutinib), 2600 ± 246 mm² (mean ± s.e.m.), resulting in a reduction in maximal thrombus size by approximately 61% compared with control (P > 0.001) (FIG. 121 and FIG. 123). Similar results were obtained with platelets pretreated with 500 nM of Formula (XVIII) or ibrutinib: thrombus size of 5946 ± 283 mm², and 2710 ± 325 mm² respectively. These initial results may provide some mechanic background and explanation on the reported 44% bleeding related adverse event rates in the Phase III RESONATE™ study comparing ibrutinib with ofatumumab. The results obtained for Formula XXVII (CC-292) were similar to that for Formula XX-A (ibrutinib), as shown in FIG. 121, 122, and 123. The effect of the BTK inhibitor concentration is shown in FIG. 124. These results demonstrate the surprising advantage of the BTK inhibitor of Formula (XVIII), which does not interfere with thrombus formation, while the BTK inhibitors of Formula XXVII (CC-292) and Formula XX-A (ibrutinib) interfere with thrombus formation.

[001019] The objective of this study was to evaluate in vivo thrombus formation in the presence of BTK inhibitors. In vivo testing of novel antiplatelet agents requires informative biomarkers. By utilizing a genetic modified mouse von Willebrand factor (VWFR1326H) model that supports human but not mouse platelet-mediated thrombosis, we evaluated the effects of Formula (XVIII), Formula XXVII (CC-292), and Formula XX-A (ibrutinib) on thrombus
formation. These results show that Formula (XVIII) had no significant effect on human platelet-mediated thrombus formation while Formula XX-A (ibritinib) was able to limit this process, resulting in a reduction in maximal thrombus size by 61% compared with control. Formula XXVII (CC-292) showed an effect similar to Formula XX-A (ibritinib). These results, which show reduced thrombus formation for ibritinib at physiologically relevant concentrations, may provide some mechanistic background for the Grade ≥ 3 bleeding events (eg, subdural hematoma, gastrointestinal bleeding, hematuria and postprocedural hemorrhage) that have been reported in ≤ 6% of patients treated with Formula XX-A (ibritinib).

[001020] GPVI platelet aggregation was measured for Formula (XVIII) and Formula XX-A (ibritinib). Blood was obtained from untreated humans, and platelets were purified from plasma-rich protein by centrifugation. Cells were resuspended to a final concentration of 350,000/µL in buffer containing 145 mmol/L NaCl, 10 mmol/L HEPES, 0.5 mmol/L Na₂HPO₄, 5 mmol/L KCl, 2 mmol/L MgCl₂, 1 mmol/L CaCl₂, and 0.1% glucose, at pH 7.4. Stock solutions of Convulxin (CVX) GPVI were prepared on the day of experimentation and added to platelet suspensions 5 minutes (37 °C, 1200 rpm) before the induction of aggregation. Aggregation was assessed with a Chronolog Lumi-Aggregometer (model 540 VS; Chronolog, Havertown, PA) and permitted to proceed for 6 minutes after the addition of agonist. The results are reported as maximum percent change in light transmittance from baseline with platelet buffer used as a reference. The results are shown in FIG. 125.

[001021] In FIG. 126, the results of CVX-induced (250 ng/mL) human platelet aggregation results before and 15 minutes after administration of the BTK inhibitors to 6 healthy individuals are shown.

[001022] The results depicted in FIG. 125 and FIG. 126 indicate that the BTK inhibitor of Formula XX-A (ibritinib) significantly inhibits GPVI platelet aggregation, while the BTK inhibitor of Formula (XVIII) does not, further illustrating the surprising benefits of the latter compound.

Example 10 – Study of a BTK Inhibitor and a Combination of a BTK Inhibitor and a PI3K Inhibitor in Canine Lymphoma

[001023] Canine B cell lymphoma exists as a pathological entity that is characterized by large anaplastic, centroblastic or immunoblastic lymphocytes with high proliferative grade, significant
peripheral lymphadenopathy and an aggressive clinical course. While some dogs respond initially to prednisone, most canine lymphomas progress quickly and must be treated with combination therapies, including cyclophosphamide, vincristine, doxorubicin, and prednisone (CHOP), or other cytotoxic agents. In their histopathologic features, clinical course, and high relapse rate after initial treatment, canine B cell lymphomas resemble diffuse large B cell lymphoma (DLBCL) in humans. Thus, responses of canine B cell lymphomas to experimental treatments are considered to provide proof of concept for therapeutic candidates in DLBCL.

[001024] In this example, companion dogs with newly diagnosed or relapsed/refractory LSA were enrolled on a veterinary clinical trial of the BTK inhibitor of Formula (XVIII) (“Arm 1”) or the BTK inhibitor of Formula (XVIII) and the PI3K-δ inhibitor of Formula (IX) (“Arm 2”). Enrollment has completed for Arm 1 and is ongoing for Arm 2. With approximately 1/3 of Arm 2 subjects treated, the preliminary results show that combined treatment with the BTK inhibitor of Formula (XVIII) and the PI3K-δ inhibitor of Formula (IX) may have greater efficacy than treatment with the BTK inhibitor of Formula (XVIII) alone in aggressive lymphoma.

[001025] Twenty-one dogs were treated in Arm 1 with the BTK inhibitor of Formula (XVIII) at dosages of 2.5 mg/kg once daily to 20 mg/kg twice daily. Intra-subject dose escalation was allowed. Six of the 11 dogs that initiated at 2.5 or 5 mg/kg once daily were escalated and completed the study with dosages of 10 mg/kg twice daily. Among all the dose cohorts, 8 dogs had shrinkage of target lesions >20%; the best tumor responses were between 45-49% reduction in the sum of target lesions in two dogs. Complete responses (“CR”, disappearance of all evidence of disease per evaluator judgment; and absence of new lesions) were not observed in Arm 1.

[001026] In the combination phase of the study (Arm 2), 7 dogs have been treated with 10 mg/kg the BTK inhibitor of Formula (XVIII) and the PI3K-δ inhibitor of Formula (IX) at 2.5 or 3.5 mg/kg, on a twice daily schedule. To date, 4 dogs had shrinkage of target lesions > 20%; and the best tumor responses were between 58-65% reduction in the sum of target lesions, with one sustained CR observed. Initial reductions in the sum of target lesions were observed to deepen during the course of therapy in 4 of the 7 dogs. A summary of the results is presented in Table 7.

TABLE 7. Summary of the results of the canine lymphoma study.

<table>
<thead>
<tr>
<th>Response Metric</th>
<th>Formula (XVIII) and</th>
<th>Formula (XVIII)</th>
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</table>

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These preliminary data suggest that in companion dogs with naturally occurring B cell lymphomas, treatment with the combination of the BTK inhibitor of Formula (XVIII) and the PI3K-δ inhibitor of Formula (IX) may provide increased biological activity (tumor shrinkage and stable disease) and may possibly lead to deeper responses than treatment with the BTK inhibitor of Formula (XVIII) alone. Although the available data represent only 1/3 of the planned Arm 2 population, the extended response time (median time to best response) and observation of a CR among the few dogs treated to date may be evidence of synergy between Formula (XVIII) and Formula (IX) in this highly aggressive disease.

Example 11 – BTK Inhibitory Effects on Solid Tumor Microenvironment in the KPC Pancreatic Cancer Model

Given the potential for BTK inhibition to affect TAMs and MDSCs, single-active pharmaceutical ingredient Formula (XVIII) was evaluated in mice with advanced pancreatic cancer arising as the result of genetic modifications of oncogenes KRAS and p53, and the pancreatic differentiation promoter PDX-1 (KPC mice). The KPC mouse model recapitulates many of the molecular, histopathologic, and clinical features of human disease (Westphalen and Olive, Cancer J. 2012, 18, 502-510). Combination therapy with gemcitabine was also evaluated in this model. Mice were enrolled after identification of spontaneously appearing tumors in the pancreas that were ≥ 100 mm³ (as assessed by high-resolution ultrasonography). Mice were treated with (1) vehicle (N=6); or (2) Formula (XVIII), 15 mg/kg BID given orally (N=6).

As shown in FIG. 127, treatment with single-active pharmaceutical ingredient Formula (XVIII) substantially slowed pancreatic cancer growth and increased animal survival. With vehicle, tumor volumes predose averaged 152 mm³, and at day 28 averaged 525 mm³. In the cohort treated with Formula (XVIII), tumor volumes predose averaged 165 mm³, and at day 28 averaged 272 mm³, indicating significant improvement. With vehicle, survival at day 14 was 5/6.
animals, and at day 28 was 0/6 animals. With Formula (XVIII), survival at day 14 was 6/6 animals, and at day 28 was 5/6 animals.

**Analysis**
The analysis of tumor tissues showed that immunosuppressive TAMs (CD11b-Ly6Clo/F4/80-Csf1r-) and Tregs (CD4-CD25-FoxP3-) were significantly reduced with Formula (XVIII) treatment (FIG. 128, FIG. 129, and FIG. 130). As expected, the decrease in these immunosuppressive cell subsets correlated with a significant increase in CD8 T cells (FIG. 131).

**Example**

**Effects of BTK Inhibitors on Antibody-Dependent NK Cell Mediated Cytotoxicity**

Rituximab-combination chemotherapy is today’s standard of care in CD20+ B-cell malignancies. Previous studies investigated and determined that ibrutinib antagonizes rituximab antibody-dependent cell mediated cytotoxicity (ADCC) mediated by NK cells. This may be due to ibrutinib’s secondary irreversible binding to interleukin-2 inducible tyrosine kinase (ITK) which is required for FcR-stimulated NK cell function including calcium mobilization, granule release, and overall ADCC. Kohrt, *et al.*, *Blood* 2014, 123, 1957-60.

**In this example,** the effects of Formula (XVIII) and ibrutinib on NK cell function were evaluated in primary NK cells from healthy volunteers and CLL patients. The activation of NK cells co-cultured with antibody-coated target cells was strongly inhibited by ibrutinib. The secretion of IFN-γ was reduced by 48% (p = 0.018) and 72% (p = 0.002) in cultures treated with ibrutinib at 0.1 and 1.0 µM respectively and NK cell degranulation was significantly (p = 0.002) reduced, compared with control cultures. Formula (XVIII) treatment at 1 µM, a clinically relevant concentration, did not inhibit IFN-γ or NK cell degranulation. Rituximab-mediated ADCC was evaluated in NK cells from healthy volunteers as well as assays of NK cells from CLL patients targeting autologous CLL cells. In both cases, ADCC was not inhibited by Formula (XVIII) treatment at 1 µM. In contrast, addition of ibrutinib to the ADCC assays strongly inhibited the rituximab-mediated cytotoxicity of target cells, and no increase over natural cytotoxicity was observed at any rituximab concentration. This result indicates that the combination of rituximab and Formula (XVIII) provides an unexpected benefit in the treatment of CLL.

**BTK** is a non-receptor enzyme in the Tec kinase family that is expressed among cells of hematopoietic origin, including B cells, myeloid cells, mast cells and platelets, where it

Ibrutinib (PCI-32765, IMBRUVICA), is a first-in-class therapeutic BTK inhibitor. This orally delivered, small-molecule drug is being developed by Pharmacyclics, Inc. for the therapy of B-cell malignancies. As described above, in patients with heavily pretreated indolent non-Hodgkin lymphoma (iNHL), mantle cell lymphoma (MCL), and CLL, ibrutinib showed substantial antitumor activity, inducing durable regressions of lymphadenopathy and splenomegaly in the majority of patients. Advani, *et al.*, *J. Clin. Oncol.* 2013, 31, 88-94; Byrd, *et al.*, *N. Engl. J. Med.* 2013, 369, 32-42; Wang, *et al.*, *N. Engl. J. Med.* 2013, 369, 507-16; O’Brien, *et al.*, *Blood* 2012, 119, 1182-89. The pattern of changes in CLL was notable. Inhibition of BTK with ibrutinib caused rapid and substantial mobilization of malignant CLL cells from tissues sites into the peripheral blood, as described in J. A. Woyach, *et al.*, *Blood* 2014, 123, 1810-17; this effect was consistent with decreased adherence of CLL to protective stromal cells. Ponader, *et al.*, *Blood* 2012, 119, 1182-89; de Rooij, *et al.*, *Blood* 2012, 119, 2590-94. ibrutinib has been generally well tolerated. At dose levels associated with total BTK occupancy, not dose-limiting toxicities were identified and subjects found the drug tolerable over periods extending to >2.5 years.

Given the homology between BTK and interleukin-2 inducible tyrosine kinase (ITK), it has been recently confirmed that ibrutinib irreversibly binds ITK. Dubovsky, *et al.*, *Blood* 2013,
ITK expression in Fc receptor (FcR)-stimulated NK cells leads to increased calcium mobilization, granule release, and cytotoxicity. Khurana, *et al.*, *J. Immunol.* 2007, 178, 3575-3582. As rituximab is a backbone of lymphoma therapy, with mechanisms of action including ADCC, as well as direct induction of apoptosis and complement-dependent cytotoxicity and FcR stimulation is requisite for ADCC, we investigated if ibrutinib or Formula (XVIII) (lacking ITK inhibition) influenced rituximab’s anti-lymphoma activity *in vitro* by assessing NK cell IFN-γ secretion, degranulation by CD107a mobilization, and cytotoxicity by chromium release using CD20⁺ cell lines and autologous patient samples with chronic lymphocytic leukemia (CLL).

**[001036]** Formula (XVIII) is a more selective inhibitor than ibrutinib, as shown previously. Formula (XVIII) is not a potent inhibitor of Itk kinase in contrast to ibrutinib (see Example 13). Itk kinase is required for FcR-stimulated NK cell function including calcium mobilization, granule release, and overall ADCC. As anti-CD20 antibodies like rituximab are standard of care drugs, often as part of combination regimens, for the treatment of CD20+ B-cell malignancies, the potential of ibrutinib or Formula (XVIII) to antagonize ADCC was evaluated *in vitro*. We hypothesized that Btk inhibitor, Formula (XVIII) which does not have activity against Itk, may preserve NK cell function and therefore synergize rather than antagonize rituximab-mediated ADCC. Rituximab-dependent NK-cell mediated cytotoxicity was assessed using lymphoma cell lines as well as autologous CLL tumor cells.

**[001037]** Cell culture conditions were as follows. Cell lines Raji and DHL-4 were maintained in RPMI 1630 supplemented with fetal bovine serum, L-glutamine, 2-mercaptoethanol and penicillin-streptomycin at 37 °C in a humidified incubator. The HER18 cells were maintained in DEM supplemented with fetal bovine serum, penicillin-streptomycin and. Prior to assay, HER18 cells were harvested using trypsin-EDTA, washed with phosphate-buffered saline (PBS) containing 5% serum and viable cells were counted. For culture of primary target cells, peripheral blood from CLL patients was subject to density centrifugation to obtain peripheral blood mononuclear cells (PBMC). Cell preparations were washed and then subject to positive selection of CD5⁺CD19⁺ CLL cells using magnetic beads (MACS, Miltenyi Biotech). Cell preparations were used fresh after selection. NK cells from CLL patients and healthy volunteers were enriched from peripheral blood collected in sodium citrate anti-coagulant tubes and then subject to density centrifugation. Removal of non NK cells was performed using negative
selection by MACS separation. Freshly isolated NK cells were washed three times, enumerated, and then used immediately for ADCC assays.

[C] Cytokine secretion was determined as follows. Rituximab and trastuzumab-dependent NK-cell mediated degranulation and cytokine release were assessed using lymphoma and HER2+ breast cancer cell lines (DHL-4 and HER18, respectively). Target cells were cultured in flat-bottom plates containing 10 µg/mL of rituximab (DHL-4) or trastuzumab (HER18) and test articles (0.1 or 1 µM ibrutinib, 1 µM Formula (XVIII), or DMSO vehicle control). NK cells from healthy donors were enriched as described above and then added to the target cells and incubated for 4 hours at 37 °C. Triplicate cultures were performed on NK cells from donors. After incubation, supernatants were harvested, centrifuged briefly, and then analyzed for interferon-γ using an enzyme-linked immunosorbent assay (ELISA) (R&D Systems, Minneapolis, MN, USA).

Lytic granule release was determined as follows. NK cells from healthy donors were enriched and cultured in the presence of target cells, monoclonal antibodies and test articles as described above. After 4 hours, the cultures were harvested and cells were pelleted, washed, and then stained for flow cytometry evaluation. Degranulation was evaluated via by flow cytometry by externalization of CD107a, a protein normally present on the inner leaflet of lytic granules, and gating on NK cells (CD3-CD16+ lymphocytes). The percentage of CD107a positive NK cells was quantified by comparison with a negative control (isotype control, unstained cells/FMO). Control cultures (NK cells cultured without target cells, or NK, target cell co-cultures in the absence of an appropriate monoclonal antibody) were also evaluated; all experiments were performed in triplicate.

ADCC assays were performed as follows. Briefly, target cells (Raji or primary CLL) were labeled by incubation at 37 °C with 100 µCi ⁵¹Cr for 4 hours prior to co-culture with NK cells. Cells were washed, enumerated, and then added in triplicate to prepared 96-well plates containing treated NK cells at an effector:target (E:T) ratio of 25:1. Rituximab (Genentech) was added to ADCC wells at concentrations of 0.1, 1.0 or 10 µg/mL and the assays were briefly mixed and then centrifuged to collect cells at the bottom of the wells. The effect of NK cell natural cytotoxicity was assessed in wells containing no rituximab. Cultures were incubated at 37 °C for 4 hours, and then centrifuged. Supernatants were harvested and ⁵¹Cr release was
measured by liquid scintillation counting. All experiments were performed in triplicate.

[Ibrutinib inhibited rituximab-induced NK cell cytokine secretion in a dose-dependent manner (0.1 and 1 µM) (FIG. 132: 48% p = 0.018; 72% p = 0.002, respectively). At 1 µM, Formula (XVIII) did not significantly inhibit cytokine secretion (FIG. 132: 3.5%). Similarly, Formula (XVIII) had no inhibitory effect on rituximab-stimulated NK cell degranulation (< 2%) while ibrutinib reduced degranulation by ~50% (p = 0.24, FIG. 133). Formula (XVIII) had no inhibitory effect while ibrutinib prevented trastuzumab-stimulated NK cell cytokine release and degranulation by ~92% and ~84% at 1µM, respectively (FIG. 132 and FIG. 133: ***p = 0.004, **p = 0.002).

In Raji cell samples, ex vivo NK cell activity against autologous tumor cells was not inhibited by addition of Formula (XVIII) at 1 µM, and increased cell lysis was observed with increasing concentrations of rituximab at a constant E:T ratio (FIG. 134). A plot highlighting the differences between Formula (XVIII) and ibrutinib at 10 µM is shown in FIG. 135. In primary CLL samples, ex vivo NK cell activity against autologous tumor cells was not inhibited by addition of Formula (XVIII) at 1 µM, and increased cell lysis was observed with increasing concentrations of rituximab at a constant E:T ratio (FIG. 136). In contrast, addition of 1 µM ibrutinib completely inhibited ADCC, with less than 10% cell lysis at any rituximab concentration and no increase in cell lysis in the presence of rituximab, compared with cultures without rituximab. The difference between Formula (XVIII) and ibrutinib was highly significant in this assay (p = 0.001).

In ADCC assays using healthy donor NK cells, antibody-dependent lysis of rituximab-coated Raji cells was not inhibited by addition of 1 µM Formula (XVIII) (FIG. 136). In these experiments, addition of rituximab stimulated a 5- to 8-fold increase in cell lysis at 0.1 and 1 µg/mL, compared with low (< 20%) natural cytotoxicity in the absence of rituximab. As previously reported, addition of 1 µM ibrutinib strongly inhibited the antibody-dependent lysis of target cells, with less than 20% cell lysis at all rituximab concentrations and no increase in ADCC with at higher rituximab concentrations.

Ibrutinib is clinically effective as monotherapy and in combination with rituximab, despite inhibition of ADCC in vitro and in vivo murine models due to ibrutinib’s secondary irreversible binding to ITK. Preclinically, the efficacy of therapeutics which do not inhibit NK
cell function, including Formula (XVIII), is superior to ibrutinib. Clinical investigation is needed to determine the impact of this finding on patients receiving rituximab as these results provide support for the unexpected property of Formula (XVIII) as a better active pharmaceutical ingredient than ibrutinib to use in combination with antibodies that have ADCC as a mechanism of action. The improved performance of Formula (XVIII) in combination with anti-CD20 antibody therapies is expected to extend to its use in combination with PI3K inhibitors and CDK4/6 inhibitors in both hematological malignancies and solid tumors, as these combinations would also benefit from reduced inhibition of NK cell function.

Example 13 – Preclinical Characteristics of BTK Inhibitors

[001045] The BTK inhibitor ibrutinib ((1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1 H-pyrazolo[3,4-d]pyrimidin-1-yl]piperidin-1-yl]prop-2-en-1-one) is a first-generation BTK inhibitor. In clinical testing as a monotherapy in subjects with hematologic malignancies, ibrutinib was generally well tolerated at dose levels through 840 mg (the highest dose tested). Advani, et al., J. Clin. Oncol. 2013, 31, 88-94; Byrd, et al., N. Engl. J. Med. 2013, 369, 32-42; Wang, et al., N. Engl. J. Med. 2013, 369, 507-16. No maximum tolerated dose (MTD) was apparent within the tested dose range. Furthermore, subjects typically found the drug tolerable over periods extending to > 2 years. No subject had tumor lysis syndrome. No overt pattern of myelosuppression was associated with ibrutinib treatment. No drug-related reductions in circulating CD4+ T cells or serum immunoglobulins were noted. Adverse events with an apparent relationship to study drug included diarrhea and rash.

[001046] In subjects with heavily pretreated non-Hodgkin lymphoma (NHL), ibrutinib showed substantial antitumor activity, inducing durable regressions of lymphadenopathy and splenomegaly in most subjects. Improvements in disease-associated anemia and thrombocytopenia were observed. The pattern of changes in subjects with CLL was notable. Single-active pharmaceutical ingredient ibrutinib caused rapid and substantial reductions in lymph node size concomitant with a redistribution of malignant sites into the peripheral blood. An asymptomatic absolute lymphocyte count (ALC) increase was observed that was maximal during the first few months of treatment and generally decreased thereafter but could be persistent in some subjects or could be seen repeatedly in subjects who had interruption and resumption of drug therapy.
Collectively, these data with ibrutinib support the potential benefits of selective BTK inhibition in the treatment of subjects with relapsed lymphoid cancers. However, while highly potent in inhibiting BTK, ibrutinib has also shown in vitro activity against other kinases with a cysteine in the same position as Cys481 in BTK to which the drug covalently binds. For example, ibrutinib inhibits epidermal growth factor receptor (EGFR), which may be the cause of ibrutinib-related diarrhea and rash. In addition, it is a substrate for both cytochrome P450 (CYP) enzymes 3A4/5 and 2D6, which increases the possibility of drug-drug interactions. These liabilities support the development of alternative BTK inhibitors for use in the therapy of lymphoid cancer.

The preclinical selectivity and potency characteristics of the second-generation BTK inhibitor of Formula (XVIII) were compared to the first-generation BTK inhibitor ibrutinib. In Table 8, a kinome screen (performed by Life Technologies or based on literature data) is shown that compares these compounds.

TABLE 8. Kinome Screen for BTK Inhibitors (IC_{50}, nM)

<table>
<thead>
<tr>
<th>3F-Cys Kinase</th>
<th>Formula (XVIII)</th>
<th>Ibrutinib (Formula (XX-A))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Btk</td>
<td>3.1</td>
<td>0.5</td>
</tr>
<tr>
<td>Tec</td>
<td>29</td>
<td>78</td>
</tr>
<tr>
<td>Bmx</td>
<td>39</td>
<td>0.80</td>
</tr>
<tr>
<td>Itk</td>
<td>&gt;1000</td>
<td>10.7</td>
</tr>
<tr>
<td>Tsk</td>
<td>291</td>
<td>2.0</td>
</tr>
<tr>
<td>EGFR</td>
<td>&gt;1000</td>
<td>5.6</td>
</tr>
<tr>
<td>ErbB2</td>
<td>912</td>
<td>9.4</td>
</tr>
<tr>
<td>ErbB4</td>
<td>13.2</td>
<td>2.7</td>
</tr>
<tr>
<td>Blk</td>
<td>&gt;1000</td>
<td>0.5</td>
</tr>
<tr>
<td>JAK-3</td>
<td>&gt;1000</td>
<td>16.1</td>
</tr>
</tbody>
</table>

The results shown in Table 8 are obtained from a 10 point biochemical assay generated from 10 point concentration curves. The BTK inhibitor of Formula (XVIII) shows much greater selectivity for BTK compared to other kinases than ibrutinib.

A comparison of the in vivo potency results for the BTK inhibitors of Formula (XVIII) and ibrutinib is shown in FIG. 137. CD86 and CD69 are cell surface proteins that are BCR activation markers. To obtain the in vivo potency results, mice were gavaged at increasing drug...
concentration and sacrificed at one time point (3 h post-dose). BCR was stimulated with IgM and the expression of activation marker CD69 and CD86 are monitored by flow cytometry and to determine EC₅₀ values.

[001051] In vitro and in vivo safety pharmacology studies with Formula (XVIII) have demonstrated a favorable nonclinical safety profile. When screened at 10 μM in binding assays evaluating interactions with 80 known pharmacologic targets such as G-protein-coupled receptors, nuclear receptors, proteases, and ion channels, Formula (XVIII) shows significant activity only against the A3 adenosine receptor; follow-up dose-response experiments indicated a IC₅₀ of 2.7 μM, suggesting a low clinical risk of off-target effects. Formula (XVIII) at 10 μM showed no inhibition of in vitro EGFR phosphorylation in an A431 human epidermoid cancer cell line whereas ibritinib had an IC₅₀ of 66 nM. The in vitro effect of Formula (XVIII) on human ether-à-go-go-related gene (hERG) channel activity was investigated in vitro in human embryonic kidney cells stably transfected with hERG. Formula (XVIII) inhibited hERG channel activity by 25% at 10 μM, suggesting a low clinical risk that Formula (XVIII) would induce clinical QT prolongation as predicted by this assay. Formula (XVIII) was well tolerated in standard in vivo Good Laboratory Practices (GLP) studies of pharmacologic safety. A functional observation battery in rats at doses of through 300 mg/kg (the highest dose level) revealed no adverse effects on neurobehavioral effects or body temperature at any dose level. A study of respiratory function in rats also indicated no treatment-related adverse effects at doses through 300 mg/kg (the highest dose level). In a cardiovascular function study in awake telemeterized male beagle dogs, single doses of Formula (XVIII) at dose levels through 30 mg/kg (the highest dose level) induced no meaningful changes in body temperature, cardiovascular, or electrocardiographic (ECG) (including QT interval) parameters. The results suggest that Formula (XVIII) is unlikely to cause serious off-target effects or adverse effects on critical organ systems.

[001052] The drug-drug interaction potential of Formula (XVIII) was also evaluated. In vitro experiments evaluating loss of parent drug as catalyzed by CYPs indicated that Formula (XVIII) is metabolized by CYP3A4. In vitro metabolism studies using mouse, rat, dog, rabbit, monkey, and human hepatocytes incubated with ¹⁴C-labeled Formula (XVIII) indicated two mono-oxidized metabolites and a glutathione conjugate. No unique human metabolite was identified. Preliminary evaluations of metabolism in the plasma, bile, and urine of rats, dogs, and monkeys indicated metabolic processes of oxidation, glutathione binding, and hydrolysis. It was shown
that Formula (XVIII) binds to glutathione but does not deplete glutathione in vitro. Nonclinical CYP interaction studies data indicate that Formula (XVIII) is very unlikely to cause clinical drug-drug interactions through alteration of the metabolism of drugs that are substrates for CYP enzymes.

Example 14 – Clinical Study of a BTK Inhibitor in Leukemia/Lymphoma and Effects on Bone Marrow and Lymphoid Microenvironments

[001053] Clinical studies have shown that targeting the BCR signaling pathway by inhibiting BTK produces significant clinical benefit in patients with non-Hodgkin’s lymphoma (NHL). The second generation BTK inhibitor, Formula (XVIII), achieves significant oral bioavailability and potency, and has favorable preclinical characteristics, as described above. The purpose of this study is to evaluate the safety and efficacy of the second generation BTK inhibitor of Formula (XVIII) in treating subjects with chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL).

[001054] The design and conduct of this study is supported by an understanding of the history and current therapies for subjects with lymphoid cancers; knowledge of the activity and safety of a first-generation BTK inhibitor, ibrutinib, in subjects with hematologic cancers; and the available nonclinical information regarding Formula (XVIII). The collective data support the following conclusions. BTK expression plays an important role in the biology of lymphoid neoplasms, which represent serious and life-threatening disorders with continuing unmet medical need. Clinical evaluation of Formula (XVIII) as a potential treatment for these disorders has sound scientific rationale based on observations that the compound selectively abrogates BTK activity and shows activity in nonclinical models of lymphoid cancers. These data are supported by clinical documentation that ibrutinib, a first-generation BTK inhibitor, is clinically active in these diseases. Ibrutinib clinical data and Formula (XVIII) nonclinical safety pharmacology and toxicology studies support the safety of testing Formula (XVIII) in subjects with B cell malignancies.

[001055] The primary objectives of the clinical study are as follows: (1) establish the safety and the MTD of orally administered Formula (XVIII) in subjects with CLL/SLL; (2) determine pharmacokinetics (PK) of orally administered Formula (XVIII) and identification of its major
metabolite(s); and (3) measure pharmacodynamic (PD) parameters including drug occupancy of BTK, the target enzyme, and effect on biologic markers of B cell function.

[001056] The secondary objective of the clinical study is to evaluate tumor responses in patients treated with Formula (XVIII).

[001057] This study is a multicenter, open-label, nonrandomized, sequential group, dose escalation study. The following dose cohorts will be evaluated:

- Cohort 1: 100 mg/day for 28 days (= 1 cycle)
- Cohort 2: 175 mg/day for 28 days (= 1 cycle)
- Cohort 3: 250 mg/day for 28 days (= 1 cycle)
- Cohort 4: 350 mg/day for 28 days (= 1 cycle)
- Cohort 5: 450 mg/day for 28 days (= 1 cycle)
- Cohort 6: To be determined amount in mg/day for 28 days (= 1 cycle)

[001058] Each cohort will be enrolled sequentially with 6 subjects per cohort. If \( \leq 1 \) dose-limiting toxicity (DLT) is observed in the cohort during Cycle 1, escalation to the next cohort will proceed. Subjects may be enrolled in the next cohort if 4 of the 6 subjects enrolled in the cohort completed Cycle 1 without experiencing a DLT, while the remaining 2 subjects are completing evaluation. If \( \geq 2 \) DLTs are observed during Cycle 1, dosing at that dose and higher will be suspended and the MTD will be established as the previous cohort. The MTD is defined as the largest daily dose for which fewer than 33% of the subjects experience a DLT during Cycle 1. Dose escalation will end when either the MTD is achieved or at 3 dose levels above full BTK occupancy, whichever occurs first. Full BTK occupancy is defined as Formula (XVIII) active-site occupancy of \( \geq 80\% \) (average of all subjects in cohort) at 24 hours postdose. Should escalation to Cohort 6 be necessary, the dose will be determined based on the aggregate data from Cohorts 1 to 5, which includes safety, efficacy, and PK/PD results. The dose for Cohort 6 will not exceed 900 mg/day.

[001059] Treatment with Formula (XVIII) may be continued for \( > 28 \) days until disease progression or an unacceptable drug-related toxicity occurs. Subjects with disease progression
will be removed from the study. All subjects who discontinue study drug will have a safety follow-up visit 30 (±7) days after the last dose of study drug unless they have started another cancer therapy within that timeframe. Radiologic tumor assessment will be done at screening and at the end of Cycle 2, Cycle 4, and Cycle 12 and at investigator discretion. Confirmation of complete response (CR) will require bone marrow analysis and radiologic tumor assessment. For subjects who remain on study for > 11 months, a mandatory bone marrow aspirate and biopsy is required in Cycle 12 concurrent with the radiologic tumor assessment.

[001060] All subjects will have standard hematology, chemistry, and urinalysis safety panels done at screening. This study also includes pancreatic function assessment (serum amylase and serum lipase) due to the pancreatic findings in the 28-day GLP rat toxicity study. Once dosing commences, all subjects will be evaluated for safety once weekly for the first 4 weeks, every other week for Cycle 2, and monthly thereafter. Blood samples will be collected during the first week of treatment for PK/PD assessments. ECGs will be done at screening, and on Day 1-2, 8, 15, 22, 28 of Cycle 1, Day 15 and 28 of Cycle 2, and monthly thereafter through Cycle 6. ECGs are done in triplicate for screening only. Thereafter, single ECG tests are done unless a repeat ECG testing is required.

[001061] Dose-limiting toxicity is defined as any of the following events (if not related to disease progression): (1) any Grade ≥ 3 non-hematologic toxicity (except alopecia) persisting despite receipt of a single course of standard outpatient symptomatic therapy (e.g., Grade 3 diarrhea that responds to a single, therapeutic dose of Imodium® would not be considered a DLT); (2) grade ≥ 3 prolongation of the corrected QT interval (QTc), as determined by a central ECG laboratory overread; (3) grade 4 neutropenia (absolute neutrophil count [ANC] < 500/µL) lasting > 7 days after discontinuation of therapy without growth factors or lasting > 5 days after discontinuation of therapy while on growth factors (i.e., Grade 4 neutropenia not lasting as long as specified will not be considered a DLT), (4) grade 4 thrombocytopenia (platelet count < 20,000/µL) lasting > 7 days after discontinuation of therapy or requiring transfusion (i.e., Grade 4 thrombocytopenia not lasting as long as specified will not be considered a DLT), and (5) dosing delay due to toxicity for > 7 consecutive days.

[001062] The efficacy parameters for the study include overall response rate, duration of response, and progression-free survival (PFS). The safety parameters for the study include DLTs

[001063] The schedule of assessments is as follows, with all days stated in the following meaning the given day or +/- 2 days from the given day. A physical examination, including vital signs and weight, are performed at screening, during cycle 1 at 1, 8, 15, 22, and 28 days, during cycle 2 at 15 and 28 days, during cycles 3 to 24 at 28 days, and at follow up (after the last dose). The screening physical examination includes, at a minimum, the general appearance of the subject, height (screening only) and weight, and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, lymphatic system, and nervous system. Symptom-directed physical exams are done thereafter. Vital signs (blood pressure, pulse, respiratory rate, and temperature) are assessed after the subject has rested in the sitting position. Eastern Cooperative Oncology Group (ECOG) status is assessed at screening, during cycle 1 at 1, 8, 15, 22, and 28 days, during cycle 2 at 15 and 28 days, during cycles 3 to 24 at 28 days, and at follow up, using the published ECOG performance status indications described in Oken, *et al.*, *Am. J. Clin. Oncol.* 1982, 5, 649-655. ECG testing is performed at screening, during cycle 1 at 1, 2, 8, 15, 22, and 28 days, during cycle 2 at 15 and 28 days, during cycles 3 to 24 at 28 days, and at follow up. The 12-lead ECG test will be done in triplicate (≥ 1 minute apart) at screening. The calculated QTc average of the 3 ECGs must be <480 ms for eligibility. On cycle 1, day 1 and cycle 1, day 8, single ECGs are done predose and at 1, 2, 4, and 6 h postdose. The single ECG on Cycle 1 Day 2 is done predose. On cycle 1, day 15, day 22, and day 28, a single ECG is done 2 hours post-dose. Starting with cycle 2, a single ECG is done per visit. Subjects should be in supine position and resting for at least 10 minutes before study-related ECGs. Two consecutive machine-read QTc > 500 ms or > 60 ms above baseline require central ECG review. Hematology, including complete blood count with differential and platelet and reticulocyte counts, is assessed at screening, during cycle 1 at 1, 8, 15, 22, and 28 days, during cycle 2 at 15 and 28 days, during cycles 3 to 24 at 28 days, and at follow up. Serum chemistry is assessed at screening, during cycle 1 at 1, 8, 15, 22, and 28 days, during cycle 2 at 15 and 28 days, during cycles 3 to 24 at 28 days, and at follow up. Serum chemistry includes albumin, alkaline phosphatase, ALT, AST, bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, glucose, lactate dehydrogenase (LDH), magnesium, phosphate, potassium,
sodium, total bilirubin, total protein, and uric acid. Cell counts and serum immunoglobulin are performed at screening, at cycle 2, day 28, and at every 6 months thereafter until last dose and include T/B/NK/monocyte cell counts (CD3, CD4, CD8, CD14, CD19, CD19, CD16/56, and others as needed) and serum immunoglobulin (IgG, IgM, IgA, and total immunoglobulin). Bone marrow aspirates are performed at cycle 12. Pharmacodynamics samples are drawn during cycle 1 at 1, 2, and 8 days, and at follow up. On days 1 and 8, pharmacodynamic samples are drawn pre-dose and 4 hours (±10 minutes) post-dose, and on day 2, pharmacodynamic samples are drawn pre-dose. Pharmacokinetics samples are drawn during cycle 1 at 1, 2, 8, 15, 22, and 28 days. Pharmacokinetic samples for Cycle 1 Day 1 are drawn pre-dose and at 0.5, 1, 2, 4, 6 and 24 hours (before dose on Day 2) post-dose. Samples for Cycle 1 Day 8 are drawn pre-dose and at 0.5, 1, 2, 4, and 6 hours post-dose. On Cycle 1 Day 15, 22, and 28, a PK sample is drawn pre-dose and the second PK sample must be drawn before (up to 10 minutes before) the ECG acquisition, which is 2 hours postdose. Pretreatment radiologic tumor assessments are performed within 30 days before the first dose. A computed tomography (CT) scan (with contrast unless contraindicated) is required of the chest, abdomen, and pelvis. In addition, a positron emission tomography (PET) or PET/CT must done for subjects with SLL. Radiologic tumor assessments are mandatory at the end of Cycle 2 (-7 days), Cycle 4 (-7 days), and Cycle 12 (-7 days). Otherwise, radiologic tumor assessments are done at investigator discretion. A CT (with contrast unless contraindicated) scan of the chest, abdomen, and pelvis is required for subjects with CLL. In addition, a PET/CT is required in subjects with SLL. Bone marrow and radiologic assessments are both required for confirmation of a complete response (CR). Clinical assessments of tumor response should be done at the end of Cycle 6 and every 3 months thereafter. Molecular markers are measured at screening, and include interphase cytogenetics, stimulated karyotype, IgHV mutational status, Zap-70 methylation, and beta-2 microglobulin levels. Urinalysis is performed at screening, and includes pH, ketones, specific gravity, bilirubin, protein, blood, and glucose. Other assessments, including informed consent, eligibility, medical history, and pregnancy test are done at the time of screening.

TABLE 9. Response Assessment Criteria for CLL. Abbreviations: ANC = absolute neutrophil count; CR = complete remission; CRi = CR with incomplete blood count recovery; PR = partial remission.

<table>
<thead>
<tr>
<th>Response</th>
<th>Peripheral Blood</th>
<th>Bone Marrow (if performed)</th>
<th>Nodes, Liver, and Spleen&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>Lymphocytes &lt; 4 x 10⁹/L ANC &gt;1.5 x 10⁹/L&lt;sup&gt;b&lt;/sup&gt; Platelets &gt; 100 x 10⁹/L&lt;sup&gt;b&lt;/sup&gt; Hemoglobin &gt; 11.0 g/dL (untransfused)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Normocellular &lt;30% lymphocytes No B-lymphoid nodules</td>
<td>Normal (e.g., no lymph nodes &gt;1.5 cm)</td>
</tr>
<tr>
<td>CRi</td>
<td>Lymphocytes &lt; 4 x 10⁹/L Persistent anemia, thrombocytopenia, or neutropenia related to drug toxicity</td>
<td>Hypocellular &lt;30% lymphocytes</td>
<td>Normal (e.g., no lymph nodes &gt;1.5 cm)</td>
</tr>
<tr>
<td>PR</td>
<td>Lymphocytes ≥ 50% decrease from baseline ANC &gt; 1.5 x 10⁹/L or Platelets &gt; 100 x 10⁹/L or 50% improvement over baseline or Hemoglobin &gt; 11.0 g/dL or 50% improvement over baseline (untransfused)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Not assessed</td>
<td>≥50% reduction in lymphadenopathy&lt;sup&gt;c&lt;/sup&gt; and/or in spleen or liver enlargement</td>
</tr>
</tbody>
</table>

<sup>a</sup> Computed tomography (CT) scan of abdomen, pelvis, and chest is required for this evaluation

<sup>b</sup> Without need for exogenous growth factors

<sup>c</sup> In the sum products of ≤ 6 lymph nodes or in the largest diameter of the enlarged lymph node(s) detected before therapy and no increase in any lymph node or new enlarged lymph nodes

[001065] The response assessment criteria for SLL are summarized in Table 10.
TABLE 10. Response Assessment Criteria for SLL. Abbreviations: CR = complete remission, CT = computed tomography, FDG = $[^{18}\text{F}]$fluorodeoxyglucose, PET = positron-emission tomography, PR = partial remission, SD = stable disease, SPD = sum of the product of the diameters.

<table>
<thead>
<tr>
<th>Response</th>
<th>Definition</th>
<th>Nodal Masses</th>
<th>Spleen, Liver</th>
<th>Bone Marrow</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>Disappearance of all evidence of disease</td>
<td>(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT</td>
<td>Not palpable, nodules disappeared</td>
<td>If infiltrate present at screening, infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative</td>
</tr>
<tr>
<td>PR</td>
<td>Regression of measurable disease and no new sites</td>
<td>$\geq 50%$ decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; $\geq 1$ PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT</td>
<td>$\geq 50%$ decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen</td>
<td>Irrelevant if positive prior to therapy; cell type should be specified</td>
</tr>
<tr>
<td>SD</td>
<td>Failure to attain CR/PR or progressive disease</td>
<td>(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease, and no new sites on CT or PET (b) Variably FDG avid or PET negative; no change in size of previous lesions on CT</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[001066] The PK parameters of the study are as follows. The plasma PK of Formula (XVIII) and a metabolite is characterized using noncompartmental analysis. The following PK parameters are calculated, whenever possible, from plasma concentrations of Formula (XVIII):
AUC\textsubscript{(0-t)}: Area under the plasma concentration-time curve calculated using linear trapezoidal summation from time 0 to time t, where t is the time of the last measurable concentration (Ct),

AUC\textsubscript{(0-24)}: Area under the plasma concentration-time curve from 0 to 24 hours, calculated using linear trapezoidal summation,

AUC\textsubscript{(0-∞)}: Area under the plasma concentration-time curve from 0 to infinity, calculated using the formula: \[ AUC\textsubscript{(0-∞)} = AUC\textsubscript{(0-t)} + \frac{Ct}{\lambda z}, \]

where \( \lambda z \) is the apparent terminal elimination rate constant,

\( C_{max} \): Maximum observed plasma concentration,

\( T_{max} \): Time of the maximum plasma concentration (obtained without interpolation),

\( t_{1/2} \): Terminal elimination half-life (whenever possible),

\( \lambda_z \): Terminal elimination rate constant (whenever possible),

Cl/F: Oral clearance.

[001067] The PD parameters of the study are as follows. The occupancy of BTK by Formula (XVIII) are measured in peripheral blood mononuclear cells (PBMCs) with the aid of a biotin-tagged Formula (XVIII) analogue probe. The effect of Formula (XVIII) on biologic markers of B cell function will also be evaluated.

[001068] The statistical analysis used in the study is as follows. No formal statistical tests of hypotheses are performed. Descriptive statistics (including means, standard deviations, and medians for continuous variables and proportions for discrete variables) are used to summarize data as appropriate.

[001069] The following definitions are used for the safety and efficacy analysis sets: Safety analysis set: All enrolled subjects who receive \( \geq 1 \) dose of study drug; Per-protocol (PP) analysis set: All enrolled subjects who receive \( \geq 1 \) dose of study drug and with \( \geq 1 \) tumor response assessment after treatment. The safety analysis set will be used for evaluating the safety parameters in this study. The PP analysis sets will be analyzed for efficacy parameters in this study.

[001070] No imputation of values for missing data is performed except for missing or partial start and end dates for adverse events and concomitant medication will be imputed according to
prespecified, conservative imputation rules. Subjects lost to follow-up (or drop out) will be included in statistical analyses to the point of their last evaluation.

[001071] The safety endpoint analysis was performed as follows. Safety summaries will include summaries in the form of tables and listings. The frequency (number and percentage) of treatment emergent adverse events will be reported in each treatment group by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class and Preferred Term. Summaries will also be presented by the severity of the adverse event and by relationship to study drug. Laboratory shift tables containing counts and percentages will be prepared by treatment assignment, laboratory parameter, and time. Summary tables will be prepared for each laboratory parameter. Figures of changes in laboratory parameters over time will be generated. Vital signs, ECGs, and physical exams will be tabulated and summarized.

[001072] Additional analyses include summaries of subject demographics, baseline characteristics, compliance, and concurrent treatments. Concomitant medications will be coded according to the World Health Organization (WHO) Drug Dictionary and tabulated.

[001073] The analysis of efficacy parameters was performed as follows. The point estimate of the overall response rate will be calculated for the PP analysis set. The corresponding 95% confidence interval also will be derived. The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started). Kaplan-Meier methodology will be used to estimate event-free curves and corresponding quantiles (including the median). Progression-free survival is measured from the time of first study drug administration until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started). Kaplan-Meier methodology will be used to estimate the event-free curves and corresponding quantiles (including the median).

[001074] The study scheme is a sequential cohort escalation. Each cohort consists of six subjects. The sample size of the study is 24 to 36 subjects, depending on dose escalation into subsequent cohorts. Cohort 1 (N = 6) consists of Formula (XVIII), 100 mg QD for 28 days. Cohort 2 (N =
6) consists of Formula (XVIII), 175 mg QD for 28 days. Cohort 3 (N = 6) consists of Formula
(XVIII), 250 mg QD for 28 days. Cohort 4 (N = 6) consists of Formula (XVIII), 350 mg QD for
28 days. Cohort 5 (N = 6) consists of Formula (XVIII), 450 mg QD for 28 days. Cohort 6 (N =
6) consists of Formula (XVIII), at a dose to be determined QD for 28 days. The dose level for
Cohort 6 will be determined based on the safety and efficacy of Cohorts 1 to 5, and will not exceed 900 mg/day. Escalation will end with either the MTD cohort or three levels above full
BTK occupancy, whichever is observed first. An additional arm of the study will explore 100
mg BID dosing. Treatment with oral Formula (XVIII) may be continued for greater than 28
days until disease progression or an unacceptable drug-related toxicity occurs.

[001075] The inclusion criteria for the study are as follows: (1) men and women ≥ 18 years of
age with a confirmed diagnosis of CLL/SLL, which has relapsed after, or been refractory to, ≥ 2
previous treatments for CLL/SLL; however, subjects with 17p deletion are eligible if they have
relapsed after, or been refractory to, 1 prior treatment for CLL/SLL; (2) body weight ≥ 60 kg, (3)
ECOG performance status of ≤ 2; (4) agreement to use contraception during the study and for 30
days after the last dose of study drug if sexually active and able to bear children; (5) willing and
able to participate in all required evaluations and procedures in this study protocol including
swallowing capsules without difficulty; or (6) ability to understand the purpose and risks of the
study and provide signed and dated informed consent and authorization to use protected health
information (in accordance with national and local subject privacy regulations).

[001076] The dosage form and strength of Formula (XVIII) used in the clinical study is a hard
gelatin capsules prepared using standard pharmaceutical grade excipients (microcrystalline
cellulose) and containing 25 mg of Formula (XVIII) each. The color of the capsules is Swedish
orange. The route of administration is oral (per os, or PO). The dose regimen is once daily or
twice daily, as defined by the cohort, on an empty stomach (defined as no food 2 hours before
and 30 minutes after dosing).
The baseline characteristics for the patients enrolled in the clinical study are given in Table 11.

TABLE 11. Relapsed/refractory CLL baseline characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CLL (N=44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Demographics</td>
<td></td>
</tr>
<tr>
<td>Age (years), median (range)</td>
<td>62 (45-84)</td>
</tr>
<tr>
<td>Sex, men (%)</td>
<td>33 (75)</td>
</tr>
<tr>
<td>Prior therapies, median (range), n</td>
<td>3 (1-10)</td>
</tr>
<tr>
<td>≥3 prior therapies, n (%)</td>
<td>26 (59)</td>
</tr>
<tr>
<td>Clinical Details</td>
<td></td>
</tr>
<tr>
<td>ECOG performance status ≥1 (%)</td>
<td>28 (63)</td>
</tr>
<tr>
<td>Rai stage III/IV</td>
<td>16 (36)</td>
</tr>
<tr>
<td>Bulky disease ≥ 5 cm, n (%)</td>
<td>15 (34)</td>
</tr>
<tr>
<td>Cytopenia at baseline</td>
<td>33 (75)</td>
</tr>
<tr>
<td>Cytopicnic Status</td>
<td></td>
</tr>
<tr>
<td>Chromosome 11q22.3 deletion (Del 11q), n (%)</td>
<td>18 (41)</td>
</tr>
<tr>
<td>Chromosome 17p13.1 (Del 17p), n (%)</td>
<td>19 (34)</td>
</tr>
<tr>
<td>IgVH status (unmutated), n (%)</td>
<td>28 (64)</td>
</tr>
</tbody>
</table>

The results of the clinical study in relapsed/refractory CLL patients are summarized in Table 12.

TABLE 12. Activity of Formula (XVIII) in relapsed/refractory CLL. (PR = partial response; PR+L = partial response with lymphocytosis; SD = stable disease; PD = progressive disease.)

<table>
<thead>
<tr>
<th>n (%)</th>
<th>All Cohorts (N=31)†</th>
<th>100 mg QD (N=8)</th>
<th>175 mg QD (N=8)</th>
<th>250 mg QD (N=7)</th>
<th>100 mg BID (N=3)</th>
<th>400 mg QD (N=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>22 (71)</td>
<td>7 (88)</td>
<td>5 (63)</td>
<td>5 (71)</td>
<td>3 (100)</td>
<td>2 (40)</td>
</tr>
<tr>
<td>PR+L</td>
<td>7 (23)</td>
<td>0 (0)</td>
<td>3 (37)</td>
<td>2 (29)</td>
<td>0 (0)</td>
<td>2 (40)</td>
</tr>
<tr>
<td>SD</td>
<td>2 (6)</td>
<td>1 (12)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (20)</td>
</tr>
<tr>
<td>PD</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Median (range) Cycles

|       | 7.3 (3.0-10.8)      | 10.0 (9.0-10.8) | 8.6 (3.0-8.8) | 7.0 (7.0-7.3) | 5.2 (4.7-5.5) | 5.0 (4.8-5.5) |

508
[001079] FIG. 138 shows the median % change in ALC and SPD from baseline in the clinical study of Formula (XVIII), plotted in comparison to the results reported for ibrutinib in Figure 1A of Byrd, et al., N. Engl. J. Med. 2013, 369, 32-42. The results show that Formula (XVIII) leads to a more rapid patient response in CLL than corresponding treatment with ibrutinib. This effect is illustrated, for example, by the median % change in SPD, which achieved the same status in the present study at 7 months of treatment with Formula (XVIII) as compared to 18 months for ibrutinib. The % change in SPD observed in the different cohorts (i.e. by dose and dosing regimen) is shown in FIG. 139, and in all cases shows significant responses.

[001080] A Kaplan-Meier curve showing PFS from the clinical CLL study of Formula (XVIII) is shown in FIG. 140. A comparison of survival curves was performed using the Log-Rank (Mantle-Cox) test, with a p-value of 0.0206 indicating that the survival curves are different. The number of patients at risk is shown in FIG. 141. Both FIG. 140 and FIG. 141 show the results for Formula (XVIII) in comparison to the results reported for ibrutinib in Byrd, et al., N. Engl. J. Med. 2013, 369, 32-42. An improvement in survival and a reduction in risk are observed in CLL patients treated with Formula (XVIII) in comparison to patients treated with ibrutinib.

[001081] Based on the data and comparisons shown in FIG. 138 to FIG. 141, the CLL study with Formula (XVIII) showed that the efficacy of Formula (XVIII) was surprisingly superior to that of ibrutinib.

[001082] In the literature study of ibrutinib, increased disease progression was associated with patients with high-risk cytogenetic lesions (17p13.1 deletion or 11q22.3 deletion), as shown in Figure 3A in Byrd, et al., N. Engl. J. Med. 2013, 369, 32-42, which shows ibrutinib PFS including PFS broken down by genetic abnormality. The 17p and 11q deletions are validated high-risk characteristics of CLL, and the 17p deletion is the highest risk. In FIG. 142, the PFS is shown for Formula (XVIII) in patients with the 17p deletion in comparison to the results obtained for ibrutinib in Byrd, et al., N. Engl. J. Med. 2013, 369, 32-42. A p-value of 0.0696 was obtained. In FIG. 143, the number of patients at risk with the 17p deletion is compared. To date, no 17p patients have progressed on Formula (XVIII).
The adverse events observed in the clinical study in relapsed/refractory CLL are given in Table 13. No DLTs were observed. The MTD was not reached. No treatment-related serious adverse events (SAEs) were observed. No prophylactic antivirals or antibiotics were needed.

**TABLE 13.** Treatment-related adverse events reported in the clinical study of Formula (XVIII) in relapsed/refractory CLL. (Reported in ≥ 5% of patients.)

<table>
<thead>
<tr>
<th>Adverse Events (Treatment-Related), n (%)</th>
<th>Grade</th>
<th>All (N=44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>1/2</td>
<td>7 (16)</td>
</tr>
<tr>
<td>Increased tendency to bruise</td>
<td>1</td>
<td>6 (14)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1</td>
<td>4 (9)</td>
</tr>
<tr>
<td>Petechiae</td>
<td>1</td>
<td>3 (7)</td>
</tr>
</tbody>
</table>

The clinical study of Formula (XVIII) thus showed other unexpectedly superior results compared to ibrutinib therapy. A lack of lymphocytosis was observed in the study. Furthermore, only grade 1 AEs were observed, and these AEs were attributable to the high BTK selectivity of Formula (XVIII).

BTK target occupancy was measured for relapsed/refractory CLL patients with the results shown in FIG. 144. For 200 mg QD dosing of the BTK inhibitor of Formula (XVIII), approximately 94% - 99% BTK occupancy was observed, with superior 24 hour coverage and less inter-patient variability also observed. For 420 mg and 840 mg QD of the BTK inhibitor ibrutinib, 80% - 90% BTK occupancy was observed, with more inter-patient variability and capped occupancy. These results indicate that the BTK inhibitor of Formula (XVIII) achieves superior BTK occupancy in CLL patients than ibrutinib.

The effects of Formula (XVIII) on cell subset percentages were also evaluated using flow cytometry analysis of peripheral blood, with the results shown in FIG. 145, FIG. 146, FIG. 147, FIG. 148, FIG. 149, and FIG. 150. PBMC samples from CLL patient samples drawn prior to (predose) and after 28 days of dosing with Formula (XVIII) were compared for potential changes in cell subsets. PBMCs were stained with monoclonal antibodies conjugated to fluorescent tags (fluorochromes) to identify cell subsets via flow cytometry. Non-viable cells were excluded from the analysis using the dye 7-aminoactinomycin D (7-AAD). To produce the
metric of percent change, the following steps were taken. First, each cell subset was defined by hierarchical flow cytometry gating. Then, the change in frequency (between day 1 and day 28) was calculated for each cell subset. MDSC subsets were measured as a % of all myeloid cells. T cell subsets were measured as a % of all CD3+ cells, and NK cells were measured as a % of all live CD45+ cells. In FIG. 145 and FIG. 146, the results show the % change in MDSC (monocytic) level over 28 days versus % ALC change at cycle 1 day 28 (C1D28) and at cycle 2 day 28 (C2D28). A cycle is 28 days. A trend is observed wherein patients with decreasing ALC % had increasing MDSC (monocytic) %. This may include patients who had quickly resolving lymphocytosis and those with no initial lymphocytosis. This provides evidence that treatment with Formula (XVIII) mobilizes MDSCs and thus affects the CLL tumor microenvironment in marrow and lymph nodes, which is an unexpected indication of superior efficacy. In FIG. 147 and FIG. 148, the results show the % change in NK cell level over 28 days versus % ALC change, measured at C1D28 or C2D28, and similar trends are observed wherein patients with decreasing ALC % had increasing NK cell %. This may include patients who had quickly resolving lymphocytosis and those having no initial lymphocytosis. The effects in FIG. 145 to FIG. 148 are observed in multiple cohorts, at doses including 100 mg BID, 200 mg QD, and 400 mg QD. In FIG. 149 and FIG. 150, the effects on NK cells and MDSC cells are compared to a number of other markers versus % change in ALC at C1D28 and C2D28. These other markers include CD4+ T cells, CD8+ T cells, CD4+/CD8+ T cell ratio, NK-T cells, PD-1+ CD4+ T cells, and PD-1+ CD8+ T cells. The effects on NK cells and MDSC cells are observed to be much more pronounced than on any of these other markers.

[001087] These indicate suggest that after Formula (XVIII) administration, the CLL microenvironment undergoes a change wherein NK cells and monocytic MDSC subsets increase in frequency in the peripheral blood in patients with falling ALC counts, an important clinical parameter in CLL. The NK cell increase may reflect an overall increase in cytolytic activity against B-CLL resulting in the ALC % to drop. The increase in MDSC % in the blood may be due to a movement of these cells out of the lymph nodes, spleen, and bone marrow, which are all possible sites of CLL proliferation. Fewer MDSCs at the CLL proliferation centers would likely result in a reduced immunosuppressive microenvironment leading to an increase in cell-mediated immunity against the tumor, decreased tumor proliferation, and eventually lower ALC% in the circulation.
Clinical results from the CLL study are shown in FIG. 151 to FIG. 156. FIG. 151 shows an update of the data presented in FIG. 138. FIG. 152 shows an update of the data presented in FIG. 144, and includes BID dosing results. Formula (XVIII) 200 mg QD dosing resulted in 94% - 99% BTK occupancy, 24 hour coverage, and less inter-patient variability. Ibrutinib 420 mg and 840 mg QD dosing resulted in 80% - 90% BTK occupancy, more inter-patient variability, and capped occupancy. Formula (XVIII) 100 mg BID dosing resulted in 97% - 99% BTK occupancy, complete BTK coverage, and less inter-patient variability. The PFS for patients with 17p deletions and 11q deletions are illustrated in FIG. 153, FIG. 154, and FIG. 155. Additional SPD results are illustrated in FIG. 156.

Treatment of CLL patients with Formula (XVIII) also resulted in increased apoptosis, as illustrated in FIG. 157. Apoptotic B-CLL was defined by flow cytometry as having cleaved PARP\(^\text{\textregistered}\), Caspase 3\(^+\), CD19\(^+\), and CD5\(^-\) phenotypes. 82% of samples tested had a baseline change greater than 25%. Treatment of CLL patients also showed that Formula (XVIII) decreased plasma chemokines associated with MDSC homing and retention. A significant decrease in CXCL12 and CCL2 levels has been observed in patients treated with Formula (XVIII), as shown in FIG. 158 and FIG. 159, respectively.

Overall, Formula (XVIII) shows superior efficacy to first generation BTK inhibitors such as ibrutinib, or to monotherapy with PI3K-\(\delta\) inhibitors such as idelalisib. Formula (XVIII) has better target occupancy and better pharmacokinetic and metabolic parameters than ibrutinib, leading to improved B cell apoptosis. Furthermore, unlike treatment with ibrutinib and PI3K-\(\delta\) inhibitors, treatment with Formula (XVIII) does not affect NK cell function. Finally, treatment with Formula (XVIII) leads to a CLL tumor microenvironmental effect by excluding MDSC cells from the marrow and lymph nodes and reducing their number.

Example 15 – Clinical Study of a BTK Inhibitor in Leukemia/Lymphoma in Combination with Obinutuzumab (GA-101)

The primary objectives of the study are (1) to determine the overall response rate (ORR) at 12 months with the combination of Formula (XVIII) and obinutuzumab in patients with relapsed or refractory CLL, (2) to determine the ORR at 12 months with the combination of Formula (XVIII) and obinutuzumab in patients with treatment-naive CLL, and (3) to establish the safety and feasibility of the combination of Formula (XVIII) and obinutuzumab.
The secondary objectives of this study are: (1) to determine the complete response (CR) rate and MRD-negative CR rate in previously untreated and relapsed and refractory CLL with this regimen; (2) to determine the progression-free survival (PFS), time to next treatment (TTNT), and overall survival (OS) with this regimen, (3) to perform baseline analysis of patients enrolled on this trial including fluorescence in situ hybridization (FISH), stimulated karyotype, Zap-70 methylation, and IgV_{H} mutational status and describe relationships between these biomarkers and ORR or PFS for patients treated with this regimen; (4) to determine pharmacokinetics (PK) of orally administered Formula (XVIII); (5) to measure pharmacodynamic (PD) parameters including drug occupancy of BTK, change in miR and gene expression on day 8 and 29 of therapy of Formula (XVIII); (6) to determine the influence of Formula (XVIII) on NK cell and T cell function in vivo; (7) to assess for serial development of resistance by baseline and longitudinal assessment of mutations of BTK and PLCG2 at regular follow up intervals and by examining diagnosis to relapse samples by whole exome sequencing; (8) to determine the influence of Formula (XVIII) on emotional distress and quality of life in CLL patients; and (9) to determine trajectory of psychological and behavioral responses to Formula (XVIII) and covariation with response to therapy.

CLL is the most prevalent form of adult leukemia and has a variable clinical course, where many patients do not require treatment for years and have survival equal to age matched controls. Other patients, however, exhibit aggressive disease and have a poor prognosis despite appropriate therapy. Byrd, et al., Chronic lymphocytic leukemia. Hematol Educ Program. 2004, 163-183. While patients with early disease have not been shown to have a survival advantage with early treatment, most patients will eventually require therapy for their disease with the onset of symptoms or cytopenias, and despite the relatively long life expectancy for early stage disease, CLL remains an incurable disease. Patients diagnosed with or progressing to advanced disease have a mean survival of 18 months to 3 years. Unfortunately these patients with advanced disease are also more refractory to conventional therapy.

The treatment of CLL has progressed significantly over the previous decades. While alkylator therapy was used in the past, randomized trials have demonstrated a higher response rate and longer progression free survival (PFS) with fludarabine and subsequently with
While fludarabine based chemoimmunotherapy is standard for younger patients, the therapy for older patients is less well defined. In the large Phase 2 and 3 trials outlined previously, median ages were typically in the early-60s, while the average age of patients diagnosed with CLL is 72, which calls into question whether these results are generalizable to the entire CLL population. In fact, the one randomized Phase 3 trial investigating primary CLL therapy in older patients demonstrated that in patients >65 years old, fludarabine is not superior to chlorambucil. Eichhorst, et al., First-line therapy with fludarabine compared with chlorambucil does not result in a major benefit for elderly patients with advanced chronic lymphocytic leukemia. Blood 2009, 114, 3382-91. This finding was corroborated by a large retrospective study of front-line trials performed by the Alliance for Clinical Trials in Oncology, which demonstrated again that fludarabine is not superior to chlorambucil in older patients, but also showed that the addition of rituximab to chemotherapy was beneficial regardless of age. Woyach, et al., Impact of age on outcomes after initial therapy with chemotherapy and different chemoimmunotherapy regimens in patients with chronic lymphocytic leukemia: Results of sequential cancer and leukemia group B studies. J. Clin. Oncol. 2013, 31, 440-7. Two studies have evaluated the combination of rituximab with chlorambucil, showing that this combination is safe and moderately effective. Hillmen, et al., rituximab plus chlorambucil in patients with CD20-positive B-cell chronic lymphocytic leukemia (CLL): Final response analysis of an open-label Phase II Study, ASH Annual Meeting Abstracts, Blood 2010, 116, 697; Foa, et al., A Phase II study of chlorambucil plus rituximab followed by maintenance versus observation in elderly patients with previously untreated chronic lymphocytic leukemia: Results of the first interim analysis, ASH Annual Meeting Abstracts, Blood 2010, 116, 2462.

Recently, the type II glycoengineered CD20 monoclonal antibody obinutuzumab was introduced. In a Phase 1 trial of previously treated CLL as monotherapy, this antibody has a 62% response rate including 1 MRD-negative complete response, suggesting that alone this antibody may be more active in CLL than rituximab. Morschhauser, et al., Phase I study of R05072759 (GA101) in relapsed/refractory chronic lymphocytic leukemia, ASH Annual Meeting Abstracts. Blood, 2009, 114, 884. The German CLL Study Group (GCLLSG) recently completed a Phase 3 trial of rituximab and chlorambucil or obinutuzumab and chlorambucil vs chlorambucil alone in patients with untreated CLL and significant comorbidities. In this population, obinutuzumab and chlorambucil (but not rituximab and chlorambucil) improved OS
over chlorambucil alone (hazard ratio 0.41, \( p=0.002 \)), and obinutuzumab and chlorambucil improved PFS over rituximab and chlorambucil (median PFS 26.7 months vs 14.9 months, \( p<0.001 \)). Goede, et al., Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions, \textit{N. Engl. J. Med.} \textbf{2014}, \textit{370}, 1101-10. On the basis of these favorable data, the combination of obinutuzumab and chlorambucil is FDA approved as frontline therapy for CLL patients.

[001097] Many older patients are also treated with the combination of bendamustine plus rituximab (BR). Although BR has not been compared directly with chlorambucil and rituximab, results of a recent Phase 2 trial show an ORR of 88% with a median event free survival of 33.9 months and 90.5% OS at 27 months. Fischer, et al., Bendamustine in combination with rituximab for previously untreated patients with chronic lymphocytic leukemia: A multicenter phase II trial of the German Chronic Lymphocytic Leukemia Study Group. \textit{J. Clin. Oncol.} \textbf{2012}, \textit{30}, 3209-16. These results held for patients \( >70 \) years old, and compare favorably with results published for chlorambucil and rituximab. While results with this regimen appear to be improved over historical controls, outcomes are not as good as those observed in younger patients with chemoimmunotherapy. Therefore, the optimal therapy for older patients remains an unmet need in clinical trials.


[001099] In an ongoing Phase Ib/2 study, the BTK inhibitor ibrutinib has shown activity in patients with relapsed or refractory CLL. In patients with relapsed or refractory CLL and measurable lymphadenopathy, the rate of lymph node shrinkage >50% is 89%. With a median follow-up of 4 months, ORR was 48% due to asymptomatic lymphocytosis, and with longer follow-up of 26 months in patients receiving the 420 mg dose, has improved to 71%, with an additional 20% of patients achieving a partial response with lymphocytosis (PR-L). Byrd, et al., Activity and tolerability of the Bruton's tyrosine kinase (Btk) inhibitor PCI-32765 in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL): Interim results of a phase Ib/II study. J. Clin. Oncol. ASCO Annual Meeting Abstracts, 2011, 29, Abstract 6508; Byrd, et al. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. N. Engl. J. Med. 2013, 369, 32-42. This lymphocytosis is likely related to B cell release from lymph node, spleen and marrow microenvironment due to disruption of homing signals or chemoattractants that are relevant to usual lymphocyte circulation dynamics. Lymphocytosis with ibrutinib is seen within 1-2 weeks of starting therapy, reaches plateau within the first 2-3 cycles, and has resolved over time in virtually all patients. The duration of lymphocytosis does not appear to be related to the depth of eventual response nor to response duration. Woyach, et al., Prolonged
lymphocytosis during ibrutinib therapy is associated with distinct molecular characteristics and does not indicate a suboptimal response to therapy. *Blood* **2014**, 123, 1810-7. Response to ibrutinib occurs independently of high-risk genomic features including IgV<sub>ni</sub> mutational status and del(17p13.1). Responses to this drug have been durable as well, with an estimated 26 month PFS of 76% and OS of 83% for these relapsed and refractory patients. This study also included a cohort of 31 previously untreated patients. With 16.6 months of follow-up, ORR is 71%, with an additional 10% of patients having persistent lymphocytosis; estimated 22 month PFS is 96%. This agent is currently in Phase 3 trials in treatment-naïve disease and is currently FDA approved for the treatment of relapsed CLL. These data with ibrutinib support the potential benefits of selective BTK inhibition in CLL. However, while highly potent in inhibiting BTK, ibrutinib has also shown in vitro activity against other kinases (*e.g.*, epidermal growth factor receptor), which may be the cause of ibrutinib-related diarrhea and rash. Honigberg, *et al.*, The Bruton tyrosine kinase inhibitor PCI-32765 blocks B-cell activation and is efficacious in models of autoimmune disease and B-cell malignancy. *Proc. Natl. Acad. Sci. USA* **2010**, 107, 13075-13080. In addition, it is a substrate for both cytochrome P450 (CYP) enzymes 3A4/5, which increases the possibility of drug-drug interactions. Finally, the inhibition of ITK that is seen with ibrutinib has the potential to abrogate NK cell ADCC, which makes combination with monoclonal antibodies less effective. Kohrt, *et al.*, Ibrutinib antagonizes rituximab-dependent NK cell-mediated cytotoxicity. *Blood* **2014**, 123, 1957-60. These liabilities support the development of alternative BTK inhibitors for use in the therapy of lymphoid cancers.

**[001100]** In this Phase 1B study, two cohorts (relapsed/refractory and treatment-naïve) will be evaluated with slightly staggered enrollment. First, 6 subjects with R/R CLL will be enrolled into Cohort 1. Once the safety has been evaluated, the R/R cohort will be expanded to 26 subjects and enrollment of 6 treatment-naïve subjects can begin in Cohort 2. Once safety is established for Cohort 2, then the cohort will be expanded to 19 subjects.

**[001101]** Formula (XVIII) will be administered starting cycle 1 day 1 and will be administered twice daily (100 mg BID) until disease progression. Obinutuzumab will be given in the standard dosing fashion starting on cycle 2 day 1. On cycle 2 day 1, patients will receive 100 mg IV. On cycle 2 day 2, patients will receive 900 mg. On cycle 2 days 8 and 15, patients will receive 1000 mg IV. On cycles 3-7, patients will receive 1000 mg on day 1 of each cycle.
For patients treated at dose level -1, 100 mg will be given on Day 1 and 650 mg on Day 2 of Cycle 2. On cycle 2 day 8 and 15, patients will receive 750 mg IV and during cycles 3-7, patients will receive 750 mg on Day 1 of each cycle. It is acceptable for cycles to begin < a 24-hour (1 business day) window before and after the protocol-defined date for Day 1 of a new cycle.

The inclusion criteria for patient eligibility are as follows: (1) Patients with a diagnosis of intermediate or high risk CLL (or variant immunophenotype), SLL, or B-PLL by IWCLL 2008 criteria" who have: (a) COHORT 1: Previously received at least one therapy for their disease; (b) COHORT 2: Previously untreated disease and > 65 years old OR under 65 years old and refuse or are ineligible for chemoimmunotherapy; (2) Patients on Cohort 1 may have received previous ibritinib (or another BTK inhibitor) as long as discontinuation was for a reason other than "on-treatment" disease progression; (3) All patients must satisfy one of the following criteria for active disease requiring therapy: (a) Evidence of marrow failure as manifested by the development or worsening of anemia or thrombocytopenia (not attributable to autoimmune hemolytic anemia or thrombocytopenia); (b) Massive (> 6 cm below the costal margin), progressive or symptomatic splenomegaly; (c) Massive nodes (> 10 cm) or progressive or symptomatic lymphadenopathy; (d) Constitutional symptoms, which include any of the following: Unintentional weight loss of 10% or more within 6 months, Significant fatigue limiting activity, Fevers > 100.5 degrees F for 2 weeks or more without evidence of infection, Night sweats > 1 month without evidence of infection; (4) Measurable nodal disease by computed tomography (CT). Measurable nodal disease is defined as > 1 lymph node > 1.5 cm in the longest diameter in a site; (5) Patients with a history of Richter's syndrome are eligible if they now have evidence of CLL only, with < 10% large cells in the bone marrow; (6) Subjects must have adequate organ function, defined as creatinine < 2.5 times the upper limit of normal (ULN), ALT and AST < 3.0 x ULN, and bilirubin < 2.5 x ULN; (7) Platelets > 50 x 10^9/L. In subjects with CLL involvement of the marrow, > 30 x 10^9/L; (8) ANC > 750/mm^3 In subjects with CLL involvement of the marrow, ANC > 500/mm^3; (9) Subject must have an ECOG performance status < 2; (10) Subject must not have secondary cancers that result in a life expectancy of < 2 years or that would confound assessment of toxicity in this study; (11) Subjects must be > 18 years of age; (12) Subject must provide written informed consent. A signed copy of the consent form will be retained in the patient’s chart; (13) Subject must be able to receive outpatient
treatment and follow-up at the treating institution; (14) Subject must have completed all CLL therapies > 4 weeks prior to first study dose. Palliative steroids are allowed, but must be at a dose equivalent of < 20 mg prednisone daily for at least 1 week prior to treatment initiation; (15) Subjects capable of reproduction and male subjects who have partners capable of reproduction must agree to use an effective contraceptive method during the course of the study and for 2 months following the completion of their last treatment. Females of childbearing potential must have a negative β-hCG pregnancy test result within 3 days of first study dose. Female patients who are surgically sterilized or who are > 45 years old and have not experienced menses for > 2 years may have their β-hCG pregnancy test waived; (16) Subjects must be able to swallow whole capsules.

The exclusion criteria for patient eligibility are as follows: (1) For cohort 1, previous therapy for CLL. Treatment of autoimmune complications of CLL with steroids or rituximab is allowed, however, CD20 must have returned on 10% of the CLL cells if rituximab was recently administered. Palliative steroids are acceptable at doses < 20 mg prednisone equivalent daily; (2) Any life-threatening illness, medical condition, or organ dysfunction which, in the investigator’s opinion, could compromise the patients’ safety, interfere with the absorption or metabolism of Formula (XVIII), or put the study outcomes at undue risk; (3) Female subjects who are pregnant or breastfeeding; (4) Subjects with active cardiovascular disease not medically controlled or those who have had myocardial infarction in the past 6 months, or QTc > 480 ms; (5) Malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel or gastric bypass, ulcerative colitis, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction; (6) Grade 2 toxicity (other than alopecia) continuing from prior anticancer therapy including radiation; (7) Major surgery within 4 weeks before first dose of study drug; (8) History of a bleeding diathesis (e.g., hemophilia, von Willebrand disease); (9) Uncontrolled autoimmune hemolytic anemia or idiopathic thrombocytopenia purpura; (10) History of stroke or intracranial hemorrhage within 6 months before the first dose of study drug; (11) Requires or receiving anticoagulation with warfarin or equivalent vitamin K antagonists (eg, phenprocoumon) within 28 days of first dose of study drug; (12) Requires treatment with long-acting proton pump inhibitors (e.g., omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole); (13) Subjects with active infections requiring IV antibiotic/antiviral therapy are not eligible for entry
onto the study until resolution of the infection. Patients on prophylactic antibiotics or antivirals are acceptable; (14) Subjects with history of or ongoing drug-induced pneumonitis; (15) Subjects with human immunodeficiency virus (HIV) or active infection with hepatitis C virus (HCV) or hepatitis B virus (HBV) or any uncontrolled active systemic infection; (16) Subjects who are known to have Hepatitis B infection or who are hepatitis B core antibody or surface antigen positive. Patients receiving prophylactic WIG may have false positive hepatitis serologies. Patients who are on WIG who have positive hepatitis serologies must have a negative hepatitis B DNA to be eligible; (17) Subjects with substance abuse or other medical or psychiatric conditions that, in the opinion of the investigator, would confound study interpretation or affect the patient's ability to tolerate or complete the study; (18) Subjects cannot concurrently participate in another therapeutic clinical trial; (19) Subjects who have received a live virus vaccination within 1 month of starting study drug.

In this study, Formula (XVIII) is administered 100 mg BID, with the second dose 11-13 hours after the first. Obinutuzumab is administered by IV infusion as an absolute (flat) dose. Obinutuzumab is administered in a single day, with the exception of the first administration when patients receive their first dose of obinutuzumab over two consecutive days (split dose) in Cycle 2: 100 mg on Day 1 and 900 mg on Day 2. For patients treated at dose level -1 (750 mg obinutuzumab), - 100 mg will be given on Day 1 and 650 mg on Day 2. On days when both Formula (XVIII) and obinutuzumab are given, the order of study treatment administration will be Formula (XVIII) followed at least 1 hour later by obinutuzumab. The full dosing schedule is given in Table 14.

TABLE 14. Dosing of obinutuzumab during 6 treatment cycles each of 28 days duration.

<table>
<thead>
<tr>
<th>Day of Treatment Cycle</th>
<th>Dose of Obinutuzumab</th>
<th>Rate of Infusion (In the absence of infusion reactions/hypersensitivity during previous infusions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>100 mg</td>
<td>Administer at 25 mg/hr over 4 hours. Do not increase the infusion rate.</td>
</tr>
</tbody>
</table>
Anti-CD20 antibodies have a known safety profile, which include infusion related reactions (IRR). Anti-CD20 antibodies, and in particular obinutuzumab, can cause severe and life threatening infusion reactions. Sequelae of the infusion reactions include patient discontinuations from antibody treatment leading to suboptimal efficacy or increased medical resource utilization, such as hospitalization for hypotension or prolonged antibody infusion time. In the initial study of obinutuzumab in relapsed/refractory CLL patients (Cartron, et al., Blood 2014, 124, 2196), all patients (n=13) in the Phase 1 portion experienced IRRs (15% Grade 3, no Grade 4, and 100% patients experienced all grade AE), with hypotension and pyrexia the most common symptoms. In the Phase 2 portion of the study, 95% of patients developed IRR, with 60% of cases developing symptoms of hypotension; of those, 25% were Grade 3 reactions. In the pivotal trial of obinutuzumab and chlorambucil in previously untreated patients, 69% developed infusion related reactions, of which 21% were grade 3-4.

The results of the Phase 1b study described in this example for Formula (XVIII) in combination with obinutuzumab for patients with relapsed/refractory or untreated CLL/SLL/PLL are as follows. 6 patients have been treated in the study to date with the combination of Formula (XVIII) and obinutuzumab. Patients are first treated with a month run-in of Formula (XVIII) alone, then on cycle 2, day 1, patients are given obinutuzumab. To date, 41 doses of obinutuzumab have been administered to 6 patients. Lymphocyte counts immediately prior to treatment with obinutuzumab have ranged from 8 to 213 × 10⁹/L. No cases of serious or Grade 3-4 IRRs have been reported. Only 2 patients have had obinutuzumab temporarily held for chills and arthralgias/sluured, respectively, and were able to complete the planned infusion. An additional 3 patients had adverse events within 24 hours of the infusion, all
grade 1 (terms: flushing, palpitations in one patient, rash, and restlessness and headache). Consequently, there has been a substantial decrease in serious or Grade 3-4 IRRs with the one month lead-in of Formula (XVIII), which could potentially lead to higher efficacy for the combination as well as better tolerability, leading to a decrease in medical resource utilization.

Example 16 – BTK Inhibitory Effects on MDSCs in the Solid Tumor Microenvironment

[001107] A molecular probe assay was used to calculate the percent irreversible occupancy of total BTK. MDSCs were purified from tumor bearing PDA mice (as described previously) dosed at 15 mg/kg BID of Formula (XVIII). Complete BTK occupancy is observed for both the granulocytic and monocytic MDSC compartment on Day 8 at 4 hours post dose (N=5). The results are shown in FIG. 160.

Example 17 – BTK Inhibitory Effects on Solid Tumor Microenvironment in a Non-small Cell Lung Cancer (NSCLC) Model

[001108] A genetic tumor model of NSCLC (KrasLA2) was studied as a model for lung cancer using the treatment schema shown in FIG. 161. The model is designed to have sporadic expression in single cells of G12D mutant Kras off its own promoter triggered by spontaneous intrachromosomal recombination. Johnson, et al. Nature 2001, 410, 1111-16. While the mutant Kras protein is expressed in a few cells in all tissues, tumor development is seen only in the lung at high penetrance. Mice treated with Formula (XVIII) showed a significant decrease in tumor volumes versus vehicle (FIG. 162) and fewer overall tumors with dosing of 15 mg/kg. The effects on TAMs (FIG. 163), MDSCs (FIG. 164), Tregs (FIG. 165), and CD8+ cells (FIG. 166) were consistent with suppression of the solid tumor microenvironment as demonstrated previously.

Example 18 – Additional Preclinical Characteristics of BTK Inhibitors

[001109] The in vitro potency in whole blood of Formula (XVIII), ibrutinib and CC-292 in inhibiting signals through the B cell receptor was also assessed. Blood from four healthy donors was incubated for 2 hours with the compounds shown over a concentration range, and then stimulated with anti-human IgD [10 µg/mL] for 18 hours. The mean fluorescent intensity (MFI) of CD69 (and CD86, data not shown) on gated CD19+ B cells was measured by flow cytometry. MFI values were normalized so that 100% represents CD69 level in stimulated cells without inhibitor, while 0% represents the unstimulated/no drug condition. The results are shown in FIG.
167. The EC$_{50}$ values obtained were 8.2 nM (95% confidence interval: 6.5 – 10.3), 6.1 nM (95% confidence interval: 5.2 – 7.2), and 121 nM (95% confidence interval: 94 - 155) for Formula (XVIII), ibrutinib, and CC-292, respectively.

[001110] The EGF receptor phosphorylation in vitro was also determined for Formula (XVIII) and ibrutinib. Epidermoid carcinoma A431 cells were incubated for 2h with a dose titration of Formula (XVIII) or ibrutinib, before stimulation with EGF (100 ng/mL) for 5 min to induce EGFR phosphorylation (p-EGFR). Cells were fixed with 1.6% paraformaldehyde and permeabilized with 90% MeOH. Phosphoflow cytometry was performed with p-EGFR (Y1069). MFI values were normalized so that 100% represents the p-EGFR level in stimulated cells without inhibitor, while 0% represents the unstimulated/no drug condition. The results are shown in FIG. 168. EGF-induced p-EGFR inhibition was determined to be 7% at 10 µM for Formula (XVIII), while ibrutinib has an EC$_{50}$ of 66 nM. The much more potent inhibition of EGF-induced p-EGFR by ibrutinib may be associated with increased side effects including diarrhea and rash.

Example 19 – Blood-Brain Barrier Penetration of BTK Inhibitors in Rats

[001111] P-glycoprotein substrates may have relatively low brain exposure, due to activity of efflux pumps including P-glycoprotein at the blood-brain barrier (BBB). In a biodistribution study using radiolabeled Formula (XVIII), low relative concentrations (3% to 4% of plasma concentrations) were observed in the brain. Preliminary brain PK experiments were performed to evaluate the potential for Formula (XVIII) to cross the blood brain barrier, with results illustrated in FIG. 169. Four Sprague-Dawley rats per group were treated by oral gavage with 5 or 30 mg/kg/day Formula (XVIII) and tissues were collected at 30 minutes after dosing – the approximate time of C$_{max}$ – on Days 1, 3 and 5. Two vehicle treated rats were sacrificed on each sampling day for comparison. Cerebral spinal fluid (CSF) was collected; and the brains were flushed with heparinized saline prior to collection and snap frozen for analysis of Formula (XVIII). Bioanalytical methods specific to CSF and brain tissue were used to measure Formula (XVIII) concentrations in these matrices. Results (FIG. 169) showed low but detectable levels of Formula (XVIII) in the brain and CSF samples. Penetration of Formula (XVIII) into the brain was surprising because of the efflux ratio observed with in vitro studies in Caco-2 cells. However, the ratio of Formula (XVIII) in the flushed brains, compared with matched plasma
concentrations, showed that brain extracts had ~3-4% of the observed plasma concentrations, consistent with the results from the biodistribution study. The ratios observed in clean CSF samples from rats treated with 5 and 30 mg/kg/day were between 1-2% of the plasma levels. The results indicate that Formula (XVIII) can penetrate the BBB, and because of the covalent binding of Formula (XVIII) and low BTK resynthesis rates, high levels of BTK occupancy in tumor cells in the brain (such as infiltrating lymphocytes and microglia) as well as in cells of the solid tumor microenvironment in order to treat cancers such as gliomas and primary central nervous system lymphoma (Schideman, et al., J. Neurosci. Res. 2006, 83(8), 1471-84).

Example 20 – Synergistic Combination of a BTK Inhibitor and a PI3K-δ Inhibitor
[001112] A study was also performed using the approach described above in Example 2 with the BTK inhibitor of Formula (XXVIII-R) (ONO-4059) and the PI3K-δ inhibitor of Formula (XVI) (idelalisib). Proliferation was again determined with MTS (CellTiter 96 AQueous, Promega). The detailed results of the additional cell line studies for the BTK inhibitor of Formula (XXVIII-R) and the PI3K-δ inhibitor of Formula (XVI) are given in FIG. 170 to FIG. 175. The results of these combination studies are summarized in Table 15.

TABLE 15. Summary of results of the combination of a BTK inhibitor with a PI3K-δ inhibitor (S = synergistic, A = additive, X = no effect).

<table>
<thead>
<tr>
<th>Cell Line</th>
<th>Indication</th>
<th>ED25</th>
<th>ED50</th>
<th>ED75</th>
<th>ED90</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMD-8</td>
<td>DLBCL-ABC</td>
<td>A</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>Mino</td>
<td>MCL</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>RI-1</td>
<td>NHL</td>
<td>A/X</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>DOHH-2</td>
<td>FL</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>S</td>
</tr>
<tr>
<td>SU-DHL-6</td>
<td>DLBCL-GCB</td>
<td>X</td>
<td>X</td>
<td>A</td>
<td>S</td>
</tr>
</tbody>
</table>

[001113] Synergistic effects of the combination of the BTK inhibitor of Formula (XXVIII-R) with the PI3K-δ inhibitor of Formula (XVI) are observed in cell lines that are representative of a number of clinically-significant B cell malignancies.

[001114] While preferred embodiments of the invention are shown and described herein, such embodiments are provided by way of example only and are not intended to otherwise limit the scope of the invention. Various alternatives to the described embodiments of the invention may be employed in practicing the invention.
CLAIMS

We claim:

1. A method of treating a cancer, comprising co-administering, to a mammal in need thereof, one or more compositions comprising therapeutically effective amounts of (1) cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, and (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

2. The method of Claim 1, further comprising the step of administering a phosphoinositide 3-kinase (PI3K) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

3. The method of Claim 2, wherein the PI3K inhibitor is a PI3K-δ inhibitor.

4. The method of any one of Claims 1 to 3, wherein the (CDK4/6) inhibitor is administered before administration of the BTK inhibitor.

5. The method of any one of Claims 1 to 3, wherein the (CDK4/6) inhibitor is administered concurrently with the administration of the BTK inhibitor.

6. The method of any one of Claims 1 to 3, wherein the (CDK4/6) inhibitor is administered to the subject after administration of the BTK inhibitor.

7. The method of any one of Claims 1 to 6, wherein the BTK inhibitor is selected from the group consisting of:
8. The method of Claim 7, further comprising the step of administering a therapeutically effective dose of an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof.

9. The method of any one of Claims 1 to 6, wherein the BTK inhibitor is selected from the group consisting of:
and pharmaceutically-acceptable salts, cocrystals, hydrates, solvates, or prodrugs thereof.

10. The method of any of Claims 1-9, wherein the CDK4/6 inhibitor is palbociclib:

![Chemical structure of palbociclib]

or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof.

11. The method of any one of Claims 2 to 10, wherein the PI3K inhibitor is administered to the subject before administration of the BTK inhibitor.

12. The method of any one of Claims 2 to 10, wherein the PI3K inhibitor is administered concurrently with the administration of the BTK inhibitor.

13. The method of any one of Claims 2 to 10, wherein the PI3K inhibitor is administered to the subject after administration of the BTK inhibitor.

14. The method of any one of Claims 2 to 13, wherein the PI3K inhibitor is selected from the group consisting of:
and pharmaceutically acceptable salts, solvates, hydrates, cocrystals, or prodrugs thereof.

15. The method of any one of Claims 1 to 14, wherein the method further comprises the step of co-administering, to a mammal in need thereof, a compositions comprising a therapeutically effective amount of a JAK-2 inhibitor.

16. The method of Claim 15, wherein the JAK-2 inhibitor is selected from the group consisting of ruxolitinib:

![Chemical structure of ruxolitinib]

and pacritinib:

![Chemical structure of pacritinib]
and pharmaceutically-acceptable salts, cocrystals, hydrates, solvates, or prodrugs thereof.

17. The method of any one of Claims 1 to 16, wherein the cancer is a B cell hematological malignancy selected from the hematological malignancy is selected from the group consisting of chronic lymphocytic leukemia (CLL), small lymphocytic leukemia (SLL), non-Hodgkin’s lymphoma (NHL), diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), Hodgkin’s lymphoma, B cell acute lymphoblastic leukemia (B-ALL), Burkitt’s lymphoma, Waldenström's macroglobulinemia (WM), Burkitt’s lymphoma, multiple myeloma, or myelofibrosis.

18. The method of any one of Claims 1 to 17, wherein the cancer is a solid tumor cancer, and wherein the solid tumor cancer is selected from the group consisting of bladder cancer, non-small cell lung cancer, cervical cancer, anal cancer, pancreatic cancer, squamous cell carcinoma including head and neck cancer, renal cell carcinoma, melanoma, ovarian cancer, small cell lung cancer, glioblastoma, glioma, gastrointestinal stromal tumor, breast cancer, lung cancer, colorectal cancer, thyroid cancer, bone sarcoma, stomach cancer, oral cavity cancer, oropharyngeal cancer, gastric cancer, kidney cancer, liver cancer, prostate cancer, colorectal cancer, esophageal cancer, testicular cancer, gynecological cancer, thyroid cancer, colon cancer, primary central nervous system lymphoma, and brain cancer.

19. The method of Claim 18, further comprising the step of administering a therapeutically effective dose of gemcitabine.

20. The method of Claim 18, further comprising the step of administering a therapeutically effective dose of albumin-bound paclitaxel

21. A method of treating a solid tumor cancer in a human comprising the steps of co-
administering (1) cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, and (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, wherein the dose is effective to inhibit signaling between the cells of the solid tumor cancer and at least one tumor microenvironment selected from the group consisting of macrophages, monocytes, mast cells, helper T cells, cytotoxic T cells, regulatory T cells, natural killer cells, myeloid-derived suppressor cells, regulatory B cells, neutrophils, dendritic cells, and fibroblasts.

22. The method of Claim 21, further comprising the step of administering a therapeutically effective amount of a phosphoinositide 3-kinase (PI3K) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.


24. The method of any one of Claims 21 to 23, wherein the dose is further effective to increase immune system recognition and rejection of the solid tumor by the human.

25. The method of Claim 22, wherein the PI3K inhibitor is:
or a pharmaceutically acceptable salt, hydrate, solvate, cocrystal, or prodrug thereof.

26. The method of any one of Claims 21 to 25, wherein the BTK inhibitor is selected from the group consisting of:
and pharmaceutically-acceptable salts, cocrystals, hydrates, solvates, or prodrugs thereof.

27. The method of any one of Claims 21 to 26, wherein the CDK4/6 inhibitor is palbociclib:
or a pharmaceutically-acceptable salt, cocrystal, hydate, solvate, or prodrug thereof.

28. A method of treating a cancer in a human sensitive to bleeding events comprising the step of administering a therapeutically effective dose of a (1) cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, and (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, wherein the BTK inhibitor is selected from the group consisting of:
and pharmaceutically-acceptable salts, cocrystals, hydrates, solvates, or prodrugs thereof.

29. The method of Claim 28, wherein the bleeding event is selected from the group consisting of subdural hematoma, gastrointestinal bleeding, hematuria, post-procedural hemorrhage, bruising, and petechiae.

30. The method of any one of Claims 28 to 29, wherein the CDK4/6 inhibitor is palbociclib:
31. The method of any of Claims 28-30, further comprising the step of administering a therapeutically effective dose of an anticoagulant or antiplatelet active pharmaceutical ingredient.

32. The method of Claim 31, wherein the anticoagulant or antiplatelet active pharmaceutical ingredient is selected from the group consisting of acenocoumarol, anagrelide, anagrelide hydrochloride, abciximab, aloxiprin, antithrombin, apixaban, argatroban, aspirin, aspirin with extended-release dipyridamole, beraprost, betrixaban, bivalirudin, carbasalate calcium, cilostazol, clopidogrel, clopidogrel bisulfate, cloridronic acid, dabigatran etexilate, darexaban, dalteparin, dalteparin sodium, defibrotide, dicumarol, dipyridamole, ditazole, desirudin, edoxaban, enoxaparin, enoxaparin sodium, eptifibatide, fondaparinux, fondaparinux sodium, heparin, heparin sodium, heparin calcium, idraparinux, idraparinux sodium, iloprost, indobufen, lepirudin, low molecular weight heparin, melagatran, nadroparin, otamixaban, parnaparin, phenindione, phenprocoumon, prasugrel, picatamide, prostacyclin, ramatroban, reviparin, rivaroxaban, sulodexide, terutroban, terutroban sodium, ticagrelor, ticlopidine, ticlopidine hydrochloride, tinzaparin, tinzaparin sodium, tirofiban, tirofiban hydrochloride, treprostinil, treprostinil sodium, triflusol, vorapaxar, warfarin, warfarin sodium, ximelagatran, salts thereof, solvates thereof, hydrates thereof, and combinations thereof.

33. The method of any of Claims 28 to 32, wherein the cancer is selected from the group consisting of bladder cancer, squamous cell carcinoma including head and neck cancer, pancreatic ductal adenocarcinoma (PDA), pancreatic cancer, colon carcinoma, mammary carcinoma, breast cancer, fibrosarcoma, mesothelioma, renal cell carcinoma, lung carcinoma, thyoma, prostate cancer, colorectal cancer, ovarian cancer, acute myeloid leukemia, thymus

34. A composition comprising therapeutically effective amounts of (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, and (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, for use in the treatment of cancer.

35. The composition of Claim 34, further comprising a therapeutically effective amount of a phosphoinositide 3-kinase (PI3K) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

36. The composition of Claim 35, wherein the PI3K inhibitor is a PI3K-δ inhibitor.

37. The composition of any one of Claims 34 to 36, wherein the (CDK4/6) inhibitor is administered before administration of the BTK inhibitor.

38. The composition of any one of Claims 34 to 36, wherein the (CDK4/6) inhibitor is administered concurrently with the administration of the BTK inhibitor.

39. The composition of any one of Claims 34 to 36, wherein the (CDK4/6) inhibitor is administered after administration of the BTK inhibitor.

40. The composition of any one of Claims 34 to 36, wherein the BTK inhibitor is selected from the group consisting of:
41. The composition of Claim 40, further comprising a therapeutically effective dose of an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof.

42. The composition of any one of Claims 34 to 39, wherein the BTK inhibitor is selected from the group consisting of:
and pharmaceutically-acceptable salts, cocrystals, hydrates, solvates, or prodrugs thereof.

43. The composition of any one of Claims 34 to 42, wherein the CDK4/6 inhibitor is palbociclib:

44. The composition of any one of Claims 35 to 43, wherein the PI3K inhibitor is administered before administration of the BTK inhibitor.

45. The composition of any one of Claims 35 to 43, wherein the PI3K inhibitor is administered concurrently with the administration of the BTK inhibitor.

46. The composition of any one of Claims 35 to 43, wherein the PI3K inhibitor is administered after administration of the BTK inhibitor.

47. The composition of any one of Claims 35 to 46, wherein the PI3K inhibitor is selected from the group consisting of:
and pharmaceutically acceptable salts, solvates, hydrates, cocrystals, or prodrugs thereof.

48. The composition of any one of Claims 34 to 47, wherein the composition further comprises a therapeutically effective amount of a JAK-2 inhibitor.

49. The composition of Claim 48, wherein the JAK-2 inhibitor is selected from the group consisting of ruxolitinib:
and pharmaceutically-acceptable salts, cocrystals, hydrates, solvates, or prodrugs thereof.

50. The composition of any one of Claims 34 to 49, wherein the cancer is a B cell hematological malignancy selected from the hematological malignancy is selected from the group consisting of chronic lymphocytic leukemia (CLL), small lymphocytic leukemia (SLL), non-Hodgkin’s lymphoma (NHL), diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), Hodgkin’s lymphoma, B cell acute lymphoblastic leukemia (B-ALL), Burkitt’s lymphoma, Waldenström's macroglobulinemia (WM), Burkitt’s lymphoma, multiple myeloma, or myelofibrosis.

51. The composition of any one of Claims 34 to 50, wherein the cancer is a solid tumor cancer, and wherein the solid tumor cancer is selected from the group consisting of bladder cancer, non-small cell lung cancer, cervical cancer, anal cancer, pancreatic cancer, squamous cell carcinoma including head and neck cancer, renal cell carcinoma, melanoma, ovarian cancer, small cell lung cancer, glioblastoma, glioma, gastrointestinal stromal tumor, breast cancer, lung cancer, colorectal cancer, thyroid cancer, bone sarcoma, stomach cancer, oral cavity cancer, oropharyngeal cancer, gastric cancer, kidney cancer, liver cancer, prostate cancer, colorectal cancer, esophageal cancer, testicular cancer, gynecological cancer, thyroid cancer, colon cancer, primary central nervous system lymphoma, and brain cancer.
52. The composition of Claim 51, further comprising the step of administering a therapeutically effective dose of gemcitabine.

53. The composition of any one of Claims 51 or 52, further a therapeutically effective dose of albumin-bound paclitaxel.

54. A composition comprising a combination of (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, and (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, for use in treating a solid tumor cancer, wherein (1) and (2) are in dose that is effective to inhibit signaling between the cells of the solid tumor cancer and at least one tumor microenvironment selected from the group consisting of macrophages, monocytes, mast cells, helper T cells, cytotoxic T cells, regulatory T cells, natural killer cells, myeloid-derived suppressor cells, regulatory B cells, neutrophils, dendritic cells, and fibroblasts.

55. The composition of Claim 54, further comprising a therapeutically effective amount of a phosphoinositide 3-kinase (PI3K) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

56. The composition of any one of Claims 54 or 55, wherein the solid tumor cancer is selected from the group consisting of bladder cancer, non-small cell lung cancer, cervical cancer, anal cancer, pancreatic cancer, squamous cell carcinoma including head and neck cancer, renal cell carcinoma, melanoma, ovarian cancer, small cell lung cancer, glioblastoma, glioma, gastrointestinal stromal tumor, breast cancer, lung cancer, colorectal cancer, thyroid cancer, bone sarcoma, stomach cancer, oral cavity cancer, oropharyngeal cancer, gastric cancer, kidney cancer, liver cancer, prostate cancer, colorectal cancer, esophageal cancer, testicular cancer, gynecological cancer, thyroid cancer, colon cancer, primary central nervous system lymphoma, and brain cancer.

57. The composition of any one of Claims 54 to 56, wherein the dosage of (1) and (2) is further effective to increase immune system recognition and rejection of the solid tumor.

58. The composition of Claim 55, wherein the PI3K inhibitor is:
or a pharmaceutically acceptable salt, hydrate, solvate, cocrystal, or prodrug thereof.

59. The composition of any one of Claims 54 to 58, wherein the BTK inhibitor is selected from the group consisting of:
and pharmaceutically-acceptable salts, cocrystals, hydrates, solvates, or prodrugs thereof.

60. The composition of any one of Claims 54 to 59, wherein the CDK4/6 inhibitor is palbociclib:
or a pharmaceutically-acceptable salt, cocrystal, hydate, solvate, or prodrug thereof.

61. A composition comprising a therapeutically effective dose of (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, and (2) a Bruton’s tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, wherein the BTK inhibitor is selected from the group consisting of:
and pharmaceutically-acceptable salts, cocrystals, hydrates, solvates, or prodrugs thereof, for the treatment of a cancer in a human sensitive to bleeding events.

62. The composition of Claim 61, wherein the bleeding event is selected from the group consisting of subdural hematoma, gastrointestinal bleeding, hematuria, post-procedural hemorrhage, bruising, and petechiae.
63. The composition of any one of Claims 61 to 62, wherein the CDK4/6 inhibitor is palbociclib:

![Chemical Structure](image)

or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof.

64. The composition of any one of Claims 61 to 63, further comprising a therapeutically effective dose of an anticoagulant or antiplatelet active pharmaceutical ingredient.

65. The composition of Claim 64, wherein the anticoagulant or antiplatelet active pharmaceutical ingredient is selected from the group consisting of acenocoumarol, anagrelide, anagrelide hydrochloride, abciximab, aloxiprin, antithrombin, apixaban, argatroban, aspirin, aspirin with extended-release dipyridamole, beraprost, betrixaban, bivalirudin, carbasalate calcium, cilostazol, clopidogrel, clopidogrel bisulfate, cloricromen, dabigatran etexilate, darexaban, dalteparin, dalteparin sodium, defibrotide, dicumarol, diphenadione, dipyridamole, ditazole, desirudin, edoxaban, enoxaparin, enoxaparin sodium, eptifibatide, fondaparinux, fondaparinux sodium, heparin, heparin sodium, heparin calcium, idraparinux, idraparinux sodium, iloprost, indobufen, lepirudin, low molecular weight heparin, melagatran, nadroparin, otamixaban, parnaparin, phenindione, phenprocoumon, prasugrel, picotamide, prostacyclin, ramatroban, reviparin, rivaroxaban, sulodexide, terutroban, terutroban sodium, ticagrelor, ticlopidine, ticlopidine hydrochloride, tinzaparin, tinzaparin sodium, tirofiban, tirofiban hydrochloride, treprostinil, treprostinil sodium, triflusali, vorapaxar, warfarin, warfarin sodium, ximelagatran, salts thereof, solvates thereof, hydrates thereof, and combinations thereof.

66. The composition of any one of Claims 61 to 65, wherein the cancer is selected from the group consisting of bladder cancer, squamous cell carcinoma including head and neck cancer, pancreatic ductal adenocarcinoma (PDA), pancreatic cancer, colon carcinoma, mammary carcinoma, breast cancer, fibrosarcoma, mesothelioma, renal cell carcinoma, lung carcinoma,

67. A combination (for example a pharmaceutical combination) comprising two or more ingredients selected from a Bruton’s tyrosine kinase (BTK) inhibitor, a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor, phosphoinositide 3-kinase (PI3K) inhibitor (for example a PI3K inhibitor selected from a PI3K-δ inhibitor, PI3K-γ inhibitor and PI3K-δ,γ inhibitor), and a Janus kinase-2 (JAK-2) inhibitor, or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

68. A combination according to Claim 67 in the form of a composition (for example a pharmaceutical composition) comprising two or more ingredients selected from a BTK inhibitor, a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor, a PI3K inhibitor (for example a PI3K inhibitor selected from a PI3K-δ inhibitor, PI3K-γ inhibitor and PI3K-δ,γ inhibitor), and a JAK-2 inhibitor, or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

69. A combination according to Claim 67 in the form of a kit comprising two or more compositions (for example two or more pharmaceutical compositions) and optionally a package insert or label providing directions for administering the compositions simultaneously, separately or sequentially, wherein:

each composition comprises at least one ingredient selected from a BTK inhibitor, a...
cyclin-dependent kinase-4/6 (CDK4/6) inhibitor, a PI3K inhibitor and a JAK-2 inhibitor, or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and

the two or more compositions together comprise two or more ingredients selected from a BTK inhibitor, a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor, a PI3K inhibitor and a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

70. A combination according to any one of Claims 67 to 69 comprising (1) a BTK inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof and (2) an ingredient selected from a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor, a PI3K inhibitor, and a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

71. A combination according to any one of Claims 67 to 69 comprising (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof and (2) an ingredient selected from a BTK inhibitor, a PI3K inhibitor, and a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

72. A combination according to any one of Claims 67 to 69 comprising (1) a cyclin-dependent kinase-4/6 (CDK4/6) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (2) a BTK inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

73. A combination according to Claim 72 further comprising (3) a PI3K inhibitor (for example a PI3K inhibitor selected from a PI3K-δ inhibitor, PI3K-γ inhibitor and PI3K-δ,γ inhibitor) or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

74. A combination according to any one of Claim 72 or Claim 73 further comprising an anti-coagulant or antiplatelet active pharmaceutical ingredient.

75. A combination according to any one of Claims 72 to 74 comprising a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

76. A combination according to any one of Claims 67 to 70 comprising (1) a BTK inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (2) a PI3K inhibitor (for example a PI3K inhibitor selected from a PI3K-δ inhibitor, PI3K-γ inhibitor
and PI3K-δ,γ inhibitor) or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

77. A combination according to any one of Claims 67 to 70 comprising (1) a BTK inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (2) a JAK-2 inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.”

78. A combination according to any one of Claims 67 to 77, wherein the BTK inhibitor is selected from the group consisting of:
and pharmaceutically acceptable salts, solvates, hydrates, cocrystals, or prodrugs thereof.

79. A combination according to any one of Claims 67-78, wherein the cyclin-dependent kinase-4/6 (CDK4/6) inhibitor is palbociclib:

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

80. A combination according to any one of claims 67-79, wherein the PI3K inhibitor of a compound of Formula (IX):
or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

81. A combination according to any one of Claims 67 to 80, wherein the JAK-2 inhibitor is a compound of Formula (XXX) or a compound of Formula (LIV)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

82. A combination according to any one of Claims 67 to 69 selected from:

a combination of a BTK inhibitor and a CDK4/6 inhibitor wherein the BTK inhibitor is a compound of formula (XVIII) or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal,
or prodrug thereof and the CDK4/6 inhibitor is palbociclib or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof;

    a combination of a BTK inhibitor, a CDK4/6 inhibitor and a PI3K inhibitor wherein the BTK inhibitor is a compound of formula (XVIII) or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, the CDK4/6 inhibitor is palbociclib or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof and the PI3K inhibitor is a compound of formula (IX) or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof;

    a combination of a BTK inhibitor, a CDK4/6 inhibitor and a JAK-2 inhibitor wherein the BTK inhibitor is a compound of formula (XVIII) or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, the CDK4/6 inhibitor is palbociclib or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof and the JAK-2 inhibitor is a compound of formula (XXX) or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof;

    a combination of a BTK inhibitor, a CDK4/6 inhibitor and a JAK-2 inhibitor wherein the BTK inhibitor is a compound of formula (XVIII) or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, the CDK4/6 inhibitor is palbociclib or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof and the JAK-2 inhibitor is a compound of formula (LIV) or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof;

    a combination of BTK inhibitor and a PI3K inhibitor wherein the BTK inhibitor is a compound of formula (XVIII) or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof and the PI3K inhibitor is a compound of formula (IX) or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof;

    a combination of a BTK inhibitor and a JAK-2 inhibitor wherein the BTK inhibitor is a compound of formula (XVIII) or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof and the JAK-2 inhibitor is a compound of formula (XXX) or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and

    a combination of a BTK inhibitor and a JAK-2 inhibitor wherein the BTK inhibitor is a compound of formula (XVIII) or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal,
or prodrug thereof and the JAK-2 inhibitor is a compound of formula (LIV) or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

83. A combination according to any one of Claims 67 to 82 for use in the treatment of hyperproliferative disease such as cancer.


85. A combination according to any one of Claims 67 to 84 for use in the treatment of: solid tumor cancer selected from the group consisting of breast, lung, colorectal, thyroid, bone sarcoma and stomach cancers;

leukemia selected from the group consisting of acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML), and acute lymphoblastic leukemia (ALL); and/or

lymphoma is follicular lymphoma, mantle cell lymphoma, diffuse large B cell lymphoma (DLBCL), B cell chronic lymphocytic leukemia, or Burkitt’s lymphoma.
86. Use of a combination according to any one of Claims 67 to 85 as a research tool in the discovery and/or development of a pharmaceutical product.

87. A composition comprising a BTK inhibitor, wherein the BTK inhibitor is selected from the group consisting of:
and a pharmaceutically-acceptable salt, cocrystal, solvate, or hydrate thereof, and a CDK4/6 inhibitor, wherein the CDK4/6 inhibitor is palbociclib:

or a pharmaceutically-acceptable salt, cocrystal, solvate, or hydrate thereof.

88. The composition of Claim 87, comprising an amount of the BTK inhibitor selected from the group consisting of 5 mg, 10 mg, 12.5 mg, 15 mg, 20 mg, 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, 300 mg, 325 mg, 350 mg, 375 mg, 400 mg, 425 mg, 450 mg, 475 mg, or 500 mg.

89. The composition of any one of Claims 87 or 88, comprising an amount of the CDK4/6 inhibitor selected from the group consisting of 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 200 mg, 300 mg, 400 mg, and 500 mg.
FIG. 1
FIG. 2
FIG. 3

MCL-4

% viability

[Concentration]

Tested Btki
Tested PI3Ki
(10 μM) Tested PI3Ki
(1.0 μM) Tested PI3Ki
(0.1 μM) Tested PI3Ki
(0.01 μM) Tested PI3Ki
FIG. 4

The graph shows the Interaction Index for different categories labeled MCL-1 to MCL-5. The x-axis represents the categories, and the y-axis represents the Interaction Index values ranging from 0 to 2.0. Each category has multiple data points indicating the spread and distribution of the Interaction Index.
FIG. 5

- Maver-1
- Jeko
- Sup-B15
- CCRF

Combination Index

ED25  ED50  ED75  ED90

Antagonistic
Additive
Synergistic
Dose-effect curve

FIG. 6
Dose-effect curve

× Inh.1+Inh.3
 tô Inh.1
○ Inh.3

FIG. 7
Dose-effect curve

Effect

Dose

x Inh.1+Inh.3
+ Inh.1
o Inh.3

FIG. 8
Dose-effect curve

\( \times \text{Inh.1+Inh.3} \)
\( \dagger \text{Inh.1} \)
\( \circ \text{Inh.3} \)

FIG. 9
FIG. 10

The diagram shows the combination index for different ED values (ED25, ED50, ED75, ED90) and two cell lines: SU-DHL-4 and Jeko. The horizontal lines indicate the thresholds for antagonistic, additive, and synergistic effects.
FIG. 11
Dose-effect curve

![Graph showing dose-effect relationship with different symbols for Inh.1 and Inh.3]

FIG. 12
FIG. 13
Dose-effect curve

Effect vs. Dose

× Inh.1+Inh.3
+ Inh.1
○ Inh.3

FIG. 14
Dose-effect curve

Effect vs Dose

- × Inh.1+Inh.3
- + Inh.1
- ○ Inh.3

FIG. 15
Dose-effect curve

Effect

Dose

× Inh.1+Inh.3
✓ Inh.1
○ Inh.3

FIG. 16
Dose-effect curve

Effect vs. Dose

- \( \times \) Inh.1 + Inh.3
- \( \div \) Inh.1
- \( \circ \) Inh.3

FIG. 17
FIG. 18
FIG. 19
Dose-effect curve

Effect

Dose

× Inh.1+Inh.3
+ Inh.1
○ Inh.3

FIG. 20
Dose-effect curve

Effect

Dose

× Inh.1+Inh.3
+ Inh.1
○ Inh.3

FIG. 21
Combination Index

Antagonistic
Additive
Synergistic

FIG. 22
Dose-effect curve

Effect

Dose

× Inh.1+Inh.3
÷ Inh.1
○ Inh.3

FIG. 23
Dose-effect curve

- x Inh.1+Inh.3
- + Inh.1
- o Inh.3

FIG. 24
Dose-effect curve

x Inh.1+Inh.3
+ Inh.1
o Inh.3

FIG. 25
Dose-effect curve

Effect

Dose

$\times$ Inh.1+Inh.3

$+$ Inh.1

$\bigcirc$ Inh.3

FIG. 26
FIG. 27

- **U937**
- **SU-DHL-6**
- **K562**
- **Daudi**

- Antagonistic
- Additive
- Synergistic

Combination Index

ED25, ED50, ED75, ED90
Dose-effect curve

× Inh.1+Inh.3
♦ Inh.1
○ Inh.3

FIG. 28
Dose-effect curve

Effect

× Inh.1 + Inh.3
✦ Inh.1
○ Inh.3

FIG. 29
Dose-effect curve

- Inh.1+Inh.3
- Inh.1
- Inh.3

FIG. 30
Rec-1: Follicular lymphoma
FIG. 32
FIG. 33

- ▼ TMD-8 (0.1:1)
- ● SU-DHL-6 (1:1)
- □ HBL-1 (1:1)
- △ Rec-1 (1:1)
Dose-effect curve

- Inh.1+Inh.3
- Inh.1
- Inh.3

FIG. 34
Dose-effect curve

\( \times \) Inh.1+Inh.3
\( \div \) Inh.1
\( \circ \) Inh.3

FIG. 35
Dose-effect curve

- x Inh.1 + Inh.3
- + Inh.1
- o Inh.3

FIG. 36
Dose-effect curve

Effect

Dose

× Inh.1+Inh.3
+ Inh.1
○ Inh.3

FIG. 37
FIG. 38

- Maver-1
- Jeko
- Sup-B16
- CCRF

Antagonistic
Additive
Synergistic
Dose-effect curve

Effect vs. Dose

- X Inh.1+Inh.2
- • Inh.1
- ○ Inh.2

FIG. 39
Dose-effect curve

Effect vs. Dose

- × Inh.1+Inh.2
- + Inh.1
- ○ Inh.2

FIG. 40
Dose-effect curve

\[ \text{Effect} \]

\[ \text{Dose} \]

\[ \times \text{Inh.1+Inh.2} \]
\[ \oplus \text{Inh.1} \]
\[ \bigcirc \text{Inh.2} \]

FIG. 41
Dose-effect curve

\[ \times \text{Inh.1+Inh.2} \]
\[ \dagger \text{Inh.1} \]
\[ \circ \text{Inh.2} \]

FIG. 42
FIG. 44
Dose-effect curve

Effect

Dose

× Inh.1+Inh.2
+ Inh.1
○ Inh.2

FIG. 45
Dose-effect curve

\[ \text{Effect} \]

\[ \text{Dose} \]

\( \times \) Inh.1+Inh.2
\( \div \) Inh.1
\( \circ \) Inh.2

FIG. 46
Dose-effect curve

- × Inh.1+Inh.2
- + Inh.1
- o Inh.2

FIG. 47
Dose-effect curve

Effect

Dose

× Inh.1+Inh.2
+ Inh.1
○ Inh.2

FIG. 48
**FIG. 49**

- **Combination Index**
  - Pfeiffer
  - SU-DHL-1

- Levels:
  - Antagonistic
  - Additive
  - Synergistic

- ED25, ED50, ED75, ED90 markers
Dose-effect curve

Effect vs. Dose

× Inh.1+Inh.2
+ Inh.1
○ Inh.2

FIG. 50
Dose-effect curve

Effect vs. Dose

- × Inh.1+Inh.2
- + Inh.1
- o Inh.2

FIG. 51
FIG. 52

- DOHH2
- SU-DHL-2
- Ly1
- Ly7
- Ly19

Antagonistic
Additive
Synergistic
Dose-effect curve

× Inh.1+Inh.2
+ Inh.1
○ Inh.2

FIG. 53
Dose-effect curve

- Inh.1+Inh.2
- Inh.1
- Inh.2

FIG. 54
Dose-effect curve

FIG. 55
Dose-effect curve

Effect vs. Dose

- x Inh.1+Inh.2
- + Inh.1
- o Inh.2

FIG. 56
Dose-effect curve

Effect vs. Dose

- Inh.1 + Inh.2
- Inh.1
- Inh.2

FIG. 58
Dose-effect curve

Effect

Dose

× Inh.1+Inh.2
⊕ Inh.1
○ Inh.2

FIG. 59
Dose-effect curve

Effect

Dose

\( \times \) Inh.1 + Inh.2
\( \dagger \) Inh.1
\( \circ \) Inh.2

FIG. 60
FIG. 61

Combination Index

ED25  ED50  ED75  ED90

Rec-1  HBL-1  TMD-8  SU-DHL-6

Antagonistic  Additive  Synergistic
Dose-effect curve

- × Inh.1+Inh.2
- ♦ Inh.1
- ○ Inh.2

FIG. 62
Dose-effect curve

Effect vs. Dose

- Inh.1 + Inh.2
- Inh.1
- Inh.2

FIG. 63
Dose-effect curve

- × Inh.1+Inh.2
- + Inh.1
- ○ Inh.2

FIG. 64
Dose-effect curve

Effect

Dose

\(\times\) Inh.1+Inh.2
\(\diamondsuit\) Inh.1
\(\circ\) Inh.2

FIG. 65
Dose-effect curve

FIG. 67
Dose-effect curve

FIG. 68
Dose-effect curve

Effect vs Dose

Inh. 1 + Inh. 4

Inh. 1

Inh. 4

FIG. 69
Dose-effect curve

FIG. 70

Inh. 1 + Inh. 4  Inh. 1  Inh. 4
Dose-effect curve

Effect

Dose

Inh.1+Inh.4  Inh.1  Inh.4

FIG. 71
Dose-effect curve

Effect

Dose

Inh.1 + Inh.4  Inh.1  Inh.4

FIG. 72
Dose-effect curve

Effect

0 2 4 6 8 10
Dose

Inh. 1+Inh. 4  Inh. 1  Inh. 4

FIG. 73
Dose-effect curve

Effect vs. Dose

Inh.1+Inh.4  Inh.1  Inh.4

FIG. 74
FIG. 75

Tumor Volumes (mm²)

- p=0.008
- p=0.001
- p=0.05

Groups:
- Vehicle
- P110d + BTK
- BTK
- P110d
FIG. 76

CD11b<sup>+</sup>LY6C<sup>low</sup>F4/80<sup>+</sup>Csf1r<sup>+</sup>

% total of live cells

Vehicle  BTK inhibitor  Pi3Kδ inhibitor  BTK/Pi3Kδ inhibitors
FIG. 77

% total of total CD45^+

Gr1^+Ly6C^hi

Vehicle
BTK inhibitor
PI3Kδ inhibitor
BTK/PI3Kδ inhibitors
FIG. 78
Dose-effect curve

Effect

Dose

X Inh.1 + Inh.4
△ Inh.1
○ Inh.4 (pacritinib)

FIG. 80
Dose-effect curve

- Inh.1 + Inh.4
- Inh.1
- Inh.4 (pacritinib)

FIG. 81
Dose-effect curve

Effect

Dose

× Inh.1 + Inh.4
÷ Inh.1
○ Inh.4 (pacritinib)

FIG. 82
Dose-effect curve

- Inh.1 + Inh.4
- Inh.1
- Inh.4 (pacritinib)

FIG. 83
Dose-effect curve

- Inh.1 + Inh.4
- Inh.1
- Inh.4 (pacritinib)

FIG. 84
Dose-effect curve

× Inh.1 + Inh.4
× Inh.1
○ Inh.4 (pacritinib)

FIG. 85
Dose-effect curve

Effect

Dose

× Inh.1 + Inh.4
+ Inh.1
○ Inh.4 (pacritinib)

FIG. 86
Dose-effect curve

Effect

Dose

× Inh.1 + Inh.4
+ Inh.1
○ Inh.4 (pacritinib)

FIG. 87
Dose-effect curve

- × Inh.1 + Inh.4
- □ Inh.1
- ○ Inh.4 (pacritinib)

FIG. 88
Dose-effect curve

- Inh.1 + Inh.4
- Inh.1
- Inh.4 (pacritinib)

FIG. 90
Dose-effect curve

Effect

Dose

× Inh.1 + Inh.4
✓ Inh.1
○ Inh.4 (pacritinib)

FIG. 91
Dose-effect curve

× Inh.1 + Inh.4
♦ Inh.1
○ Inh.4 (pacritinib)

FIG. 92
Dose-effect curve

Effect vs. Dose

- Inh.1 + Inh.4
- Inh.1
- Inh.4 (pacritinib)

FIG. 93
Dose-effect curve

- Inh.1 + Inh.4
- Inh.1
- Inh.4 (pacritinib)

FIG. 94
Dose-effect curve

× Inh.1 + Inh.4
+ Inh.1
○ Inh.4 (pacritinib)

FIG. 95
Dose-effect curve

- Inh.1 + Inh.4
- Inh.1
- Inh.4 (pacritinib)

FIG. 96
Dose-effect curve

- Inh.1 + Inh.4
- Inh.1
- Inh.4 (pacritinib)

FIG. 97
Dose-effect curve

\[ \text{Effect} \]

\[ \text{Dose} \]

- Inh.1 + Inh.4
- Inh.1
- Inh.4 (pacritinib)

FIG. 98
Combination Index

- Ramos
- SU-DHL-6
- TMD-8
- SU-DHL-10
- HBL-1
- OCI-Ly3
- OCI-Ly7
- Jeko

Antagonistic
Additive
Synergistic

ED25  ED50  ED75  ED90

FIG. 99
Dose-effect curve

- Inh.1 + Inh.4
- Inh.1
- Inh.4 (pacritinib)

FIG. 100
Dose-effect curve

Effect

Dose

× Inh.1 + Inh.4
△ Inh.1
○ Inh.4 (pacritinib)

FIG. 101
Dose-effect curve

Effect vs. Dose

- Inh.1 + Inh.4
- Inh.1
- Inh.4 (pacritinib)

FIG. 102
Dose-effect curve

Effect vs. Dose

- × Inh.1 + Inh.4
- + Inh.1
- ○ Inh.4 (pacritinib)

FIG. 103
Dose-effect curve

Effect vs. Dose

- X Inh.1 + Inh.4
- * Inh.1
- O Inh.4 (pacritinib)

FIG. 104
Dose-effect curve

- Inh.1 + Inh.4
- Inh.1
- Inh.4 (pacritinib)

FIG. 105
Dose-effect curve

Effect

Dose

× Inh.1 + Inh.4
+ Inh.1
○ Inh.4 (pacritinib)

FIG. 106
Dose-effect curve

- X Inh.1 + Inh.4
- • Inh.1
- ○ Inh.4 (pacritinib)

FIG. 107
Vehicle

Flux (10^5)

Day 1  Day 16

X=6.1  X=30.8

FIG. 108
Formula XVIII

![Graph showing flux over days]

- Flux (10^5)
- X=9.2
- X=9.6
- Day 1
- Day 16

FIG. 109
FIG. 110
Tumor volume (mm$^3$)

Vehicle

Formula XVIII

p = 0.0001

FIG. 111
Total B cells
CD19+

% of CD45+ Cells

Vehicle  Formula XVIII

P < 0.0001

FIG. 112
Bregs
CD25⁺CD19⁺B220⁺

% of CD45⁺ Cells

Vehicle
Formula XVIII

P < 0.0001

FIG. 113
Tregs
CD4^+CD25^+FoxP3^+

% of CD45^+ Cells

Vehicle  Formula XVIII

P=0.001

FIG. 114
T cells
CD8^+ 

% of CD45^+ Cells

Vehicle  Formula XVIII

P=0.002

FIG. 115
FIG. 116

- Tumor Volume mm³

Vehicle  Formula XVIII  Formula XVIII + Gem  Gem
FIG. 117
%CD4CD25FoxP3

CD4^+CD25^{FoxP3} % total of CD3

Vehicle  Formula XVII  Formula XVII + Gem  Gem

FIG. 118
FIG. 119

CD11bLY6CF4/80Csf1r (Macro)

% total of CD45+

Vehicle  Formula XVIII  Formula XVIII + Gem  Gem
FIG. 120
FIG. 121
FIG. 123
GPVI Induced aggregation

% Aggregation (normalized)

-●- Formula XVIII
-□- Formula XX-A (ibrutinib)

log [Drug]

FIG. 125
GPVI Induced aggregation

% Inhibition

Compound [nM]

- Formula XVIII
- Formula XX-A (ibrutinib)

FIG. 126
FIG. 127
FIG. 128
FIG. 129
FIG. 130

CD4^+CD25^+FoxP3^+
% total of CD3

Vehicle
Formula (XVIII)

Tregs
p=0.01
FIG. 131
Induced IFN-γ release

FIG. 132
CD107a⁺ expression
(NK activation marker)

FIG. 133
FIG. 134
FIG. 135

[Bar chart showing % Lysis across different groups: Control, Abs, AbsFormula XVIII, Ab/brutinib.]

135/175
Expression in B Cells (3h)

- **CD86**
  - BTK inhibitor: 0.34
  - Ibrutinib: 0.91

- **CD69**
  - BTK inhibitor: 0.16
  - Ibrutinib: 0.45

**FIG. 137**
FIG. 138
FIG. 139
FIG. 140
FIG. 142

Graph showing progression-free survival over days for Ibrutinib (N = 28) and Formula (XVIII) (N = 18).
FIG. 144

- 200mg QD Formula (XVIII) (N=12)
- 420mg QD ibrutinib
- 840mg QD ibrutinib
FIG. 145
FIG. 146

Cohort
- 100mg BID R/R
- 200mg QD Naive
- 400mg QD R/R
- Combo

%CD4+ CD11b+ CD33+ (Monocytes, Myelocytes, Band Neutrophils)

ALC % change from baseline C2D2B
FIG. 147
FIG. 149

% NK (P value = 0.067)

% Monocytic MDSCs (P value = 0.012)
FIG. 150
FIG. 151
Figure Kaplan-Meier Curves for PFS
Relapsed/Refractory Treated Subjects with Deletion 17p

Note: This figure includes Relapsed/Refractory Cohorts 1, 2a/2b/2c, 3 and 4a/4b.

FIG. 153
Figure: Kaplan-Meier Curves for PFS Relapsed/Refractory Treated Subjects

Note: This figure includes Relapsed/Refractory Cohorts 1, 2a/2b/2c, 3 and 4a/4b

FIG. 154
Figure Kaplan-Meier Curves for PFS
Relapsed/Refractory Treated Subjects with Deletion 11q (and no Deletion 17p)

Progression-Free Survival (Proportion)

Censored

0.0 0.2 0.4 0.6 0.8 1.0

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18

Months from Initiation of Study Treatment

Number At Risk
16 15 12 12 12 10 6 6 6 3 3 2 1 1 0

Note: This figure includes Relapsed/Refractory Cohorts 1, 2a/2b/2c, 3 and 4a/4b.

FIG. 155
Sum of Product Diameters of Enlarged Lymph Nodes* in R/R Patients

R/R (N= 58)

*Any node with a diameter > 1.5 cm.
Ns are subjects with observed lymphadenopathy and overall response data. Subjects with overall response but no observed lymphadenopathy, 01-025 = PR, 06-002 = PR, 06-003 = PR, 03-015 = PRL, 05-001 = PRL, 05-002 = PRL, 25-001 = PRL, 01-026 = SD, 01-035 = SD, 06-004 = SD

FIG. 156
FIG. 157

P < 0.0001
N=33

% Change from Baseline

Apoptosis

No Drug  Formula (XVIII) [1uM]
FIG. 158
FIG. 159

CCL2

Concentration, pg/mL

Pre-treatment  Day 28
Complete Btk Occupancy (>90%)
Mice are enrolled at 8-10 week of age, the stage at which several lung tumors are visible on micro-CT scanning.

<table>
<thead>
<tr>
<th>Days</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
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<th>25</th>
<th>26</th>
<th>27</th>
<th>28</th>
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<tbody>
<tr>
<td>T1 Scan</td>
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<tr>
<td>T2 Scan</td>
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</tbody>
</table>

**BTK inhibition (Formula XVII)** 15 mg/kg BID

FIG. 161
FIG. 162
FIG. 164
Example: Donor 1

![Graph showing CD69% of Control vs Compound [nM]]

FIG. 167
FIG. 169

Brain Tissue

CSF

Formula (XIII) ng/mL

Vehicle
5 mg/kg
30 mg/kg
FIG. 170
Dose-effect curve

Effect

Dose

\( \text{Inh.6 + Inh.7} \), \( \text{Inh.6} \), \( \text{Inh.7} \)

FIG. 171
Dose-effect curve

FIG. 173
Dose-effect curve

FIG. 174
Dose-effect curve

Effect vs. Dose

- Inh.6 + Inh.7
- Inh.6
- Inh.7

FIG. 175
INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2015/056128

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/00 A61K31/4155 A61K31/416 A61K31/454 A61K31/519
A61K39/395 A61K45/06...

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, BIOSIS, CHEMABS Data, EMBASE, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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</thead>
<tbody>
<tr>
<td>A, P</td>
<td>WO 2015/061752 AI (PHARMACYCLICS INC [US]; UNIV LELAND STANFORD JUNIOR [US])</td>
<td>1</td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to person skilled in the art

"Z" document member of the same patent family

Date of the actual completion of the international search: 16 October 2015

Date of mailing of the international search report: 11/01/2016

Name and mailing address of the ISA/Authorized officer:

Bonzano, Camilla

European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016
<table>
<thead>
<tr>
<th>Category</th>
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<th>Relevant to claim No.</th>
</tr>
</thead>
</table>
INFORMATION SEARCH REPORT

DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>BRIAN J. PARK ET AL: &quot;Dasatinib synergizes with both cytotoxic and signal transduction inhibitors in heterogeneous breast cancer cell lines - Lessons for design of combinations on targeted therapy&quot;, CANCER LETTERS, vol. 320, no. 1, 2 February 2012 (2012-02-02), pages 104-110, XP055217954, US ISSN: 0304-3835, DOI: 10.1016/j.canlet.2012.01.039 abstract</td>
<td>1</td>
</tr>
<tr>
<td>A</td>
<td>Wo 2013/010868 AI (MSD OSS BV [NL]; BARF TJEERD A [NL]; JANS CHRISTIAAN GERARDUS JOHANNES) 24 January 2013 (2013-01-24) cited in the application on page 78 - page 93; claim 1 page 1, paragraph 3</td>
<td>1-89</td>
</tr>
<tr>
<td>A</td>
<td>D'Cruz OJ ET AL: &quot;Novel Bruton's tyrosine kinase inhibitors currently in development&quot;, ONCOTARGETS AND THERAPY, vol. 6, 6 March 2013 (2013-03-06), pages 161-176, XP055217561, GB ISSN: 1178-6930, DOI: 10.2147/OTT.S33732 table 1 page 168, column 2</td>
<td>1</td>
</tr>
</tbody>
</table>

Form PCT/ISA/210 (continuation of second sheet) (April 2006)
<table>
<thead>
<tr>
<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>VAN DEN AKKER EMILE ET AL: “The Btk inhibitor LFM-A13 is a potent inhibitor of Jak2 kinase activity”, BIOLOGICAL CHEMISTRY, vol 385, no. 5, May 2004 (2004-05), pages 409-413, ISSN: 1431-6730 abstract page 412, column 1, paragraph 3</td>
<td>1</td>
</tr>
<tr>
<td>A, P</td>
<td>GI ROTTI MARIA ROMINA ET AL: “No longer an untreatable disease: How targeted and immunotherapies have changed the management of melanoma patients”, MOLECULAR ONCOLOGY, ELSEVIER, AMSTERDAM, NL, vol 8, no. 6, 15 August 2014 (2014-08-15), pages 1140-1158, ISSN: 1574-7891, DOI: 10.1016/j.molnc.2014.07 .027 page 1151, column 1, paragraph 3 - column 2, paragraph 1</td>
<td>1</td>
</tr>
<tr>
<td>A, P</td>
<td>HANTSCHEL 0: “Targeting BCR-ABL and JAK2 in Ph+ ALL”, BLOOD 20150226 AMERICAN SOCIETY OF HEMATOLOGY USA, vol. 125, no. 9, 26 February 2015 (2015-02-26), pages 1362-1363, ISSN: 0006-4971 the whole document</td>
<td>1-89</td>
</tr>
<tr>
<td>A, P</td>
<td>QINGJI E LIU ET AL: “Design and synthesis of carbazole carboxamides as promising Bruton’s tyrosine kinase (BTK) and Janus kinase 2 (JAK2) inhibitors”, BIOORGANIC &amp; MEDICINAL CHEMISTRY LETTERS, vol 25, no. 19, 6 August 2015 (2015-08-06), pages 4265-4269, ISSN: 0960-894X, DOI: 10.1016/j.bmcl.2015 .07 .102 page 4266, column 1, paragraph 2 - column 2, paragraph 2 page 4268, column 2, paragraph 5</td>
<td>1-89</td>
</tr>
</tbody>
</table>

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Form PCT/ISA/2/10 (continuation of second sheet) (April 2005)
<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>STEPHENS DEBORAH M ET AL: &quot;Changin g The Treatment Paradigm For Previously T reated Chronic Lymphocytic Leukemia Pati ents With De l (17p) Karyotype&quot; , BLOOD, vol. 122, no. 21, November 2013 (2013-11), page 2872, XP008177696, &amp; 55TH ANNUAL MEETING OF THE AMERICAN-SOCY-OF-H EMATOLOGY; NEW ORLEANS, LA, USA; DECEMBER 07 -10, 2013 the whole document</td>
<td>1-89</td>
</tr>
</tbody>
</table>
| A        | J. SCHWAMB ET AL: "B-cell receptor tri ggers drug sensiti vity of primary CLL cells by control ling glucosylation of ceramides", BLOOD, vol. 120, no. 19, 8 November 2012 (2012-11-08), pages 3978-3985, XP055218383, U.S. ISSN: 0006-4971, DOI: 10.1182/blood-2012-05-431783 abstract page 3983, column 1 page 3984, column 2, paragraph 1 | 1--/

Form PCT/ISA/210 (continuation of second sheet) (April 2005)
<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
</table>
### Observations where certain claims were found unsearchable (Continuation of Item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [ ] Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

2. [ ] Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Observations where unity of invention is lacking (Continuation of Item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

- see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

   1-66, 72-75, 87-89 (completely) ; 67-71, 76-86 (partially)

**Remark on Protest**

- [ ] The additional search fees were accompanied by the applicant’s protest and, where applicable, the payment of a protest fee.

- [ ] The additional search fees were accompanied by the applicant’s protest but the applicable protest fee was not paid within the time limit specified in the invitation.

- [ ] No protest accompanied the payment of additional search fees.
This International Search Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-66, 72-75, 87-89 (completely) ; 67-71, 76-86 (partially)

   Use of a composition comprising a CDK4/6 inhibitor and a BTK inhibitor, and optionally other ingredients, for treating cancer, solid tumors, cancer in human sensitive to bleeding events, to treat hyperproliferative diseases, leukemia, lymphoma; or as a research tool in the discovery and development of a pharmaceutical product.

2. claims: 67-71, 76-86 (partially)

   Use of a composition comprising a combination of a BTK inhibitor with PI3K inhibitor for treating cancer, solid tumors, cancer in human sensitive to bleeding events, to treat hyperproliferative diseases, leukemia, lymphoma; or as a research tool in the discovery and development of a pharmaceutical product.

3. claims: 67-71, 76-86 (partially)

   Use of a composition comprising a combination of a BTK inhibitor with JAK-2 inhibitor for treating cancer, solid tumors, cancer in human sensitive to bleeding events, to treat hyperproliferative diseases, leukemia, lymphoma; or as a research tool in the discovery and development of a pharmaceutical product.

4. claims: 67-71, 78-86 (partially)

   Use of a composition comprising a combination of a CDK4/6 inhibitor with PI3K inhibitor for treating cancer, solid tumors, cancer in human sensitive to bleeding events, to treat hyperproliferative diseases, leukemia, lymphoma; or as a research tool in the discovery and development of a pharmaceutical product.

5. claims: 67-71, 78-86 (partially)

   Use of a composition comprising a combination of a CDK4/6 inhibitor with JAK-2 inhibitor for treating cancer, solid tumors, cancer in human sensitive to bleeding events, to treat hyperproliferative diseases, leukemia, lymphoma; or as a research tool in the discovery and development of a pharmaceutical product.

6. claims: 67-71, 78-86 (partially)
Use of a composition comprising a combination of a PI3K (such as a delta, gamma or a delta, gamma) inhibitor with a JAK-2 inhibitor for treating cancer, solid tumors, cancer in human sensitive to bleeding events, to treat hyperproliferative diseases, leukemia, lymphoma; or as a research tool in the discovery and development of a pharmaceutical product.
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