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CERTAIN SUBSTITUTED AMIDES, METHOD OF MAKING, AND METHOD OF USE THEREOF
BESTIMMTE SUBSTITUIERTE AMIDE, VERFAHREN ZU DEREN HERSTELLUNG UND VERFAHREN ZU DEREN ANWENDUNG
AMIDES SUBSTITUÉS, PROCÉDÉ DE PRODUCTION ET D’UTILISATION DESDITS AMIDES

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References cited:
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Remarks:
The file contains technical information submitted after the application was filed and not included in this specification

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Description

[0001] This application claims the benefit of the filing date of U.S. Provisional Application Serial No. 60/843,959 filed September 11, 2006.

[0002] Provided herein are certain substituted amides and related compounds, compositions comprising such compounds, and methods of their use.

[0003] Protein kinases, the largest family of human enzymes, encompass well over 500 proteins. Bruton’s Tyrosine Kinase (Btk) is a member of the Tec family of tyrosine kinases, and is a regulator of early B-cell development as well as mature B-cell activation, signaling, and survival.

[0004] B-cell signaling through the B-cell receptor (BCR) can lead to a wide range of biological outputs, which in turn depend on the developmental stage of the B-cell. The magnitude and duration of BCR signals must be precisely regulated. Aberrant BCR-mediated signaling can cause disregulated B-cell activation and/or the formation of pathogenic auto-antibodies leading to multiple autoimmune and/or inflammatory diseases. Mutation of Btk in humans results in X-linked agammaglobulinaemia (XLA). This disease is associated with the impaired maturation of B-cells, diminished immunoglobulin production, compromised T-cell- independent immune responses and marked attenuation of the sustained calcium sign upon BCR stimulation.

[0005] Evidence for the role of Btk in allergic disorders and/or autoimmune disease and/or inflammatory disease has been established in Btk-deficient mouse models. For example, in standard murine preclinical models of systemic lupus erythematosus (SLE), Btk deficiency has been shown to result in a marked amelioration of disease progression. Moreover, Btk deficient mice can also be resistant to developing collagen-induced arthritis and can be less susceptible to Staphylococcus-induced arthritis.

[0006] A large body of evidence supports the role of B-cells and the humoral immune system in the pathogenesis of autoimmune and/or inflammatory diseases. Protein-based therapeutics (such as Rituxan) developed to deplete B-cells, represent an approach to the treatment of a number of autoimmune and/or inflammatory diseases. Because of Btk’s role in B-cell activation, inhibitors of Btk can be useful as inhibitors of B-cell mediated pathogenic activity (such as autoantibody production).

[0007] Btk is also expressed in osteoclasts, mast cells and monocytes and has been shown to be important for the function of these cells. For example, Btk deficiency in mice is associated with impaired IgE-mediated mast cell activation (marked diminution of TNF-alpha and other inflammatory cytokine release), and Btk deficiency in humans is associated with greatly reduced TNF-alpha production by activated monocytes.

[0008] Thus, inhibition of Btk activity can be useful for the treatment of allergic disorders and/or autoimmune and/or inflammatory diseases such as: SLE, rheumatoid arthritis, multiple vasculitides, idiopathic thrombocytopenic purpura (ITP), myasthenia gravis, allergic rhinitis, and asthma. In addition, Btk has been reported to play a role in apoptosis; thus, inhibition of Btk activity can be useful for cancer, as well as the treatment of B-cell lymphoma and leukemia. Moreover, given the role of Btk in osteoclast function, the inhibition of Btk activity can be useful for the treatment of bone disorders such as osteoporosis.


[0011] WO 2007/027729 A describes 3,5-disubstituted pyrid-2-ones to be useful as inhibitors of Tec family of non-receptor tyrosine kinases. Said compounds are inter alia characterized by the substituents -X2-X1- being always amide.

[0012] WO 00/43373 A describes kinase inhibitors, compositions comprising said inhibitors, and methods of using said inhibitors and compositions thereof. Said compounds are inter alia characterized by the presence of a pyrimidinone, and phenyl amine. Further, WO 00/43373 A inter alia describes compounds having a cyano substituent on the central ring.

[0013] Provided is at least one chemical entity chosen from compounds of Formula 1:
and pharmaceutically acceptable salts, solvates, chelates, non-covalent complexes, and mixtures thereof, wherein

R is chosen from aryl, heteroaryl and

in which;

aryl encompasses 5- and 6-membered carbocyclic aromatic rings; bicyclic ring systems wherein at least one ring is

carbocyclic and aromatic; and tricyclic ring systems wherein at least one ring is carbocyclic and aromatic; and wherein

aryl includes 5- and 6-membered carbocyclic aromatic rings fused to a 5- to 7-membered heterocycloalkyl ring containing

1 or more heteroatoms chosen from N, O, and S;

heteroaryl encompasses 5- to 7-membered aromatic, monocyclic rings containing one or more heteroatoms chosen

from N, O, and S, with the remaining ring atoms being carbon; and bicyclic heterocycloalkyl rings containing one or more

heteroatoms chosen from N, O, and S, with the remaining ring atoms being carbon and wherein at least one heteroatom

is present in an aromatic ring; and wherein heteroaryl includes a 5- to 7-membered heterocycloalkyl, aromatic ring fused
to a 5- to 7-membered cy cloalkyl ring;

R₅ is chosen from hydrogen, hydroxyl, alkyl groups having one to four carbons, sulfonyl, amino, alkoxy groups having

one to four carbons, alkyl groups having one to four carbons substituted with one or more halo, alkoxy groups having

one to four carbons substituted with hydroxy, heterocycloalcyl, an heteroaryl; and

X is chosen from N and CH.

R₄ is chosen from hydrogen, alkyl groups having one to four carbons, alkoxy groups having one to four carbons, halo,

and hydroxyl.

R₂₁ and R₂₂ are independently chosen from hydrogen and alkyl groups having one to four carbons;

R₁₆ is chosen from hydrogen, cyano, cycloalkyl, and alkyl groups having one to four carbons substituted with a group

chosen from alkoxy, amino, and acyl;

L is chosen from C₀₋₄alkylene, -O- C₀₋₄alkylene, -(C₀₋₄alkylene)(SO)₋₋,(C₀₋₄alkylene)(SO₂)₋₋, and

-(C₀₋₄alkylene)(C=O)₋₋; and

G is chosen from hydrogen, halo, hydroxy, alkoxy, nitro, alkyl, -NR₇R₈, wherein R₇ and R₈ are independently chosen

from hydrogen, acyl, and (C₁₋₄)alkyl; or wherein R₇ and R₈, together with the nitrogen to which they are bound, form

a 5- to 7-membered nitrogen containing heterocycloalkyl which optionally further includes one or two additional heter-
oatoms chosen from N, O, and S, carbamimidoyl, heterocycloalkyl, cycloalkyl, aryl, heteroaryl, 4-acyl-piperazin-1-yl, 4-
alkyl groups having one to four carbons-piperazin-1-yl, 4-alkyl groups having one to four carbons-piperidin-1-yl, 4-
hydroxy-4-alkyl groups having one to four carbons-piperidin-1-yl, 3-oxo-piperazin-1-yl, 4-alkyl groups having one to four
carbons-homopiperazin-1-yl.

[0014]  Provided is a pharmaceutical composition, comprising at least one chemical entity described herein, together

with at least one pharmaceutically acceptable vehicle chosen from carriers, adjuvants, and excipients.
Provided is a packaged pharmaceutical composition, comprising a pharmaceutical composition described here-in; and instructions for using the composition to treat a patient suffering from a disease responsive to inhibition of Btk activity.

Provided is at least one chemical entity described herein for use in a method for treating a patient having a disease responsive to inhibition of Btk activity, comprising administering to the patient an effective amount of at least one chemical entity described herein.

Provided is at least one chemical entity described herein for use in a method for treating a patient having a disease chosen from cancer, bone disorders, autoimmune diseases, inflammatory diseases, acute inflammatory reactions, and allergic disorders comprising administering to the patient an effective amount of at least one chemical entity described herein.

Provided is at least one chemical entity described herein for use in a method for increasing sensitivity of cancer cells to chemotherapy, comprising administering to a patient undergoing chemotherapy with a chemotherapeutic agent an amount of at least one chemical entity described herein, sufficient to increase the sensitivity of cancer cells to the chemotherapeutic agent.

Provided is an in vitro method for inhibiting ATP hydrolysis, the method comprising contacting cells expressing Btk with at least one chemical entity described herein in an amount sufficient to detectably decrease the level of ATP hydrolysis in vitro.

Provided is the use of at least one chemical entity described herein in an in vitro method for determining the presence of Btk in a sample, comprising contacting the sample with at least one chemical entity described herein under conditions that permit detection of Btk activity, detecting a level of Btk activity in the sample, and therefrom determining the presence or absence of Btk in the sample.

Provided is an in vitro method for inhibiting B-cell activity comprising contacting cells expressing Btk with at least one chemical entity described herein in an amount sufficient to detectably decrease the B-cell activity in vitro.

Provided is at least one chemical entity described herein for use in a method for increasing sensitivity of cancer cells to chemotherapy, comprising administering to a patient undergoing chemotherapy with a chemotherapeutic agent an effective amount of at least one chemical entity described herein.

Provided is at least one chemical entity described herein for use in a method for treating a patient suffering from a disease chosen from cancer, bone disorders, autoimmune diseases, inflammatory diseases, acute inflammatory reactions, and allergic disorders comprising administering to the patient an effective amount of at least one chemical entity described herein.

Provided is at least one chemical entity described herein for use in a method for treating a patient suffering from a disease responsive to inhibition of Btk activity, comprising administering to the patient an effective amount of at least one chemical entity described herein.

By "optional" or "optionally" is meant that the subsequently described event or circumstance may or may not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. It will be understood by those skilled in the art, with respect to any group containing one or more substituents, that such groups are not intended to introduce any substitution or substitution patterns that are sterically impractical, synthetically non-feasible and/or inherently unstable.

"Alykyl" encompasses straight chain and branched chain having the indicated number of carbon atoms, usually from 1 to 20 carbon atoms, for example 1 to 8 carbon atoms, such as 1 to 6 carbon atoms. For example C1-C6 alkyl encompasses both straight and branched chain alkyl of from 1 to 6 carbon atoms. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl, 3-methylpentyl, and the like. Alkylene is another subset of alkyl, referring to the same residues as alkyl, but having two points of attachment. Alkylene groups will usually have from 2 to 20 carbon atoms, for example 2 to 8 carbon atoms, such as from 2 to 6 carbon atoms. For example, Co alkylene indicates a covalent bond and C1 alkylene is a methylene group. When an alkyl residue having a specific number of carbons is named, all geometric isomers having that number of carbons are intended to be encompassed; thus, for example, "butyl" is meant to include n-butyl, sec-butyl, iso-butyl and t-butyl; "propyl" includes n-propyl and isopropyl. "Lower alkyl" refers to alkyl groups having one to four carbons.

"Cycloalkyl" indicates a saturated hydrocarbon ring group, having the specified number of carbon atoms, usually from 3 to 7 ring carbon atoms. Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl as well as bridged and caged saturated ring groups such as norbornane.

By "alkoxy" is meant an alkyl group of the indicated number of carbon atoms attached through an oxygen bridge such as, for example, methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, sec-butoxy, tert-butoxy, pentoxy, 2-pentyloxy,
isopentoxy, neopentoxy, hexoxy, 2-hexoxy, 3-hexoxy, 3-methylpentoxy, and the like. Alkoxy groups will usually have from 1 to 6 carbon atoms attached through the oxygen bridge. "Lower alkoxy" refers to alkoxy groups having one to four carbons.

[0031] "Acyl" refers to the groups (alkyl)-C(O)-; (cycloalkyl)-C(O)-; (aryl)-C(O)-; (heteroaryl)-C(O)-; and (heterocycloalkyl)-C(O)-, wherein the group is attached to the parent structure through the carbonyl functionality and wherein alkyl, cycloalkyl, aryl, heteroaryl, and heterocycloalkyl are as described herein. Acyl groups have the indicated number of carbon atoms, with the carbon of the keto group being included in the numbered carbon atoms. For example a C₂ acyl group is an acetyl group having the formula CH₃(C=O)-.

[0032] By "amino" is meant the group -NH₂.

[0033] "Aryl" encompasses:

5- and 6-membered carbocyclic aromatic rings, for example, benzene; bicyclic ring systems wherein at least one ring is carbocyclic and aromatic, for example, naphthalene, indane, and tetralin; and tricyclic ring systems wherein at least one ring is carbocyclic and aromatic, for example, fluorene.

For example, aryl includes 5- and 6-membered carbocyclic aromatic rings fused to a 5-to 7-membered heterocycloalkyl ring containing 1 or more heteroatoms chosen from N, O, and S. For such fused, bicyclic ring systems wherein only one of the rings is a carbocyclic aromatic ring, the point of attachment may be at the carbocyclic aromatic ring or the heterocycloalkyl ring. 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. Aroyl, however, does not encompass or overlap in any way with heteroaryl, separately defined below. Hence, if one or more carbocyclic aromatic rings is/are fused with a heterocycloalkyl aromatic ring, the resulting ring system is heteroaryl, not aryl, as defined herein.

[0034] The term "aryloxy" refers to the group -O-aryl.

[0035] The term "halo" includes fluoro, chloro, bromo, and iodo, and the term "halogen" includes fluorine, chlorine, bromine, and iodine.

[0036] "Heteroaryl" encompasses: 5- to 7-membered aromatic, monocyclic rings containing one or more, for example, from 1 to 4, or in certain embodiments, from 1 to 3, heteroatoms chosen from N, O, and S, with the remaining ring atoms being carbon; and bicyclic heterocycloalkyl rings containing one or more, for example, from 1 to 4, or in certain embodiments, from 1 to 3, heteroatoms chosen from N, O, and S, with the remaining ring atoms being carbon and wherein at least one heteroatom is present in an aromatic ring.

For example, heteroaryl includes a 5- to 7-membered heterocycloalkyl, aromatic ring fused to a 5- to 7-membered cycloalkyl ring. For such fused, bicyclic heteroaryl ring systems wherein only one of the rings contains one or more heteroatoms, the point of attachment may be at the heteroaromatic ring or the cycloalkyl ring. When the total number of S and O atoms in the heteroaryl group exceeds 1, those heteroatoms are not adjacent to one another. In certain embodiments, the total number of S and O atoms in the heteroaryl group is not more than 2. In certain embodiments, the total number of S and O atoms in the aromatic heterocycle is not more than 1. Examples of heteroaryl groups include, but are not limited to, (as numbered from the linkage position assigned priority 1), 2-pyridyl, 3-pyridyl, 4-pyridyl, 2,3-pyrazinyl, 3,4-pyrazinyl, 2,3-pyrimidinyl, 2,3-pyrazolinyl, 2,4-imidazolinyl, isoxazolinyl, oxazolinyl, thiazolinyl, thiadiazolinyl, tetrazolinyl, thienyl, benzothiophenyl, furanyl, benzofuranyl, benzimidazolinyl, indolinyl, pyridizinyl, triazolinyl, quinolinyl, pyrazolyl, and 5,6,7, 8-tetrahydroisoquinoline. 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 pyridylidene. Heteroaryl does not encompass or overlap with aryl as defined above.

[0037] By "heterocycloalkyl" is meant a single aliphatic ring, usually with 3 to 7 ring atoms, containing 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. Suitable heterocycloalkyl groups include, for example (as numbered from the linkage position assigned priority 1), 2-pyrollinyl, 2,4-pyrimidinyl, 2,3-pyrazolinyl, 2,5-piperazinyl, and 2,5-piperidyl. Morpholinyl groups are also contemplated, including 2- morpholinyl and 3-morpholinyl (numbered wherein the oxygen is assigned priority 1).

[0038] "Carbamimidoyl" refers to the group -C(=NH)-NH₂.

[0039] As used herein, "modulation" refers to a change in kinase activity as a direct or indirect response to the presence of compounds of Formula 1, relative to the activity of the kinase in the absence of the compound. The change may be an increase in activity or a decrease in activity, and may be due to the direct interaction of the compound with the kinase, or due to the interaction of the compound with one or more other factors that in turn affect kinase activity. For example, the presence of the compound may, for example, increase or decrease kinase activity by directly binding to the kinase,
by causing (directly or indirectly) another factor to increase or decrease the kinase activity, or by (directly or indirectly) increasing or decreasing the amount of kinase present in the cell or organism.

[0040] The term "sulfonyl" includes the groups: -S(O)₂-H, -S(O)₂-(substituted (C₁-C₆)alkyl), -S(O)₂-substituted aryl), -S(O)₂-(substituted heteroaryl), -S(O)₂-(substituted heterocycloalkyl), -S(O)₂-(substituted alkoxy), -S(O)₂-(substituted heterocyclyloxy), -S(O)₂-(substituted heteroaryloxy), and -SO₃H-(substituted amino).

[0041] The term "substituted", as used herein, means that any one or more hydrogens on the designated atom or group is replaced with a selection from the indicated group, provided that the designated atom's normal valence is not exceeded. When a substituent is oxo (i.e., =O) then 2 hydrogens on the atom are replaced. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds or useful synthetic intermediates. A stable compound or stable structure is meant to imply a compound that is sufficiently robust to survive isolation from a reaction mixture, and subsequent formulation as an agent having at least practical utility. Unless otherwise specified, substituents are named into the core structure. For example, it is to be understood that when (cycloalkyl)alkyl is listed as a possible substituent, the point of attachment of this substituent to the core structure is in the alkyl portion. Heteroatoms present in heteroaryls or heterocycloalkyls described herein include the oxidized forms of such heteroatoms such as N⁺→O⁻, S(O), and S(O)₂.

[0042] Compounds of Formula 1 include, but are not limited to, optical isomers of compounds of Formula 1, racemates, and other mixtures thereof. In those situations, the single enantiomers or diastereomers, i.e., optically active forms, can be obtained by asymmetric synthesis or by resolution of the racemate. Resolution of the racemate can be accomplished, for example, by conventional methods such as crystallization in the presence of a resolving agent, or chromatography, using, for example a chiral high-pressure liquid chromatography (HPLC) column. In addition, compounds of Formula 1 include Z- and E-forms (or cis- and trans- forms) of compounds with carbon-carbon double bonds. Where compounds of Formula 1 exists in various tautomeric forms, chemical entities of the present invention include all tautomeric forms of the compound. Compounds of Formula 1 also include crystal forms including polymorphs and clathrates.

[0043] Chemical entities of the present invention include, but are not limited to compounds of Formula 1 and all pharmaceutically acceptable forms thereof. Pharmaceutically acceptable forms of the compounds recited herein include pharmaceutically acceptable salts, solvates, chelates, non-covalent complexes, and mixtures thereof. In certain embodiments, the compounds described herein are in the form of pharmaceutically acceptable salts. Hence, the terms "chemical entity" and "chemical entities" also encompass pharmaceutically acceptable salts, solvates, chelates, non-covalent complexes, and mixtures.

[0044] "Pharmaceutically acceptable salts" include, but are not limited to salts with inorganic acids, such as hydrochloric acid, phosphoric acid, diphosphoric acid, hydrobromic acid, sulfuric acid, nitric acid, and like acids; as well as salts with an organic acid, such as maleic acid, maleic acid, fumaric acid, tartaric acid, succinic acid, citric acid, acetic acid, lactate, methanesulfonate, p-toluenesulfonate, 2-hydroxyethylsulfonate, benzoate, salicylate, stearate, and alkanoate such as acetic, HOOC- (CH₃)n-COOH where n is 0-4, and like acids. Similarly, pharmaceutically acceptable cations include, but are not limited to sodium, potassium, calcium, aluminum, lithium, and ammonium.

[0045] In addition, if the compound of Formula 1 is obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid salt. Conversely, if the product is a free base, an addition salt, particularly a pharmaceutically acceptable addition salt, may be produced by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds. Those skilled in the art will recognize various synthetic methodologies that may be used to prepare non-toxic pharmaceutically acceptable addition salts.

[0046] The term "solvate" refers to the chemical entity formed by the interaction of a solvent and a compound. Suitable solvates are pharmaceutically acceptable solvates, such as hydrates, including monohydrates and hemi-hydrates.

[0047] The term "chelate" refers to the chemical entity formed by the coordination of a compound to a metal ion at two (or more) points.

[0048] The term "non-covalent complex" refers to the chemical entity formed by the interaction of a compound and another molecule wherein a covalent bond is not formed between the compound and the molecule. For example, complexation can occur through van der Waals interactions, hydrogen bonding, and electrostatic interactions (also called ionic bonding).

[0049] The term "hydrogen bond" refers to a form of association between an electronegative atom (also known as a hydrogen bond acceptor) and a hydrogen atom attached to a second, relatively electronegative atom (also known as a hydrogen bond donor). Suitable hydrogen bond donor and acceptors are well understood in medicinal chemistry (G. C. Pimentel and A. L. McClellan, The Hydrogen Bond, Freeman, San Francisco, 1960; R. Taylor and O. Kennard, "Hydrogen Bond Geometry in Organic Crystals", Accounts of Chemical Research, 17, pp. 320-326 (1984)).

[0050] As used herein the terms "group", "radical" or "fragment" are synonymous and are intended to indicate functional groups or fragments of molecules attachable to a bond or other fragments of molecules.

[0051] The term "active agent" is used to indicate a chemical entity, which has biological activity. In certain embodiments, an "active agent" is a compound having pharmaceutical utility. For example an active agent may be an anti-cancer
therapeutic.

[0052] The term “therapeutically effective amount” of a chemical entity of this invention means an amount effective, when administered to a human or non-human patient, to provide a therapeutic benefit such as amelioration of symptoms, slowing of disease progression, or prevention of disease e.g., a therapeutically effective amount may be an amount sufficient to decrease the symptoms of a disease responsive to inhibition of Btk activity. In some embodiments, a therapeutically effective amount is an amount sufficient to reduce cancer symptoms, the symptoms of bone disorders, the symptoms of an allergic disorder, the symptoms of an autoimmune and/or inflammatory disease, or the symptoms of an acute inflammatory reaction. In some embodiments a therapeutically effective amount is an amount sufficient to decrease the number of detectable cancerous cells in an organism, detectably slow, or stop the growth of a cancerous tumor. In some embodiments, a therapeutically effective amount is an amount sufficient to shrink a cancerous tumor. In certain circumstances a patient suffering from cancer may not present symptoms of being affected. In some embodiments, a therapeutically effective amount of a chemical entity is an amount sufficient to prevent a significant increase or significantly reduce the detectable level of cancerous cells or cancer markers in the patient’s blood, serum, or tissues. In methods described herein for treating allergic disorders and/or autoimmune and/or inflammatory diseases and/or acute inflammatory reactions, a therapeutically effective amount may also be an amount sufficient, when administered to a patient, to detectably slow progression of the disease, or prevent the patient to whom the chemical entity is given from presenting symptoms of the allergic disorders and/or autoimmune and/or inflammatory disease, and/or acute inflammatory response. In certain methods described herein for use in treating allergic disorders and/or autoimmune and/or inflammatory diseases and/or acute inflammatory reactions, a therapeutically effective amount may also be an amount sufficient to produce a detectable decrease in the amount of a marker protein or cell type in the patient’s blood or serum. For example, in some embodiments a therapeutically effective amount is an amount of a chemical entity described herein sufficient to significantly decrease the activity of B- cells. In another example, in some embodiments a therapeutically effective amount is an amount of a chemical entity described herein sufficient to significantly decrease the number of B-cells. In another example, in some embodiments a therapeutically effective amount is an amount of a chemical entity described herein sufficient to decrease the level of anti-acetylcholine receptor antibody in a patient’s blood with the disease myasthenia gravis.

[0053] The term “inhibition” indicates a significant decrease in the baseline activity of a biological activity or process. “Inhibition of Btk activity” refers to a decrease in Btk activity as a direct or indirect response to the presence of at least one chemical entity described herein, relative to the activity of Btk in the absence of the at least one chemical entity. The decrease in activity may be due to the direct interaction of the compound with Btk, or due to the interaction of the chemical entity(ies) described herein with one or more other factors that in turn affect Btk activity. For example, the presence of the chemical entity(ies) may decrease Btk activity by directly binding to the Btk, by causing (directly or indirectly) another factor to decrease Btk activity, or by (directly or indirectly) decreasing the amount of a chemical entity described herein sufficient to significantly decrease the activity of B- cells. In another example, in some embodiments a therapeutically effective amount is an amount of a chemical entity described herein sufficient to significantly decrease the activity of Btk. In one or more embodiments, a therapeutically effective amount of a chemical entity is an amount sufficient to significantly decrease the activity of Btk present in the cell or organism.

[0054] Inhibition of Btk activity also refers to observable inhibition of Btk activity in a standard biochemical assay for Btk activity, such as the ATP hydrolysis assay described below. In some embodiments, the chemical entity described herein has an IC50 value less than or equal to 1 micromolar. In some embodiments, the chemical entity has an IC50 value less than or equal to 500 nanomolar. In some embodiments, the IC50 value less than or equal to 10 nanomolar.

[0055] “Inhibition of B-cell activity” refers to a decrease in B-cell activity as a direct or indirect response to the presence of at least one chemical entity described herein, relative to the activity of B-cells in the absence of the at least one chemical entity. The decrease in activity may be due to the direct interaction of the compound with Btk or with one or more other factors that in turn affect B-cell activity.

[0056] Inhibition of B-cell activity also refers to observable inhibition of CD86 expression in a standard assay such as the assay described below. In some embodiments, the chemical entity described herein has an IC50 value less than or equal to 1 micromolar. In some embodiments, the chemical entity has an IC50 value less than or equal to 500 nanomolar.

[0057] “B cell activity” also includes activation, redistribution, reorganization, or capping of one or more various B cell membrane receptors, e.g., CD40, CD86 and Toll-like receptors TLRs (in particular TLR4), or membrane-bound immunoglobulins, e.g., IgM, IgG, and IgD. Most B cells also have membrane receptors for Fc portion of IgG in the form of either antigen-antibody complexes or aggregated IgG. B cells also carry membrane receptors for the activated components of complement, e.g., C3b, C3d, C4, and Clq. These various membrane receptors and membrane-bound immunoglobulins have membrane mobility and can undergo redistribution and capping that can initiate signal transduction.

[0058] B cell activity also includes the synthesis or production of antibodies or immunoglobulins. Immunoglobulins are synthesized by the B cell series and have common structural features and structural units. Five immunoglobulin classes, i.e., IgG, IgA, IgM, IgD, and IgE, are recognized on the basis of structural differences of their heavy chains including the amino acid sequence and length of the polypeptide chain. Antibodies to a given antigen may be detected in all or several classes of immunoglobulins or may be restricted to a single class or subclass of immunoglobulin. Autoantibodies or
autoimmune antibodies may likewise belong to one or several classes of immunoglobulins. For example, rheumatoid factors (antibodies to IgG) are most often recognized as an IgM immunoglobulin, but can also consist of IgG or IgA.

In addition, B cell activity also is intended to include a series of events leading to B cell clonal expansion (proliferation) from precursor B lymphocytes and differentiation into antibody-synthesizing plasma cells which takes place in conjunction with antigen-binding and with cytokine signals from other cells.

"Inhibition of B-cell proliferation" refers to inhibition of proliferation of abnormal B-cells, such as cancerous B-cells, e.g. lymphoma B-cells and/or inhibition of normal, non-diseased B-cells. The term "inhibition of B-cell proliferation" indicates no increase or any significant decrease in the number of B-cells, either in vitro or in vivo. Thus an inhibition of B-cell proliferation in vitro would be any significant decrease in the number of B-cells in an in vitro sample contacted with at least one chemical entity described herein as compared to a matched sample not contacted with the chemical entity(ies).

Inhibition of B-cell proliferation also refers to observable inhibition of B-cell proliferation in a standard thymidine incorporation assay for B-cell proliferation, such as the assay described herein. In some embodiments, the chemical entity has an IC$_{50}$ value less than or equal to 10 micromolar. In some embodiments, the chemical entity has an IC$_{50}$ value less than or equal to 1 micromolar. In some embodiments, the chemical entity has an IC$_{50}$ value less than or equal to 500 nanomolar.

"An "allergy" or "allergic disorder" refers to acquired hypersensitivity to a substance (allergen). Allergic conditions include eczema, allergic rhinitis or coryza, hay fever, bronchial asthma, urticaria (hives) and food allergies, and other atopic conditions.

"Asthma" refers to a disorder of the respiratory system characterized by inflammation, narrowing of the airways and increased reactivity of the airways to inhaled agents. Asthma is frequently, although not exclusively associated with atopic or allergic symptoms.

By "significant" is meant any detectable change that is statistically significant in a standard parametric test of statistical significance such as Student’s T-test, where p < 0.05.

"Treatment" or "treating" means the mere use of at least one chemical entity of the present invention in a method for treating a disease in accordance with the invention, including: a) preventing the disease, that is, causing the clinical symptoms of the disease not to develop; b) inhibiting the disease; c) slowing or arresting the development of clinical symptoms; and/or d) relieving the disease, that is, causing the regression of clinical symptoms.

"Patient" refers to an animal, such as a mammal, that has been or will be the object of the use of at least one chemical entity of the present invention in a method of treatment a disease in accordance with the invention, observation or experiment. The methods of the invention can be useful in both human therapy and veterinary applications. In some embodiments, the patient is a mammal; in some embodiments the patient is human; and in some embodiments the patient is chosen from cats and dogs.

Provided is at least one chemical entity chosen from compounds of Formula 1:

![Chemical structure](Formula 1)

and pharmaceutically acceptable salts, solvates, chelates, non-covalent complexes, and mixtures thereof, wherein R is chosen from aryl, heteroaryl and
in which:

aryl encompasses 5- and 6-membered carbocyclic aromatic rings; bicyclic ring systems wherein at least one ring is carbocyclic and aromatic; and tricyclic ring systems wherein at least one ring is carbocyclic and aromatic; and wherein aryl includes 5- and 6-membered carbocyclic aromatic rings fused to a 5- to 7-membered heterocycloalkyl ring containing 1 or more heteroatoms chosen from N, O, and S;
heteroaryl encompasses 5- to 7-membered aromatic, monocyclic rings containing one or more heteroatoms chosen from N, O, and S, with the remaining ring atoms being carbon; and bicyclic heterocycloalkyl rings containing one or more heteroatoms chosen from N, O, and S, with the remaining ring atoms being carbon and wherein at least one heteroatom is present in an aromatic ring; and wherein heteroaryl includes a 5- to 7-membered heterocycloalkyl, aromatic ring fused to a 5- to 7-membered cycloalkyl ring;

R₅ is chosen from hydrogen, hydroxyl, alkyl groups having one to four carbons, sulfonyl, amino, alkoxy groups having one to four carbons, alkyl groups having one to four carbons substituted with one or more halo, alkoxy groups having one to four carbons substituted with halo, alkyl groups having one to four carbons substituted with hydroxy, heterocycloalkyl, an heteroaryl; and

X is chosen from N and CH.

R₄ is chosen from hydrogen, alkyl groups having one to four carbons, halo groups having one to four carbons, halo, and hydroxy.

R₂₁ and R₂₂ are independently chosen from hydrogen and alkyl groups having one to four carbons;

R₁₆ is chosen from hydrogen, cyano, cycloalkyl, and alkyl groups having one to four carbons substituted with a group chosen from halo, amino, and acyl; L is chosen from C₀₋₄alkylene, -O-C₀₋₄ alkylene, -(C₀₋₄ alkylene)(SO)-, -(C₀₋₄ alkylene)(SO₂)-; and -(C₀₋₄ all- cylene)(C=O)-; and G is chosen from hydrogen, halo, hydroxy, alkoxy, nitro, alkyl, -NR₇R₈, wherein R₇ and R₈ are independently chosen from hydrogen, acyl, and (C₁₋₄)alkyl; or wherein R₇ and R₈ together with the nitrogen to which they are bound, form a 5- to 7-membered nitrogen containing heterocycloalkyl which optionally further includes one or two additional heteroatoms chosen from N, O, and S, carbamimidyl, heterocycloalkyl, cycloalkyl, aryl, heteroaryl, 4-acyl-piperazin-1-yl, 4-alkyl groups having one to four carbons-piperazin-1-yl, 4-alkyl groups having one to four carbons-piperidin-1-yl, 4-hydroxy-4-alkyl groups having one to four carbons-piperazin-1-yl, 3-oxo-piperazin-1-yl, 4-alkyl groups having one to four carbons-homopiperazin-1-yl.

[0069] In certain embodiments, R is chosen from 4,5,6,7-tetrahydrobenzo[b] thiophen-2-yl.

[0070] In certain embodiments, R₄ is chosen from hydrogen, alkyl groups having one to four carbons, alkyl groups having one to four carbons, halo, and hydroxy. In certain embodiments, R₄ is chosen from methyl, trifluoromethyl, difluoromethyl, methoxy, trifluoromethoxy, difluoromethoxy, and fluoro. In certain embodiments, R₄ is methyl.

[0071] In certain embodiments, R₂₂ is chosen from hydrogen and alkyl groups having one to four carbons. In certain embodiments, R₂₂ is hydrogen.

[0072] In certain embodiments, R₂₁ is chosen from hydrogen and alkyl groups having one to four carbons. In certain embodiments, R₂₁ is hydrogen.

[0073] In certain embodiments, R₁₆ is chosen from hydrogen and alkyl groups having one to four carbons. In certain embodiments, R₁₆ is hydrogen.

[0074] In certain embodiments, L is chosen from C₀₋₄alkylene, -O-C₀₋₄ alkylene, -(C₀₋₄ alkylene)(SO)-; and -(C₀₋₄ alkylene)(C=O)-. In certain embodiments, L is chosen from C₀₋₄alkylene and -(C₀₋₄ alkylene) (C=O)-. In certain embodiments, L is -(C=O)-.

[0075] In certain embodiments, G is chosen from hydrogen, hydroxy, -NR₇R₈ wherein R₇ and R₈ are independently chosen from hydrogen, optionally substituted acyl, and optionally substituted (C₁₋₄)alkyl; or wherein R₇ and R₈ together with the nitrogen to which they are bound, form an optionally substituted 5- to 7-membered nitrogen containing heterocycloalkyl which optionally further includes one or two additional heteroatoms chosen from N, O, and S.

[0076] In certain embodiments, G is chosen from hydrogen, 4-acyl-piperazin-1-yl, 4-alkyl groups having one to four carbons -piperazin-1-yl, 4-alkyl groups having one to four carbons -piperidin-1-yl, 4-hydroxy-4-alkyl groups having one to four carbons-piperazin-1-yl, 3-oxo-piperazin-1-yl, and 4-alkyl groups having one to four carbons-homopiperazin-1-yl.

[0077] In certain embodiments, G is chosen from 4-alkyl groups having one to four carbons -piperazin-1-yl, halo.

[0078] Also provided is at least one chemical entity chosen from compounds of Formula 2:
and pharmaceutically acceptable salts, solvates, chelates, non-covalent complexes, and mixtures thereof,
wherein R₄, R₁₆, R₂₁, R₂₂, L, and G are as described for compounds of Formula 1 or as defined in any one of the
preceding embodiments, and wherein R₅ is chosen from hydrogen, hydroxy, alkyl groups having one to four carbons,
sulfonyl, amino, alkoxy groups having one to four carbons, alkyl groups having one to four carbons substituted with one
or more halo, alkoxy groups having one to four carbons substituted with one or more halo, alkyl groups having one to
four carbons substituted with hydroxy, heterocycloalkyl, and heteroaryl;
and X is chosen from N and CH.

[0079] In certain embodiments, X is CH. In certain embodiments, X is N.
[0080] In certain embodiments, R₅ is chosen from hydrogen, piperidinyl, and alkyl groups having one to four carbons.
[0081] In certain embodiments, the compound of Formula 1 is chosen from

N-[3-[5-(6-Amino-pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydro-pyridin-3-yl]-2- methylphenyl]-4-tert-butyl-benzo-
mande;
4-tert-Butyl-N-(2-methyl-3-[1-methyl-5-[5-(morpholine-4-carbonyl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-pyridin- 3-
yl]-phenyl)-benzamide;
N-[3-[5-(4-Amino-pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydro-pyridin-3-yl]-2-methylphenyl]-4-tert-butyl-benzo-
mande;
4-tert-Butyl-N-(2-methyl-3-[1-methyl-6-oxo-5-(pyridin-2-ylamino)-1,6-dihydro-pyridin-3-yl]-phenyl]-benzamide;
4,5,6,7-Tetrahydro-benzo[b]thiophene-2-carboxylic acid (2-methyl-3-[1-methyl-5-[5-(morpholine-4-carbonyl)-pyrid-
in-2-ylamino]-6-oxo-1,6-dihydro-pyridin-3-yl]-phenyl)-amide;
4-tert-Butyl-N-(2-methyl-3-[5-[5-(morpholine-4-carbonyl)-pyridin-2-ylamino]-6- oxo-1,6-dihydro-pyridin-3-yl]-phe-
nyl]-benzamide;
4-tert-Butyl-N-(2-methyl-3-[1-methyl-5-(5-morpholin-4-yl-pyridin-2-ylamino)-6-oxo-1,6-dihydro-pyridin-3-yl]-phe-
nyl]-benzamide;
4,5,6,7-Tetrahydro-benzo[b]thiophene-2-carboxylic acid (2-methyl-3-[5-[5-(morpholine-4-carbonyl)-pyridin-2-ylami-
ño]-6-oxo-1,6-dihydro-pyridin-3-yl]-phenyl)-amide;
4,5,6,7-Tetrahydro-benzo[b]thiophene-2-carboxylic acid (2-methyl-3-[1-methyl-5-(5-hydroxy-4-ethyl-2H-[1,3]bi-
pyridinyl-6'-ylamino)-1-methyl-6-oxo-1,6-dihydro-pyridin-3-yl]-phenyl)-amide;
4,5,6,7-Tetrahydro-benzo[b]thiophene-2-carboxylic acid (2-methyl-3-[1-methyl-5-(5-hydroxy-4-ethyl-2H-[1,3]bi-
pyridinyl-6'-ylamino)-1-methyl-6-oxo-1,6-dihydro-pyridin-3-yl]-phenyl)-amide;
4,5,6,7-Tetrahydro-benzo[b]thiophene-2-carboxylic acid (2-methyl-3-[1-methyl-5-(5-hydroxy-4-ethyl-2H-[1,3]bi-
pyridinyl-6'-ylamino)-1-methyl-6-oxo-1,6-dihydro-pyridin-3-yl]-phenyl)-amide;
4,5,6,7-Tetrahydro-benzo[b]thiophene-2-carboxylic acid (2-methyl-3-[1-methyl-5-(5-hydroxy-4-ethyl-2H-[1,3]bi-
pyridinyl-6'-ylamino)-1-methyl-6-oxo-1,6-dihydro-pyridin-3-yl]-phenyl)-amide;
4,5,6,7-Tetrahydro-benzo[b]thiophene-2-carboxylic acid (2-methyl-3-[1-methyl-5-(5-hydroxy-4-ethyl-2H-[1,3]bi-
pyridinyl-6'-ylamino)-1-methyl-6-oxo-1,6-dihydro-pyridin-3-yl]-phenyl)-amide;
4,5,6,7-Tetrahydro-benzo[b]thiophene-2-carboxylic acid (2-methyl-3-[1-methyl-5-(5-hydroxy-4-ethyl-2H-[1,3]bi-
pyridinyl-6'-ylamino)-1-methyl-6-oxo-1,6-dihydro-pyridin-3-yl]-phenyl)-amide;
N-[3-[5-(6-Amino-pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydro-pyridin-3-yl]-2-methylphenyl]-4-tert-butyl-benzo-
mande;
N-(2-Methyl-3-(5-(4-methylpiperazin-1-yl)pypyridine-2-ymino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide;
4-tert-Butyl-N-(2-methyl-3-(1-methyl-5-(4-methyl piperazine-1-carbonyl)pypyridine-2-ymino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl]benzamide;
N-(3-(5-(4-Amino-5-(4-methyl piperazine-1-carbonyl)pyridine-2-ymino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)-4-tert-butyl benzamide;
4-tert-Butyl-N-(2-methyl-3-(1-methyl-6-oxo-5-(5-(piperidine-1-carbonyl)pyridin-2-ylamino)-1,6-dihydropyridin-3-yl)phenyl]benzamide;
N-(2-Methyl-3-(1-methyl-5-(5-(morpholine-4-carbonyl)pyridine-2-ymino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl]benzamide;
N-(3-(5-(5-(4-Hydroxy-5-(4-hydroxypiperidine-1-carbonyl)pyridine-2-ymino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)-4,5,6,7-tetrahydro benzo[b]thiophene-2-carboxamide;
6-(5-(3-(4-tert-Butylbenzamido)-2-methylphenyl)-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)phenyl]benzamide;
N-(2-Methyl-3-(1-methyl-5-(5-(morpholine-4-carbonyl)pyridine-2-ymino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl]benzamide;
N-(3-(5-(5-(1,4-Oxazepane-4-carbonyl)pyridine-2-ymino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)-4-tert-butyl benzamide;
4-tert-Butyl-N-(2-methyl-3-(1-methyl-5-(5-(morpholinomethyl)pyridine-2-ymino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl]benzamide;
N,N-bis(2-Methoxyethyl)-6-(1-methyl-5-(2-methyl-3-(4,5,6,7-tetrahydro-4H-cyclohepta[b]thiophene-2-carboxamido)phenyl)-2-oxo-1,2-dihydropyridin-3-yl)nicotinamide;
N,N-bis(2-Methoxyethyl)-6-(1-methyl-5-(2-methyl-3-(4,5,6,7-tetrahydro-4H-cyclohepta[b]thiophene-2-carboxamido)phenyl)-2-oxo-1,2-dihydropyridin-3-yl)nicotinamide;
4-tert-Butyl-N-(2-chloro-5-fluoro-3-(1-methyl-5-(5-(morpholine-4-carbonyl)pyridine-2-ymino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl]benzamide;
N,N-bis(2-Methoxyethyl)-6-(1-methyl-5-(2-methyl-3-(4,5,6,7-tetrahydro-4H-cyclohepta[b]thiophene-2-carboxamido)phenyl)-2-oxo-1,2-dihydropyridin-3-yl)nicotinamide;
4-tert-Butyl-N-(2-methyl-3-(1-methyl-6-oxo-5-(5-(piperidine-1-carbonyl)pyridine-2-ymino)-1,6-dihydropyridin-3-yl)phenyl]benzamide;
N,N-bis(2-Methoxyethyl)-6-(1-methyl-5-(2-methyl-3-(4,5,6,7-tetrahydro-4H-cyclohepta[b]thiophene-2-carboxamido)phenyl)-2-oxo-1,2-dihydropyridin-3-yl)nicotinamide;
4-tert-Butyl-N-(2-chloro-5-fluoro-3-(1-methyl-5-(5-(morpholine-4-carbonyl)pyridine-2-ymino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl]benzamide;
N,N-bis(2-Methoxyethyl)-6-(1-methyl-5-(2-methyl-3-(4,5,6,7-tetrahydro-4H-cyclohepta[b]thiophene-2-carboxamido)phenyl)-2-oxo-1,2-dihydropyridin-3-yl)nicotinamide;
4-tert-Butyl-N-(2-chloro-5-fluoro-3-(1-methyl-5-(5-(morpholine-4-carbonyl)pyridine-2-ymino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl]benzamide;
4-tert-Butyl-N-(3-(5-(5-(hydroxymethyl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)benzamide;
N-(3-(5-(5-(Hydroxymethyl)pyridin-2-ylamino)phenyl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)benzamide;
4-tert-Butyl-N-(3-((isopropyl(methyl)amino)phenyl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)benzamide;
N-(3-(5-(5-(Isopropyl(methyl)amino)phenyl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)benzamide;
N-(3-(5-(5-(Isopropyl(methyl)amino)phenyl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)benzamide;
4-tert-Butyl-N-(3-(5-(5-(4-(2-hydroxyethyl)piperazine-1-carbonyl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)benzamide;
N-(3-(5-(5-(4-Acetylpiperazine-1-carbonyl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)benzamide;
N-(3-(5-(5-(4-Acetylpiperazine-1-carbonyl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)benzamide;
N-(3-(5-(5-(4-Acetylpiperazine-1-carbonyl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)benzamide;
N-(3-(5-(5-(4-Acetylpiperazine-1-carbonyl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)benzamide;
N-(3-(5-(5-(4-Acetylpiperazine-1-carbonyl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)benzamide;
5-Methyl-N-(2-methyl-3-(1-methyl-5-(5-(morpholine-4-carbonyl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide; 6-(5-(3-(4-tert-Butylbenzamido)-2-methylphenyl)-1-methyl-2-oxo-1,2-dihydropyridin-3-ylamino)nicotinamide;
N-(2-Chloro-3-(1-methyl-5-(5-(morpholine-4-carbonyl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide; 6-(5-(3-(4-tert-Butylbenzamido)-2-methylphenyl)-1-methyl-2-oxo-1,2-dihydropyridin-3-ylamino)nicotinamide;
N-(2-Chloro-3-(1-methyl-5-(5-(morpholine-4-carbonyl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide; 6-(5-(3-(4-tert-Butylbenzamido)-2-methylphenyl)-1-methyl-2-oxo-1,2-dihydropyridin-3-ylamino)nicotinamide;
6-(5-(3-(4-tert-Butylbenzamido)-2-methylphenyl)-1-methyl-2-oxo-1,2-dihydropyridin-3-ylamino)nicotinamide; 6-(5-(3-(4-tert-Butylbenzamido)-2-methylphenyl)-1-methyl-2-oxo-1,2-dihydropyridin-3-ylamino)nicotinamide; 6-(5-(3-(4-tert-Butylbenzamido)-2-methylphenyl)-1-methyl-2-oxo-1,2-dihydropyridin-3-ylamino)nicotinamide; 6-(5-(3-(4-tert-Butylbenzamido)-2-methylphenyl)-1-methyl-2-oxo-1,2-dihydropyridin-3-ylamino)nicotinamide; 6-(5-(3-(4-tert-Butylbenzamido)-2-methylphenyl)-1-methyl-2-oxo-1,2-dihydropyridin-3-ylamino)nicotinamide; 6-(5-(3-(4-tert-Butylbenzamido)-2-methylphenyl)-1-methyl-2-oxo-1,2-dihydropyridin-3-ylamino)nicotinamide; 6-(5-(3-(4-tert-Butylbenzamido)-2-methylphenyl)-1-methyl-2-oxo-1,2-dihydropyridin-3-ylamino)nicotinamide; 6-(5-(3-(4-tert-Butylbenzamido)-2-methylphenyl)-1-methyl-2-oxo-1,2-dihydropyridin-3-ylamino)nicotinamide; 6-(5-(3-(4-tert-Butylbenzamido)-2-methylphenyl)-1-methyl-2-oxo-1,2-dihydropyridin-3-ylamino)nicotinamide; 6-(5-(3-(4-tert-Butylbenzamido)-2-methylphenyl)-1-methyl-2-oxo-1,2-dihydropyridin-3-ylamino)nicotinamide; 6-(5-(3-(4-tert-Butylbenzamido)-2-methylphenyl)-1-methyl-2-oxo-1,2-dihydropyridin-3-ylamino)nicotinamide; 6-(5-(3-(4-tert-Butylbenzamido)-2-methylphenyl)-1-methyl-2-oxo-1,2-dihydropyridin-3-ylamino)nicotinamide; 6-(5-(3-(4-tert-Butylbenzamido)-2-methylphenyl)-1-methyl-2-oxo-1,2-dihydropyridin-3-ylamino)nicotinamide;
N-(2-Methyl-3-(1-methyl-6-oxo-5-(4-oxopiperidine-1-carbonyl)pyridin-2-ylamino)-1,6-dihydropyridin-3-yl)phenyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide;
N-(2-Methyl-3-(1-methyl-6-oxo-5-(4-oxopiperidine-1-carbonyl)pyridin-2-ylamino)-1,6-dihydropyridin-3-yl)phenyl)-5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophene-2-carboxamide;
4-tert-Butyl-N-(3-(5-(4-(methoxymethyl)piperidine-1-carbonyl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)benzamide;
N-(3-(5-(4-Methoxypiperidine-1-carbonyl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)benzamide;
4-tert-Butyl-N-(3-(5-(5-(4-(methoxymethyl)piperidine-1-carbonyl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)benzamide;
N-(2-Methyl-3-(1-methyl-5-(5-(4-morpholinopiperidin-1-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide;
N-(2-Methyl-3-(1-methyl-5-(5-(4-morpholinopiperidin-1-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophene-2-carboxamide;
4-tert-Butyl-N-(3-(5-(4-cyanopiperidine-1-carbonyl)pyridin-2-ylamino)-5-fluoro-2-methylphenyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide;
N-(5-Fluoro-2-methyl-3-(1-methyl-5-(5-(4-methylpiperazine-1-carbonyl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide;
N-(5-Fluoro-2-methyl-3-(1-methyl-5-(5-(morpholino)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-5-fluoro-2-methylphenyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide;
N-Ethyl-6-(5-(5-fluoro-2-methyl-3-(4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamido)phenyl)-1-methyl-2-oxo-1,2-dihydropyridin-3-ylamino)-N-methylnicotinamide;
N-(3-(5-(5-(4-Dimethylamino)piperidine-1-carbonyl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide;
4-tert-Butyl-N-(2-methyl-3-(1-methyl-5-(5-(4-methylpiperazine-1-carbonyl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)benzamide;
N-(2-Methyl-3-(1-methyl-5-(5-(4-morpholinopiperidin-1-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide;
4-tert-Butyl-N-(5-fluoro-2-methyl-3-(1-methyl-5-(5-morpholinopyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-5-fluoro-2-methylphenyl)benzamide;
4-tert-Butyl-N-(5-fluoro-3-(5-(5-(4-hydroxy-4-methylpiperidin-1-yl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)benzamide;
4-tert-Butyl-N-(5-fluoro-2-methyl-3-(1-methyl-5-(5-morpholinopyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)benzamide;
4-tert-Butyl-N-(5-fluoro-2-methyl-3-(1-methyl-5-(5-oxiranopyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)benzamide;
N-(3-(5-(4-Ethylpiperazin-1-yl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide;
4-tert-Butyl-N-(3-(5-(4-isopropylpiperazin-1-yl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide;
N-(2-Methyl-3-(1-methyl-5-(5-(4-methylpiperazin-1-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)benzo[b]thiophene-2-carboxamide;
5-tert-Butyl-N(2-methyl-3-(1-methyl-5-(5-(4-methylpiperazin-1-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)pyrazine-2-carboxamide;
4-tert-Butyl-N(3-(5-(5-(4-(2-hydroxyethyl)piperazin-1-yl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)-benzamide;
N-(2-Methyl-3-(1-methyl-5-(5-(4-methylpiperazin-1-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-4-(piperidin-1-yl)benzamide;
N-(3-(5-(5-(4-(2-Hydroxyethyl)piperazin-1-yl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide;
4-tert-Butyl-N(2-methyl-3-(1-methyl-6-oxo-5-(5-(piperazin-1-yl)pyridin-2-ylamino)-1,6-dihydropyridin-3-yl)phenyl)benzamide;
N-(3-(5-(5-(4-Hydroxy-4-methylpiperidin-1-yl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)-5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophene-2-carboxamide;
4-(Ethyl-methyl-amino)-N-(2-methyl-3-{1-methyl-5-[5-(4-methyl-piperazin-1-yl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-pyridin-3-yl}-phenyl)-benzamide;
4,5,6,7-Tetrahydro-benzo[b]thiophene-2-carboxylic acid (2,5-difluoro-3-{1-methyl-5-[5-(4-methyl-piperazin-1-yl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-pyridin-3-yl}-phenyl)-amide;
5,6,7,8-Tetrahydro-4H-cyclohepta[b]thiophene-2-carboxylic acid (2,5-difluoro-3-{1-methyl-5-[5-(4-methyl-piperazin-1-yl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-pyridin-3-yl}-phenyl)-amide;
4-(1-Methyl-cyclopropyl)-N-(2-methyl-3-{1-methyl-5-[5-(4-methyl-piperazin-1-yl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-pyridin-3-yl}-phenyl)-benzamide;
4,5,6,7-Tetrahydro-benzo[b]thiophene-2-carboxylic acid (2-methyl-3-{5-[4-(4-methyl-piperazin-1-yl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-pyridin-3-yl}-phenyl)-amide;
5,6,7,8-Tetrahydro-4H-cyclohepta[b]thiophene-2-carboxylic acid (2-fluoro-3-{1-methyl-5-[5-(4-methyl-piperazin-1-yl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-pyridin-3-yl}-phenyl)-amide;
4-(1-Ethyl-cyclopropyl)-N-(2-methyl-3-{1-methyl-5-[5-(4-methyl-piperazin-1-yl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-pyridin-3-yl}-phenyl)-benzamide;
N-(3-(5-(4-Cyclopropylpiperazin-1-yl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-fluorophenyl)-5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophene-2-carboxamide;
N-(3-(5-(4-(2-Cyanoethyl)piperazin-1-yl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-fluorophenyl)-5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophene-2-carboxamide;
N-(2-Fluoro-3-(5-(5-(4-(2-methoxyethyl)piperazin-1-yl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophene-2-carboxamide;
N-(2-Fluoro-3-(1-methyl-5-(5-(4-(2-(methylsulfonyl)ethyl)piperazin-1-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophene-2-carboxamide;
N-(2-Fluoro-3-(1-methyl-6-oxo-5-(5-(1,1-dioxo-1,6-thiomorpholin-4-yl)-pyridin-2-ylamino)-1,6-dihydropyridin-3-yl)phenyl)-5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophene-2-carboxamide;
N-(3-(5-(4-Cyclopropylpiperazin-1-yl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)-5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophene-2-carboxamide;
N-(2-Fluoro-3-(1-methyl-6-oxo-5-(5-(4-methyl-1,4-diazepan-1-yl)pyridin-2-ylamino)-1,6-dihydropyridin-3-yl)phenyl)-5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophene-2-carboxamide;
N-(3-(5-(4-Cyclopropylpiperazin-1-yl)pyridin-2-ylamino)-2-fluorophenyl)-5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophene-2-carboxamide;
The chemical entities described herein are potent inhibitors of Btk. While not being bound by any theory, that increased potency may result from the combination of a 2-aminopyridine head group with a pyridone core. In other words, the chemical entities described herein are more potent Btk inhibitors than similar compounds having a pyrazinone core or a different head group. For example, a compound having a 6-pyridone core with a phenylamino head group showed IC₅₀ of 273 nM in a Btk biochemical assay (in the presence of 10 micromolar ATP) (see, Example 6), while a compound that is otherwise structurally identical except for the replacement of the phenylamino head group by 2-aminopyridyl showed IC₅₀ of 12nM in the same assay. A compound having a 5-pyrazinone core with a 2-aminopyridyl head group showed IC₅₀ of 193 nM in a Btk biochemical assay (in the presence of 10 micromolar ATP) as described in Example 6, while a compound that is otherwise structurally identical except for the replacement of the 5-pyrazinone core by 6-pyridone showed IC₅₀ of 12nM in the same assay.

Methods for obtaining the novel compounds described herein will be apparent to those of ordinary skill in the art, suitable procedures being described, for example, in the reaction scheme and examples below, and in the references cited herein.

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Methods for obtaining the novel compounds described herein will be apparent to those of ordinary skill in the art, suitable procedures being described, for example, in the reaction scheme and examples below, and in the references cited herein.
Referring to Reaction Scheme 1, Step 1, a compound of Formula 101 in a suitable solvent, such as anhydrous DMF, and an excess (such as at least 2 equivalents) of powdered potassium carbonate is stirred for about 15 minutes. An excess (such as about 1.1 equivalents) of a compound of Formula R16X where X is a leaving group, such as iodide, is added. The mixture is stirred at room temperature. The product, a compound of Formula 103 is isolated and optionally purified.

Referring to Reaction Scheme 1, Step 2, to a solution of an excess (such as about 1.2 equivalents) of diaminopyridine, a compound of Formula 103, 0.05 equivalent of Pd2(dba)3, about 0.15 equivalent of 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene, and an excess (such as about 1.5 equivalents) of Cs2CO3 in dioxane is heated at
about 95 °C for about 16 h. The product, a compound of Formula 105, was isolated and optionally purified.

[0086] Referring to Reaction Scheme 1, Step 3, a mixture of a compound of Formula 105, an excess (such as about 1.2 equivalents) of a compound of Formula 106, and about 0.05 equivalent of Pd(PPh₃)₄ in a suitable solvent such as DMF is heated at about 95 °C for about 16 h. The product, a compound of Formula 107, is isolated and optionally purified.
Referring to Reaction Scheme 2, Step 1, a mixture of an excess (such as about 1.2 equivalents) of benzophenone imine, a compound of Formula 103, about 0.6 equivalent of Pd(OAc)$_2$, 0.07 equivalent of 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (rac-BINAP), and an excess (such as about 1.4 equivalents) of Cs$_2$CO$_3$ in a suitable solvent such as dioxane is heated at about 95 °C for about 16 h. The product, a compound of Formula 203, is isolated and optionally purified.

Referring to Reaction Scheme 2, Step 2, a mixture of a compound of Formula 203, an excess (such as about 1.4 equivalents) of a compound of Formula 106, and 0.05 equivalent of Pd(PPh$_3$)$_4$ in a suitable solvent such as DME with aqueous base, such as 1N Na$_2$CO$_3$ is heated at about 95 °C for about 16 h. The product, a compound of Formula 205, is isolated and optionally purified.

Referring to Reaction Scheme 2, Step 3, a mixture of a compound of Formula 205, an excess (such as about 1.09 equivalents) of 2-chloronitropyridine, about 0.09 equivalent of Pd$_2$(dba)$_3$, about 0.1 equivalent of 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene and an excess (such as about 2 equivalents) of Cs$_2$CO$_3$ in a suitable solvent such as dioxane is heated at about 95 °C for about 16 h. The product, a compound of Formula 207, is isolated and optionally purified.

Referring to Reaction Scheme 2, Step 4, a compound of Formula 207, 10% Pd/C, and cyclohexene in a suitable solvent such as EtOAc:MeOH is microwaved using 300 W of power at about 135 °C for about 10 min. The product, a compound of Formula 209, is isolated and optionally purified.
Reaction Scheme 3

\[ \text{Step 1} \]

\[ \text{Step 2} \]

\[ \text{Step 3} \]
Referring to Reaction Scheme 3, Step 1, to a compound of Formula 301, an excess (such as about 1.2 equivalents) of a compound of Formula 303 and aqueous base such as 2 M sodium carbonate in a suitable solvent such as
1,4-dioxane is added about 0.1 equivalent of tetrakis(triphenylphosphine)palladium and the reaction mixture is stirred at reflux for about 18 h. The product, a compound of Formula 305, is isolated and optionally purified.

Referring to Reaction Scheme 3, Step 2, a compound of Formula 305 and an excess (such as about 4 equivalents) of pyridine hydrochloride is placed for about five min into an oil bath preheated to about 165 °C. The product, a compound of Formula 307, is isolated and optionally purified.

Referring to Reaction Scheme 3, Step 2, a compound of Formula 307, an excess (such as about 1.1 equivalents) of a compound of Formula R16X where X is a leaving group, such as iodide, and a base such as potassium carbonate in a suitable solvent such as DMF is stirred at room temperature for about 2 h. The product, a compound of Formula 309, is isolated and optionally purified.

Referring to Reaction Scheme 3, Step 4, to a solution of a compound of Formula 309 and glacial acetic acid is added an excess (such as about 1.5 equivalents) of bromine. The reaction is stirred for about 18 h at room temperature. The product, a compound of Formula 311, is isolated and optionally purified.

Referring to Reaction Scheme 3, Step 5, a mixture of a compound of Formula 311, iron powder and aqueous hydrochloric acid such as 2N hydrochloric acid is stirred at reflux for about 4 h. The product, a compound of Formula 313, is isolated and optionally purified.

Referring to Reaction Scheme 3, Step 6, a compound of Formula 313, a base such as triethylamine, and an excess (such as about 1.1 equivalents) of a compound of formula RCOC1 is stirred at room temperature for about 18 h. The product, a compound of Formula 315, is isolated and optionally purified.

Referring to Reaction Scheme 3, Step 7, a compound of Formula 315, a compound of Formula 316, about 0.09 equivalent of Pd2(dba)3,0.14 equivalent of 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene, and an excess (such as about 1.9 equivalents) of Cs2CO3 in a suitable solvent such as dioxane is heated at about 95 °C for about 16 h. Then, the reaction mixture was cooled to room temperature and poured into H2O (10 mL). The product, a compound of Formula 317, is isolated and optionally purified.

In some embodiments, the chemical entities described herein are administered as a pharmaceutical composition or formulation. Accordingly, the invention provides pharmaceutical formulations comprising at least one chemical entity chosen from compounds of Formula 1 and pharmaceutically acceptable salts, solvates, chelates, non-covalent complexes, and mixtures thereof, together with at least one pharmaceutically acceptable vehicle chosen from carriers, adjuvants, and excipients.

Pharmaceutically acceptable vehicles must be of sufficiently high purity and sufficiently low toxicity to render them suitable for administration to the animal being treated. The vehicle can be inert or it can possess pharmaceutical benefits. The amount of vehicle employed in conjunction with the chemical entity is sufficient to provide a practical quantity of material for administration per unit dose of the chemical entity.

Exemplary pharmaceutically acceptable carriers or components thereof are sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose, and methyl cellulose; powdered tragacanth; malt; gelatin; t alc; solid lubricants, such as stearic acid and magnesium stearate; calcium sulfate; synthetic oils; vegetable oils, such as peanut oil, cottonseed oil, sesame oil, olive oil, and corn oil; polysaccharides such as propylene glycol, glycerine, sorbitol, mannitol, and polyethylene glycol; alginic acid; phosphate buffer solutions; emulsifiers, such as the TWEENs; wetting agents, such as sodium lauryl sulfate; coloring agents; flavoring agents; tableting agents; stabilizers; antioxidants; preservatives; pyrogen-free water; isotonic saline; and phosphate buffer solutions.

Optional active agents may be included in a pharmaceutical composition, which do not substantially interfere with the activity of the chemical entity of the present invention.

Effective concentrations of at least one chemical entity chosen from compounds of Formula 1 and pharmaceutically acceptable salts, solvates, chelates, non-covalent complexes, and mixtures thereof, are mixed with a suitable pharmaceutical acceptable vehicle. In instances in which the chemical entity exhibits insufficient solubility, methods for solubilizing compounds may be used. Such methods are known to those of skill in this art, and include, but are not limited to, using cosolvents, such as dimethylsulfoxide (DMSO), using surfactants, such as TWEEN, or dissolution in aqueous sodium bicarbonate.

Upon mixing or addition of the chemical entity described herein, the resulting mixture may be a solution, suspension, emulsion or the like. The form of the resulting mixture depends upon a number of factors, including the intended mode of administration and the solubility of the chemical entity in the chosen vehicle. The effective concentration sufficient for ameliorating the symptoms of the disease treated may be empirically determined.

Chemical entities described herein may be administered orally, topically, parenterally, intravenously, by intramuscular injection, by inhalation or spray, sublingually, transdermally, via buccal administration, rectally, as an ophthalmic solution, or by other means, in dosage unit formulations.

Dosage formulations suitable for oral use, include, for example, tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical
compositions and such compositions may contain one or more agents, such as sweetening agents, flavoring agents, coloring agents and preserving agents, in order to provide pharmaceutically elegant and palatable preparations. In some embodiments, oral formulations contain from 0.1 to 99% of at least one chemical entity described herein. In some embodiments, oral formulations contain at least 5% (weight %) of at least one chemical entity described herein. Some embodiments contain from 25% to 50% or from 5% to 75% of at least one chemical entity described herein.

[0106] Orally administered compositions also include liquid solutions, emulsions, suspensions, powders, granules, elixirs, tinctures, syrups, and the like. The pharmaceutically acceptable carriers suitable for preparation of such compositions are well known in the art. Oral formulations may contain preservatives, flavoring agents, sweetening agents, such as sucrose or saccharin, taste-masking agents, and coloring agents.

[0107] Typical components of carriers for syrups, elixirs, emulsions and suspensions include ethanol, glycerol, propylene glycol, polyethylene glycol, liquid sucrose, sorbitol and water. Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol, or sucrose. Such formulations may also contain a demulcent.

[0108] Chemical entities described herein can be incorporated into oral liquid preparations such as aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, for example. Moreover, formulations containing these chemical entities can be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations can contain conventional additives, such as suspending agents (e.g., sorbitol syrup, methyl cellulose, glucose/sugar, syrup, gelatin, hydroxyethyl cellulose, carboxymethyl cellulose, aluminum stearate gel, and hydrogenated edible fats), emulsifying agents (e.g., lecithin, sorbitan monoleate, or acacia), non-aqueous vehicles, which can include edible oils (e.g., almond oil, fractionated coconut oil, silyl esters, propylene glycol and ethyl alcohol), and preservatives (e.g., methyl or propyl p-hydroxybenzoate and sorbic acid).

[0109] For a suspension, typical suspending agents include methylcellulose, sodium carboxymethyl cellulose, AVICEL RC-591, tragacanth and sodium alginate; typical wetting agents include lecithin and polysorbate 80; and typical preservatives include methyl paraben and sodium benzoate.

[0110] Aqueous suspensions contain the active material(s) in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients include suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydropropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents; naturally-occurring phosphatides, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoctoxetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol substitute, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan substitute. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate.

[0111] Oily suspensions may be formulated by suspending the active ingredients in a vegetable oil, for example peanut oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

[0112] Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or peanut oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol, anhydrides, for example sorbitan monoleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monoleate.

[0113] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above.

[0114] Tablets typically comprise conventional pharmaceutically acceptable adjuvants as inert diluents, such as calcium carbonate, sodium carbonate, mannitol, lactose and cellulose; binders such as starch, gelatin and sucrose; disintegrants such as starch, alginic acid and croscarmellose; lubricants such as magnesium stearate, stearic acid and talc. Gidants such as silicon dioxide can be used to improve flow characteristics of the powder mixture. Coloring agents, such as the FD&C dyes, can be added for appearance. Sweeteners and flavoring agents, such as aspartame, saccharin, menthol, peppermint, and fruit flavors, can be useful adjuvants for chewable tablets. Capsules (including time release and sustained release formulations) typically comprise one or more solid diluents disclosed above. The selection of carrier components often depends on secondary considerations like taste, cost, and shelf stability.

[0115] Such compositions may also be coated by conventional methods, typically with pH or time-dependent coatings,
such that the chemical entity is released in the gastrointestinal tract in the vicinity of the desired topical application, or at various times to extend the desired action. Such dosage forms typically include, but are not limited to, one or more of cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropyl methylcellulose phthalate, ethyl cellulose, Eudragit coatings, waxes and shellac.

[0116] Formulations for oral use may 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.

[0117] Pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents that have been mentioned above. The sterile injectable preparation may also be sterile injectable solution or suspension in a non-toxic parentally acceptable vehicle, for example as a solution in 1,3-butandiol. Among the acceptable vehicles that may be employed are water, Ringer’s solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid can be useful in the preparation of injectables.

[0118] Chemical entities described herein may be administered parenterally in a sterile medium. Parenteral administration includes subcutaneous injections, intravenous, intramuscular, intrathecal injection or infusion techniques. Chemical entities described herein, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as local anesthetics, preservatives and buffering agents can be dissolved in the vehicle. In many compositions for parenteral administration the carrier comprises at least 90% by weight of the total composition. In some embodiments, the carrier for parenteral administration is chosen from propylene glycol, ethyl oleate, pyrrolidone, ethanol, and sesame oil.

[0119] Chemical entities described herein may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient that is solid at ordinary temperatures but liquid at rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter and polyethylene glycols.

[0120] Chemical entities described herein may be formulated for local or topical application, such as for topical application to the skin and mucous membranes, such as in the eye, in the form of gels, creams, and lotions and for application to the eye. Topical compositions may be in any form including, for example, solutions, creams, ointments, gels, lotions, milks, cleansers, moisturizers, sprays, skin patches, and the like.

[0121] Such solutions may be formulated as 0.01% -10% isotonic solutions, pH 5-7, with appropriate salts. Chemical entities described herein may also be formulated for transdermal administration as a transdermal patch.

[0122] Topical compositions comprising at least one chemical entity described herein can be admixed with a variety of carrier materials well known in the art, such as, for example, water, alcohols, aloe vera gel, allantoin, glycerine, vitamin A and E oils, mineral oil, propylene glycol, PPG-2 myristyl propionate, and the like.

[0123] Other materials suitable for use in topical carriers include, for example, emollients, solvents, humectants, thickeners and powders. Examples of each of these types of materials, which can be used singly or as mixtures of one or more materials, are as follows:

- Representative emollients include stearyl alcohol, glyceryl monoricinoleate, glyceryl monostearate, propane-1,2-diol, butane-1,3-diol, mink oil, cetyl alcohol, iso-propyl isostearate, stearic acid, iso-butyl palmitate, isocetyl stearate, oleyl alcohol, isopropyl laurate, hexyl laurate, decyl oleate, octadecan-2-ol, isocetyl alcohol, cetyl palmitate, dimethylpolysiloxane, di-n-butyl sebacate, iso-propyl myristate, iso-propyl palmitate, butyl stearate, polyethylene glycol, Methylene glycol, lanolin, sesame oil, coconut oil, arachis oil, castor oil, acetylated lanolin alcohols, petrolatum, mineral oil, butyl myristate, isostearic acid, palmitic acid, isopropyl linoleate, lauryl lactate, myristyl lactate, decyl oleate, and myristyl myristate; propellants, such as propane, butane, iso-butane, dimethyl ether, carbon dioxide, and nitrous oxide; solvents, such as ethyl alcohol, methylene chloride, isopropanol, castor oil, ethylene glycol monoethyl ether, diethylene glycol monobutyl ether, diethylene glycol monoethyl ether, dimethyl sulphoxide, dimethyl formamide, tetrahydrofuran; humectants, such as glycerin, sorbitol, sodium 2-pyrrolidone-5-carboxylate, soluble collagen, dibutyl phthalate, and gelatin; and powders, such as chalk, talc, fullers earth, kaolin, starch, gums, colloidal silicon dioxide, sodium polyacrylate, tetra alkyl ammonium smectites, trialkyl aryl ammonium smectites, chemically modified magnesium aluminium silicate, organically modified montmorillonite clay, hydrated aluminium silicate, fumed silica, carboxyvinyl polymer, sodium carboxymethyl cellulose, and ethylene glycol monostearate.

[0125] Chemical entities described herein may also be topically administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine and phosphatidylcholines.

[0126] Other compositions useful for attaining systemic delivery of the chemical entity include sublingual, buccal and nasal dosage forms. Such compositions typically comprise one or more of soluble fillers such as sucrose, sorbitol and mannitol, and binders such as acacia, microcrystalline cellulose, carboxymethyl cellulose, and hydroxypropyl...
Compositions for inhalation typically can be provided in the form of a solution, suspension or emulsion that can be administered as a dry powder or in the form of an aerosol using a conventional propellant (e.g., dichlorodifluoromethane or trichlorofluoromethane).

The compositions of the present invention may also optionally comprise an activity enhancer. The activity enhancer can be chosen from a wide variety of molecules that function in different ways to enhance or be independent of therapeutic effects of the chemical entities described herein. Particular classes of activity enhancers include skin penetration enhancers and absorption enhancers.

Pharmaceutical compositions of the invention may also contain additional active agents that can be chosen from a wide variety of molecules, which can function in different ways to enhance the therapeutic effects of at least one chemical entity described herein. These optional other active agents, when present, are typically employed in the compositions of the invention at a level ranging from 0.01% to 15%. Some embodiments contain from 0.1% to 10% by weight of the composition. Other embodiments contain from 0.5% to 5% by weight of the composition.

The invention includes packaged pharmaceutical formulations. Such packaged formulations include a pharmaceutical composition comprising at least one chemical entity chosen from compounds of Formula 1 and pharmaceutically acceptable salts, solvates, chelates, non-covalent complexes, and mixtures thereof, and instructions for using the pharmaceutical composition to treat a patient suffering from a disease responsive to inhibition of Btk activity and/or inhibition of B-cell and/or myeloid-cell activity. The invention can include providing prescribing information; for example, to a patient or health care provider, or as a label in a packaged pharmaceutical formulation. Prescribing information may include for example efficacy, dosage and administration, contraindication and adverse reaction information pertaining to the pharmaceutical formulation.

In all of the foregoing the chemical entities can be administered alone, as mixtures, or in combination with other active agents.

Accordingly, the invention includes at least one of the chemical entity(ies) for use in a method of treating a patient, for example, a mammal, such as a human, having a disease responsive to inhibition of Btk activity, comprising administering to the patient having such a disease, an effective amount of at least one chemical entity chosen from compounds of Formula 1 and pharmaceutically acceptable salts, solvates, chelates, non-covalent complexes, and mixtures thereof.

To the extent that Btk is implicated in disease, alleviation of the disease, disease symptoms, preventative, and prophylactic treatment is within the scope of this invention. In some embodiments, the chemical entities described herein may also inhibit other kinases, such that alleviation of disease, disease symptoms, preventative, and prophylactic treatment of conditions associated with these kinases is also within the scope of this invention.

The at least one of the chemical entity(ies) of the invention for use in methods of treatment also include inhibiting Btk activity and/or inhibiting B-cell and/or myeloid-cell activity, by inhibiting ATP binding or hydrolysis by Btk or by some other mechanism, in vivo, in a patient suffering from a disease responsive to inhibition of Btk activity, by administering an effective concentration of at least one chemical entity chosen from compounds of Formula 1 and pharmaceutically acceptable salts, solvates, chelates, non-covalent complexes, and mixtures thereof. An example of an effective concentration would be that concentration sufficient to inhibit Btk activity in vitro. An effective concentration may be ascertained experimentally, for example by assaying blood concentration in vitro of the chemical entity, or theoretically, by calculating bioavailability in vitro.

The condition responsive to inhibition of Btk activity and/or B-cell and/or myeloid-cell activity is cancer, a bone disorder, an allergic disorder and/or an autoimmune and/or inflammatory disease, and/or an acute inflammatory reaction.

The invention includes the use of at least one of the chemical entity(ies) of the invention in a method of treating a patient having cancer, a bone disorder, an allergic disorder and/or an autoimmune and/or inflammatory disease, and/or an acute inflammatory reaction, by administering an effective amount of at least one chemical entity chosen from compounds of Formula 1 and pharmaceutically acceptable salts, solvates, chelates, non-covalent complexes, and mixtures thereof.

In some embodiments, the conditions and diseases that can be affected using chemical entities described herein in methods of treatment, include, but are not limited to: allergic disorders, including but not limited to eczema, allergic rhinitis or coryza, hay fever, bronchial asthma, urticaria (hives) and food allergies, and other atopic conditions; autoimmune and/or inflammatory diseases, including but not limited to psoriasis, Crohn's disease, irritable bowel syndrome, Sjogren's disease, tissue graft rejection, and hyperacute rejection of transplanted organs, asthma, systemic lupus erythematosus (and associated glomerulonephritis), dermatomyositis, multiple sclerosis, scleroderma, vasculitis (ANCA-associated and other vasculitides), autoimmune hemolytic and thrombocytopenic states, Goodpasture's syndrome (and associated glomerulonephritis and pulmonary hemorrhage), atherosclerosis, rheumatoid arthritis, osteoar-
thritis, chronic idiopathic thrombocytopenic purpura (ITP), Addison’s disease, Parkinson’s disease, Alzheimer’s disease, diabetes mellitus (type 1), septic shock, myasthenia gravis, ulcerative colitis, aplastic anemia, coeliac disease, Wegener’s granulomatosis and other diseases in which the cells and antibodies arise from and are directed against the individual’s own tissues; acute inflammatory reactions, including but not limited to skin sunburn, inflammatory pelvic disease, inflammatory bowel disease, urethritis, vulvar, sinusitis, pneumonitis, encephalitis, meningitis, myocarditis, nephritis, osteomyelitis, myositis, hepatitis, gastitis, enteritis, dermatitis, gingivitis, appendicitis, pancreatitis, and cholecystitis, and cancer, including but not limited to hematological malignancies, such as B-cell lymphoma, and a cute lymphoblastic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, chronic and acute lymphocytic leukemia, hairy cell leukemia, Hodgkin’s disease, Non-Hodgkin lymphoma, multiple myeloma, and other diseases that are characterized by cancer of the blood or lymphatic system, bone disorders, including but not limited to osteoporosis.

0138] Btk is a known inhibitor of apoptosis in lymphoma B-cells. Defective apoptosis contributes to the pathogenesis and drug resistance of human leukemias and lymphomas. Thus, further provided is the use of at least one of the chemical entity(ies) of the invention in a method of promoting or inducing apoptosis in cells expressing Btk comprising contacting the cell with at least one chemical entity chosen from compounds of Formula 1 pharmaceutically acceptable salts, solvates, chelates, non-covalent complexes, and mixtures thereof.

0139] The invention provides at least one of the chemical entity(ies) for use in methods of treatment in which at least one chemical entity chosen from compounds of Formula 1 pharmaceutically acceptable salts, solvates, chelates, non-covalent complexes, and mixtures thereof, is the only active agent given to a patient and also includes at least one of the chemical entity(ies) for use in methods of treatment in which at least one chemical entity chosen from compounds of Formula 1 and pharmaceutically acceptable salts, solvates, chelates, non-covalent complexes, and mixtures thereof, is given to a patient in combination with one or more additional active agents.

0140] Thus in one embodiment the invention provides at least one of the chemical entity(ies) for use in a method of treating cancer, a bone disorder, an allergic disorder and/or an autoimmune and/or inflammatory disease, and/or an acute inflammatory reaction, which comprises administering to a patient in need thereof an effective amount of at least one chemical entity chosen from compounds of Formula 1 and pharmaceutically acceptable salts, solvates, chelates, non-covalent complexes, and mixtures thereof, together with a second active agent, which can be useful for treating a cancer, a bone disorder, an allergic disorder and/or an autoimmune and/or inflammatory disease, and/or an acute inflammatory reaction. For example the second agent may be an anti-inflammatory agent. The use of at least one of the chemical entity(ies) in a method of treatment with the second active agent may be prior to, concomitant with, or following treatment with at least one chemical entity chosen from compounds of Formula 1 and pharmaceutically acceptable salts, solvates, chelates, non-covalent complexes, and mixtures thereof. In certain embodiments, at least one chemical entity chosen from compounds of Formula 1 and pharmaceutically acceptable salts, solvates, chelates, non-covalent complexes, and mixtures thereof, is combined with another active agent in a single dosage form. Suitable antitumor therapeutics that may be used in combination with at least one chemical entity described herein include, but are not limited to, chemotherapeutic agents, for example mitomycin C, carboplatin, taxol, cisplatin, paclitaxel, etoposide, doxorubicin, or a combination comprising at least one of the foregoing chemotherapeutic agents. Radiotherapeutic antitumor agents may also be used, alone or in combination with chemotherapeutic agents.

0141] Chemical entities described herein can be useful as chemosensitizing agents, and, thus, can be useful in combination with other chemotherapeutic drugs, in particular, drugs that induce apoptosis.

0142] At least one of the chemical entity(ies) for use in a method for increasing sensitivity of cancer cells to chemotherapy, comprising administering to a patient undergoing chemotherapy a chemotherapeutic agent together with at least one chemical entity chosen from compounds of Formula 1 and pharmaceutically acceptable salts, solvates, chelates, non-covalent complexes, and mixtures thereof, in an amount sufficient to increase the sensitivity of cancer cells to the chemotherapeutic agent is also provided herein.

0143] Examples of other chemotherapeutic drugs that can be used in combination with chemical entities described herein include topoisomerase I inhibitors (camptothecin or topotecan), topoisomerase II inhibitors (e.g. daunomycin and etoposide), alkylating agents (e.g. cyclophosphamide, melphalan and BCNU), tubulin directed agents (e.g. taxol and vinblastine), and biological agents (e.g. antibodies such as anti CD20 antibody (e.g., Rituxan®), IDEC 8, immunotoxins, and cytokines), tyrosine kinase inhibitors (e.g., Gleevec®), and the like.

0144] Included herein is at least one of the chemical entity(ies) of the invention for use in methods of treatment in which at least one chemical entity chosen from compounds of Formula 1 and pharmaceutically acceptable salts, solvates, chelates, non-covalent complexes, and mixtures thereof, is administered in combination with an anti-inflammatory agent. Anti-inflammatory agents include but are not limited to NSAIDs, non-specific and COX-2 specific cyclooxygenase enzyme inhibitors, gold compounds, corticosteroids, methotrexate, tumor necrosis factor receptor (TNF) receptors antagonists, immunosuppressants and methotrexate.

0145] Examples of NSAIDs include, but are not limited to ibuprofen, flurbiprofen, naproxen and naproxen sodium, diclofenac, combinations of diclofenac sodium and misoprostol, sulindac, oxicaprin, diffunisal, piroxicam, indomethacin, etodolac, fenoprofen calcium, ketoprofen, sodium naphometone, sulfasalazine, tolmetin sodium, and hydroxychloroquine.
Examples of NSAIDs also include COX-2 specific inhibitors (i.e., a compound that inhibits COX-2 with an IC50 that is at least 50-fold lower than the IC50 for COX-1) such as celecoxib, valdecoxib, lumiracoxib, etoricoxib and/or rofecoxib.

In a further embodiment, the anti-inflammatory agent is a salicylate. Salicylates include but are not limited to acetylsalicylic acid or aspirin, sodium salicylate, and choline and magnesium salicylates.

The anti-inflammatory agent may also be a corticosteroid. For example, the corticosteroid may be chosen from cortisone, dexamethasone, methylprednisolone, prednisolone, prednisolone sodium phosphate, and prednisone.

In additional embodiments the anti-inflammatory therapeutic agent is a gold compound such as gold sodium thiomalate or auranofin.

The invention also includes embodiments in which the anti-inflammatory agent is a metabolic inhibitor such as a dihydrofolate reductase inhibitor, such as methotrexate or a dihydroorotate dehydrogenase inhibitor, such as leflunomide.

Other embodiments of the invention pertain to combinations in which at least one anti-inflammatory compound is an anti-C5 monoclonal antibody (such as eculizumab or pexelizumab), a TNF antagonist, such as entanercept, infliximab and adalimumab (Humira®) which are anti-TNF alpha monoclonal antibodies.

Still other embodiments of the invention pertain to combinations in which at least one active agent is an immunosuppressant compound such as methotrexate, leflunomide, cyclosporine, tacrolimus, azathioprine, or mycophenolate mofetil.

Dosage levels of the order, for example, of from 0.1 mg to 140 mg per kilogram of body weight per day can be useful in the methods of treatment of the above-indicated conditions (0.5 mg to 7 g per patient per day). The amount of active ingredient that may be combined with the vehicle to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. Dosage unit forms will generally contain from 1 mg to 500 mg of an active ingredient.

Frequency of dosage may also vary depending on the compound used and the particular disease treated. In some embodiments, for example, for the treatment of an allergic disorder and/or autoimmune and/or inflammatory disease, a dosage regimen of 4 times daily or less is used. In some embodiments, a dosage regimen of 1 or 2 times daily is used. It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the particular disease in the patient undergoing therapy.

A labeled form of a compound of the invention can be used as a diagnostic for identifying and/or obtaining compounds that have the function of modulating an activity of a kinase as described herein. The compounds of the invention may additionally be used for validating, optimizing, and standardizing bioassays.

By "labeled" herein is meant that the compound is either directly or indirectly labeled with a label which provides a detectable signal, e.g., radioisotope, fluorescent tag, enzyme, antibodies, particles such as magnetic particles, chemiluminescent tag, or specific binding molecules, etc. Specific binding molecules include pairs, such as biotin and streptavidin, digoxin and antidigoxin etc. For the specific binding members, the complementary member would normally be labeled with a molecule which provides for detection, in accordance with known procedures, as outlined above. The label can directly or indirectly provide a detectable signal.

The invention is further illustrated by the following examples.

Example 1

N-[3-[5-(6-Amino-pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydro-pyridin-3-yl]-2-methyl-phenyl]-4-tert-butylbenzamide (3)

Example 1

N-[3-[5-(6-Amino-pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydro-pyridin-3-yl]-2-methyl-phenyl]-4-tert-butylbenzamide (3)
3,5-Dibromo-1-methyl-1H-pyridin-2-one (1)

[0158]

A 1-L round-bottomed flask equipped with a magnetic stirrer was charged with 3,5-dibromo-1H-pyridin-2-one (7.0 g, 27.7 mmol), anhydrous DMF (280 mL) and powdered potassium carbonate (-350 mesh, 8.4 g, 61.1 mmol), and the suspension stirred for 15 min at ambient temperature. After this time, methyl iodide (4.3 g, 30.5 mmol) was added, and the mixture was stirred at room temperature under nitrogen for an additional 18 h. The reaction mixture was then diluted with water (200 mL), extracted with ethyl acetate (3 x 250 mL), dried over sodium sulfate and concentrated in vacuo. The resulting residue was purified by flash chromatography on silica to give an 84% yield (6.2 g) of 3,5-dibromo-1-methyl-1H-pyridin-2-one (1) as an off-white solid; mp 87-88 °C; MS (ESI+) \( m/z \) 266 (M+H).

3-{6-Amino-pyridin-2-ylamino}-5-bromo-1-methyl-1H-pyridin-2-one (2)

[0160]

N-{3-[5-(6-Amino-pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydro-pyridin-3-yl]-2-methyl-phenyyl}-4-tert-butyl-benzamide (3)

[0162]
A 48-mL sealed tube equipped with a magnetic stirring bar was charged with 3-(6-amino-pyridin-2-ylamino)-5-bromo-1-methyl-1H-pyridin-2-one (2) (0.054 g, 0.18 mmol), 4-tert-butyl-N42-methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl-benzamide (0.086 g, 0.22 mmol), and Pd(PPh3)4 (0.010 g, 0.010 mmol) in DME (10 mL) and 1N Na2CO3 (5 mL). After the mixture was degassed for 15 min., it was heated at 95 °C for 16 h. Then, the reaction mixture was cooled to room temperature and poured into H2O (10 mL). To this was added dichloromethane (10 mL) and the layers were separated. The aqueous phase was extracted with dichloromethane (3 x 10 mL), and the combined organic extracts were washed with H2O (5 mL) and brine (5 mL), dried (Na2SO4), and concentrated. The crude mixture was purified by column chromatography, gradient 0-10 %, MeOH in dichloromethane/ether (1/1), to afford 0.035 g (40 %) of N-{3-(5-(6-amino-pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydro-pyridin-3-yl)-2-methyl-phenyl}-4-tert-butyl-benzamide (3) as a solid; LCMS m/z 482.2018 (M+).

Example 2

N-{3-[5-(4-Amino-pyridin-2-ylamino)-1-methyl-6-oxo,1,6-dihydro-pyridin-yl]-2-methyl-phenyl}-4-tert-butyl-benzamide (7)

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A 48-mL sealed tube equipped with a magnetic stirring bar was charged with benzophenone imine (0.43 g, 2.4 mmol), 3,5-dibromo-1-methyl-1H-pyridin-2-one (1) (0.51 g, 2.0 mmol), Pd(OAc)2 (0.025 g, 0.040 mmol), rac-BINAP (0.082 g, 0.13 mmol), and Cs2CO3 (0.92 g, 2.8 mmol) in dioxane (15 mL). After the mixture was degassed for 15 min., it was heated at 95 °C for 16 h. Then, the reaction mixture was cooled to room temperature and poured into H2O (10 mL). To this was added dichloromethane and the layers were separated. The aqueous phase was extracted with dichloromethane (3 x 10 mL), and the combined organic extracts were washed with H2O (5 mL) and brine (5 mL), dried (Na2SO4), and concentrated. The crude product was dissolved in 1 N HCl/MeOH (3 mL) and stirred for 1 h at room temperature. Then, to the reaction mixture was added sat. NaHCO3 (10 mL) and dichloromethane (10 mL), and the phases were separated. The aqueous layer was extracted with dichloromethane, and the combined organic layers were washed with H2O (5 mL) and brine (5 mL), dried (Na2SO4), and concentrated. The crude mixture was purified by column chromatography, gradient 0-10 % MeOH in dichloromethane/ether (1/1), to afford 0.22 g (54 %) of 3-amino-5-bromo-1-methyl-1H-pyridin-2-one (4) as a solid.

N-{3-[5-(Amino-pyridin-2-ylamino)-1-methyl-6-oxo,1,6-dihydro-pyridin-3-yl]-2-methyl-phenyl}-4-tert-butyl-benzamide (5)
A 48-mL sealed tube equipped with a magnetic stirring bar was charged with 3-amino-5-bromo-1-methyl-1H-pyridin-2-one (4) (0.10 g, 0.50 mmol), 4-tert-butyl-N-[2-methyl-3-(4,4,5,5-tetramethyl-1,3,2)dioxaborolan-2-yl]-phenyl]-benzamide (0.24 g, 0.70 mmol), and Pd(PPh 3)4 (0.030 g, 0.025 mmol) in DME (10 mL) and 1N Na 2CO3 (5 mL). After the mixture was degassed for 15 min., it was heated at 95 °C for 16 h. Then, the reaction mixture was cooled to room temperature and poured into H 2O (10 mL). To this was added dichloromethane and the phases were separated. The aqueous layer was extracted with dichloromethane, and the combined organic layers were washed with H 2O (5 mL) and brine (5 mL), dried (Na2SO4), and concentrated. The crude mixture was purified by column chromatography, gradient 0-10 % MeOH in dichloromethane/ether (1/1), to afford 0.14 g (68 %) of N-[3-(5-amino-1-methyl-6-oxo-1,6-dihydro-pyridin-3-yl)-2-methyl-phenyl]-4-tert-butyl-benzamide (5) as a solid.

A 48-mL sealed tube equipped with a magnetic stirring bar was charged with N-[3-(5-amino-1-methyl-6-oxo-1,6-dihydro-pyridin-3-yl)-2-methyl-phenyl]-4-tert-butyl-benzamide (5) (0.14 g, 0.34 mmol), 2-chloro-4-nitropyridine (0.058 g, 0.37 mmol), Pd 2(dba)3 (0.027 g, 0.030 mmol), 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (0.020 g, 0.034 mmol), and Cs2CO3 (0.25 g, 0.70 mmol) in dioxane (10 mL). After the mixture was degassed for 15 min., it was heated at 95 95 °C for 16 h. Then, the reaction mixture was cooled to room temperature and poured into H 2O (10 mL). To this was added dichloromethane (10 mL) and the layers were separated. The aqueous phase was extracted with dichloromethane (3 x 10 mL), and the combined organic extracts were washed with H 2O (5 mL) and brine (5 mL), dried (Na2SO4), and concentrated. The crude mixture was purified by column chromatography, gradient 0-10 %, MeOH in dichloromethane/ether (1/1), to afford 0.15 g (85 %) of 4-tert-butyl-N-[2-methyl-3-[1-methyl-5-(4-nitro-pyridin-2-ylamino)-6-oxo-1,6-dihydro-pyridin-2-yl]-2-methyl-phenyl]-4-tert-butyl-benzamide (6) as a solid.

N-[3-(5-Amino-pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydro-pyridin-3-yl]-2-methyl-phenyl]-4-tert-butyl-benzamide (7)
A 10-mL vial equipped with a magnetic stirring bar was charged with 4-tert-butyl-N-(2-methyl-3-[1-methyl-5-(4-nitro-pyridin-2-ylamino)-6-oxo-1,6-dihydro-pyridin-2-yl]-phenyl)-benzamide (6) (0.10 g, 0.20 mmol), 10% Pd/C (0.10 g), and cyclohexene (2 mL) in EtOAc:MeOH (1:1, 4 mL). After the mixture was degassed for 5 min., it was microwaved using 300 W of power at 135 °C for 10 min. Then, the reaction mixture was cooled to room temperature and filtered through a pad of Celite. The filtrate was concentrated and purified by column chromatography, gradient 0-10 % MeOH in dichloromethane/ether (1/1), to afford 0.015 g (15 %) of N-{3-[5-(4-amino-pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydro-pyridin-3-yl]-2-methyl-phenyl}-4-tert-butyl-benzamide (7) as a solid; LCMS m/z 482.2635 (M+).

Example 3

4-tert-Butyl-N-(2-methyl-3-[1-methyl-5-(5-morpholin-4-yl-pyridin-2-ylamino)-6-oxo-1,6-dihydro-pyridin-3-yl]-phenyl)-benzamide (14)

2-methoxy-5-(2-methyl-3-nitrophenyl)pyridine (8)
5-(2-Methyl-3-nitrophenyl)pyridin-2-one (9)

A 10-mL single-neck round-bottomed flask equipped with a magnetic stirrer, and nitrogen inlet was charged with 2-methoxy-5-(2-methyl-3-nitrophenyl) pyridine (8) (1.00 g, 4.10 mmol) and pyridine hydrochloride (1.90 g, 16.4 mmol) and purged with nitrogen. The flask was place for five min into an oil bath preheated to 165 °C. After this time the reaction was cooled to room temperature, and water (70 mL) was added. The resulting suspension was filtered, and the filter cake was washed with water (2 x 25 mL) and then dried in a 43 °C vacuum oven for 3 h to afford 0.97 g (99 %) of 5-(2-methyl-3-nitrophenyl)pyridin-2-one (9) as a white solid: mp 214-216 °C; 1H NMR (300 MHz, DMSO-d6) δ 11.87 (br s, 1H), 7.85 (dd, 1H, J = 8.1, 1.2 Hz), 7.56 (dd, 1H, J = 7.8, 1.5 Hz), 7.54 (dd, 1H, J = 8.4, 2.4 Hz), 7.53 (d, 1H, J = 9.3 Hz), 7.46 (dd, 1H, J = 7.8, 1.5 Hz), 6.41 (d, 1H, J = 9.3 Hz), 2.30 (s, 3H); MS (ESI+) m/z 231 (M+H).

1-Methyl-5-(2-methyl-3-nitrophenyl)pyridin-2-one (10)

A 250-mL single-neck round-bottomed flask equipped with a magnetic stirrer and nitrogen inlet was charged with 5-(2-methyl-3-nitrophenyl)pyridin-2-one (9) (0.92 g, 4.0 mmol), DMF (40 mL), potassium carbonate (1.21 g, 8.80 mmol) and iodomethane (625 mg, 4.40 mmol) and purged with nitrogen. The reaction mixture was stirred at room temperature for 2 h. After this time the reaction was cooled to room temperature and partitioned between ethyl acetate (150 mL) and water (75 mL). The organic layer was separated and washed with water (2 x 50 mL) followed by brine (100 mL) and dried over magnesium sulfate. The drying agent was then removed by filtration and the filtrate concentrated under reduced pressure to afford 0.92 g (94 %) of 1-methyl-5-(2-methyl-3-nitrophenyl)pyridin-2-one (10) as a white solid: mp 157-159 °C; 1H NMR (300 MHz, CDCl3) δ 7.81 (dd, 1H, J = 7.8, 1.8 Hz), 7.41 (dd, 1H, J = 7.8, 1.8 Hz), 7.38(d, 1H, J = 7.5 Hz), 7.53 (d, 1H, J = 9.3 Hz), 7.32 (dd, 1H, J = 9.3, 2.7 Hz), 7.27 (d, 1H, J = 1.5 Hz), 6.68 (d, 1H, J = 9.3 Hz), 3.62 (s, 3H), 2.37 (s, 3H); MS (ESI+) m/z 245 (M+H).

3-Bromo-1-methyl-5-(2-methyl-3-nitrophenyl)pyridin-2-one (11)

A 250-mL single-neck round-bottomed flask equipped with a magnetic stirrer and nitrogen inlet was charged with 5-(2-methyl-3-nitrophenyl)pyridin-2-one (9) (0.92 g, 4.0 mmol), DMF (40 mL), potassium carbonate (1.21 g, 8.80 mmol) and iodomethane (625 mg, 4.40 mmol) and purged with nitrogen. The reaction mixture was stirred at room temperature for 2 h. After this time the reaction was cooled to room temperature and partitioned between ethyl acetate (150 mL) and water (75 mL). The organic layer was separated and washed with water (2 x 50 mL) followed by brine (100 mL) and dried over magnesium sulfate. The drying agent was then removed by filtration and the filtrate concentrated under reduced pressure to afford 0.92 g (94 %) of 3-bromo-1-methyl-5-(2-methyl-3-nitrophenyl)pyridin-2-one (11) as a white solid: mp 157-159 °C; 1H NMR (300 MHz, CDCl3) δ 7.81 (dd, 1H, J = 7.8, 1.8 Hz), 7.41 (dd, 1H, J = 7.8, 1.8 Hz), 7.38(d, 1H, J = 7.5 Hz), 7.53 (d, 1H, J = 9.3 Hz), 7.32 (dd, 1H, J = 9.3, 2.7 Hz), 7.27 (d, 1H, J = 1.5 Hz), 6.68 (d, 1H, J = 9.3 Hz), 3.62 (s, 3H), 2.37 (s, 3H); MS (ESI+) m/z 245 (M+H).
A 10-mL single-neck round-bottomed flask equipped with a magnetic stirrer and nitrogen inlet was purged with nitrogen and charged with 1-methyl-5-(2-methyl-3-nitrophenyl)pyridin-2-one (10) (0.60 mg, 2.46 mmol) and glacial acetic acid (5 mL). To the resulting solution bromine (0.59 g, 3.70 mmol) was added. The reaction was stirred for 18 h at room temperature. After this time the reaction was partitioned between water (25 mL) and ethyl acetate (75 mL). The organic layer was separated and washed with saturated aqueous sodium bicarbonate (2 x 25 mL), brine (50 mL) and dried over magnesium sulfate. The drying agent was removed by filtration and the filtrate concentrated to a constant weight under reduced pressure to afford 0.075 g (93 %) of 3-bromo-1-methyl-5-(2-methyl-3-nitrophenyl)pyridin-2-one (11) as a yellow oil: 1H NMR (300 MHz, CDCl3) δ 7.83 (dd, 1H, J = 7.2, 2.1 Hz), 7.75 (d, 1H, J = 2.4 Hz), 7.42 (dd, 1H, J = 7.8, 2.4 Hz), 7.38 (t, 1H, J = 7.5 Hz), 7.29 (d, 1H, J = 2.4 Hz), 3.70 (s, 3H), 2.40 (s, 3H); MS (ESI+) m/z 323 (M+H).

5-(3-Amino-2-methylphenyl)-3-bromo-1-methylpyridin-2-one (12).

A 50-mL single-neck round-bottomed flask equipped with a mechanical stirrer was charged with 3-bromo-1-methyl-5-(2-methyl-3-nitrophenyl)pyridin-2-one (11) (0.70 g, 2.17 mmol), ethanol (15 mL), iron powder (-325 mesh, 1.20 g, 21.7 mmol), 2N hydrochloric acid (1.09 mL, 2.17 mmol) and stirred at reflux for 4 h. After this time the reaction was cooled to room temperature and solid potassium carbonate (0.738 g, 5.35 mmol) was added. The suspension was stirred for 0.5 h and then filtered through a pad of Celite 521. The filter cake was washed with ethanol (3 x 15 mL) and the combined filtrates were concentrated to a constant weight under reduced pressure to afford 0.71 g (88 %) of 5-(3-amino-2-methylphenyl)-3-bromo-1-methylpyridin-2-one (12) as a yellow oil: 1H NMR (300 MHz, CDCl3) δ 7.75 (dd, 1H, J = 2.1 Hz), 7.23 (d, 1H, J = 2.1 Hz), 7.05 (t, 1H, J = 7.8 Hz), 6.72 (d, 1H, J = 7.8 Hz), 6.60 (d, 1H, J = 7.2 Hz), 3.75 (br s, 2H), 3.66 (s, 3H), 2.07 (s, 3H); MS (ESI+) m/z 293 (M+H).

N-(3-(5-Bromo-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)-4-tert-butylbenzamide (13)

A 25-mL round bottomed flask was cooled to 0°C with an ice/water bath and charged with 5-(3-amino-2-
methylphenyl)-3-bromo-1-methylpyridin-2-one (12) (0.71 g, 2.20 mmol), triethylamine (489 mg, 4.84 mmol), methylene chloride (10 mL) and 4-tert-butyl-benzoyl chloride (0.48 g, 2.42 mmol) and the reaction mixture stirred at room temperature for 18 h. After this time the reaction was partitioned between water (25 mL) and ethyl acetate (50 mL). The organic layer was separated and washed with saturated aqueous sodium bicarbonate (2 x 25 mL), brine (50 mL) and dried over magnesium sulfate. The drying agent was removed by filtration and the filtrate concentrated under reduced pressure. The resulting residue was subjected to flash chromatography to afford 0.75 g (75 %) of N-(3-(5-bromo-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)-4-tert-butylbenzamide (13) as a white solid: mp 149-151 °C; 1H NMR (300 MHz, CDCl₃) δ 7.87 (dd, 1H, J = 2.4 Hz), 7.86 (d, 2H, J = 8.4 Hz), 7.71 (br s, 1H), 7.54 (d, 2H, J = 8.7 Hz), 7.30 (t, 1H, J = 7.8 Hz), 7.27 (d, 1H, J = 1.8 Hz), 3.75 (br s, 2H), 7.05 (dd, 1H, J = 7.8, 1.5 Hz), 3.67 (s, 3H), 2.24 (s, 3H), 1.37 (s, 9H); MS (ESI+) m/z 453 (M+H).

4-tert-butyl-N-[2-methyl-3-[1-methyl-5-(5-morpholin-4-yl-pyridin-2-ylamino)-6-oxo-1,6-dihydro-pyridin-3-yl]-phenyl]-benzamide (14)

A 48-mL sealed tube equipped with a magnetic stirring bar was charged with 5-morpholin-4-yl-pyridin-2-ylamine (0.065 g, 0.36 mmol), N-[3-(5-bromo-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methyl-phenyl]-4-tert-butyl-benzamide (13) (0.16 g, 0.35 mmol), Pd₂(dba)₃ (0.030 g, 0.030 mmol), 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (0.030 g, 0.050 mmol), and Cs₂CO₃ (0.22 g, 0.66 mmol) in dioxane (10 mL). After the mixture was degassed for 15 min., it was heated at 95 °C for 16 h. Then, the reaction mixture was cooled to room temperature and poured into H₂O (10 mL). To this was added dichloromethane (10 mL) and the layers were separated. The aqueous phase was extracted with dichloromethane (3 x 10 mL), and the combined organic extracts were washed with H₂O (5 mL) and brine (5 mL), dried (Na₂SO₄), and concentrated. The crude mixture was purified by column chromatography, gradient 0-10 % MeOH in dichloromethane/ether (1/1), to afford 0.080 g (41 %) of 4-tert-butyl-N-[2-methyl-3-[1-methyl-5-(5-morpholin-4-yl-pyridin-2-ylamino)-6-oxo-1,6-dihydro-pyridin-3-yl]-phenyl]-benzamide (8) as a solid; LCMS m/z 552.2342 (M+).

Example 4

N-(2-Methyl-3-(5-(4-methylpiperazin-1-yl)pyridine-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide (19)
5-bromo-2-methoxy-3-nitropyridine (15)

In a 1 L, round-bottomed, single-necked flask equipped with a magnetic stirring bar was placed 5-bromo-3-nitropyridin-2-ol (50.0 g, 0.23 mol) in CHCl₃ (500 mL) under nitrogen in the dark (wrapped in aluminum foil.) To this solution was added Ag₂CO₃ (75.5 g, 0.28 mol) and MeI (142.0 mL, 2.3 mol). After the mixture was stirred for 48 h at room temperature, it was filtered through a pad of Celite, washed with CH₂Cl₂, and concentrated. The crude mixture was purified by column chromatography (EtOAc:Hexane, 1:4) to give 24.0 g (45%) of 5-bromo-2-methoxy-3-nitropyridine (15) as a solid.

5-Bromo-2-methoxypiridin-3-amine (16)

In a 500 mL, round-bottomed, single-necked flask equipped with a magnetic stirring bar was placed 5-bromo-2-methoxy-3-nitropyridine (15) (20.0 g, 0.086 mol), Fe (20.0 g, 0.36 mol), and NH₄Cl (20.0 g, 0.36 mol) in EtOH/H₂O (150 mL, 1:1). After heating at 95 °C for 1 h, the reaction mixture was filtered through a pad of Celite. The filtrate was concentrated to give 16.5 g (95 %) of 5-bromo-2-methoxypiridin-3-amine (16) as a solid.

N-(3-(5-Amino-6-methoxypiridin-3-yl)-2-methylphenyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide (17)

In a 48 mL sealed tube equipped with a magnetic stirring bar was placed 5-bromo-2-methoxypiridin-3-amine (16) (1.0 g, 4.0 mmol), N-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2yl)phenyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide (1(2.4 g, 6.7 mmol), and Pd(PPh₃)₄ (0.30 g, 0.20 mmol) in DME/1N Na₂CO₃ (10 mL, 1/1). After the reaction mixture was degassed for 15 min., it was heated at 95 °C for 16 h. Then, the mixture was cooled to room temperature and diluted with dichloromethane (10 mL) and H₂O (10 mL), and the layers were separated. The aqueous phase was extracted with dichloromethane (3 x 10 mL), and the combined organic extracts were washed with H₂O (5 mL) and brine (5 mL), dried (Na₂SO₄), and concentrated. The crude mixture was purified by column chromatography, gradient 0-25% MeOH in dichloromethane, to afford 1.0 g (65 %) of N-(3-(5-amino-6-methoxypiridin-3-yl)-2-methylphenyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide (17) as a solid.

N-(3-(6-Methoxy-5-(5-(4-methylpiperazin-1-yl)pyridin-2-ylamino)pyridine-3-yl)-2-methylphenyl)-4,5,6,7-tetrahydrobenzo[b]thiophen-2-carboxamide (18)
In a 48-mL seal tube equipped with a magnetic stirring bar was placed N-(3-(5-Amino-6-methoxypyridin-3-yl)-2-methylphenyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide (17) (0.20 g, 0.5 mmol), 1-(6-chloro-pyridin-3-yl)-4-methyl-piperazine (0.11 g, 0.5 mmol), Pd$_2$(dba)$_3$ (0.046 g, 0.050 mmol), 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (0.040 g, 0.070 mmol), and Cs$_2$CO$_3$ (0.33 g, 1.0 mmol) in dioxane (10 mL). After the mixture was degassed for 15 min., it was heated at 95°C for 16 h. Then, the reaction mixture was cooled to room temperature and poured into H$_2$O (10 mL). To this was added dichloromethane (10 mL) and the layers were separated. The aqueous phase was extracted with dichloromethane (3 x 10 mL), and the combined organic extracts were washed with H$_2$O (5 mL) and brine (5 mL), dried (Na$_2$SO$_4$), and concentrated. The crude mixture was purified by column chromatography, gradient 0-33 % MeOH in dichloromethane, to afford 0.140 g (50 %) of N-(3-(6-Methoxy-5-(5-(4-methylpiperazin-1-yl)pyridin-2-ylamino)pyridine-3-yl)-2-methylphenyl)-4,5,6,7-tetrahydrobenzo[b]thiophen-2-carboxamide (18) as a solid.

N-(2-Methyl-3-(5-(5-(4-methylpiperazin-1-yl)pyridine-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide (19)

In a 25 mL, round-bottomed, single-necked flask equipped with a magnetic stirring bar and a condenser was placed N-(3-(6-methoxy-5-(4-methylpiperazin-1-yl)pyridin-2-ylamino)pyridine-3-yl)-2-methylphenyl)-4,5,6,7-tetrahydrobenzo[b]thiophen-2-carboxamide (18) (0.070 g, 0.13 mmol) and 3 N HCl (1 mL) in dioxane (3 mL). The reaction mixture was heated at 100 °C for 2 h. To this was added dichloromethane (10 mL) and H$_2$O (10 mL), and the layers were separated. The aqueous phase was extracted with dichloromethane (3 x 5 mL), and the combined organic extracts were washed with H$_2$O (5 mL) and brine (5 mL), dried (Na$_2$SO$_4$), and concentrated. The crude mixture was purified by column chromatography, gradient 0-33 % MeOH in dichloromethane, to afford 0.053 g (80 %) of N-(2-methyl-3-(5-(4-methylpiperazin-1-yl)pyridine-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide (19); Exact mass m/z 554.25; M=H m/z 555.20.

Example 5

The following compounds were prepared using procedures similar to those described in Examples 1, 2, 3 and 4.
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(continued)
Example 6

Biochemical Btk Assay

A generalized procedure for one standard biochemical Btk Kinase Assay that can be used to test compounds disclosed in this application is as follows.

A master mix minus Btk enzyme is prepared containing 1X Cell Signaling kinase buffer (25 mM Tris-HCl, pH 7.5, 5 mM beta-glycerophosphate, 2 mM dithiothreitol, 0.1 mM Na3VO4, 10 mM MgCl2), 0.5 μM Promega PTK Biotinylated peptide substrate 2, and 0.01% BSA. A master mix plus Btk enzyme is prepared containing 1X Cell Signaling kinase buffer, 0.5 μM PTK Biotinylated peptide substrate 2, 0.01% BSA, and 100 ng/well (0.06 mU/well) Btk enzyme. Btk enzyme is prepared as follows: full length human wildtype Btk (accession number NM-000061) with a C-terminal V5 and 6x His tag was subcloned into pFastBac vector for making baculovirus carrying this epitope-tagged Btk. Generation of baculovirus is done based on Invitrogen’s instructions detailed in its published protocol “Bac-to-Bac Baculovirus Expression Systems” (Cat. Nos. 10359-016 and 10608-016). Passage 3 virus is used to infect SF9 cells to overexpress the recombinant Btk protein. The Btk protein is then purified to homogeneity using Ni-NTA column. The purity of the final protein preparation is greater than 95% based on the sensitive Sypro-Ruby staining. A solution of 200 μM ATP is prepared in water and adjusted to pH 7.4 with 1N NaOH. A quantity of 1.25 μL of compounds in 5% DMSO is transferred to a 96-well ½ area Costar polystyrene plate. Compounds are tested singly and with an 11-point dose-responsive curve (starting concentration is 10 μM; 1:2 dilution). A quantity of 18.75 μL of master mix minus enzyme (as a negative control) and master mix plus enzyme is transferred to appropriate wells in 96-well ½ area costar polystyrene plate. 5 μL of 200 μM ATP is added to that mixture in the 96-well ½ area Costar polystyrene plate for final ATP concentration of 40 μM. The reaction is allowed to incubate for 1 hour at room temperature. The reaction is stopped with Perkin Elmer 1X detection buffer containing 30 mM EDTA, 20 mM SA-APC, and 1 nM PT66 Ab. The plate is read using time-resolved fluorescence with a Perkin Elmer Envision using excitation filter 330 nm, emission filter 665 nm, and 2nd emission filter 615 nm. IC50 values are subsequently calculated.

Example 7

Biochemical Btk Assay

A generalized procedure for another standard biochemical Btk Kinase Assay that can be used to test compounds disclosed in this application is as follows.

A master mix minus Btk enzyme is prepared containing 1x Lanthascreen buffer (50 mM Hepes, pH 7.5, 2 mM dithiothreitol, 0.2 mM Na3VO4, 2 mM MnCl2, 10 mM MgCl2), 0.4 μM Fluorescein poly-Glu-Ala-Tyr peptide substrate, and 0.01% BSA. A master mix plus Btk enzyme is prepared containing 1X Lanthascreen buffer, 0.4 μM Fluorescein poly-Glu-Ala-Tyr peptide substrate, 0.01% BSA, and 100 pg/well Btk enzyme. Btk enzyme is prepared as follows: full length human wildtype Btk (accession number NM-000061) with a C-terminal V5 and 6x His tag was subcloned into pFastBac vector for making baculovirus carrying this epitope-tagged Btk. Generation of baculovirus is done based on Invitrogen’s instructions detailed in its published protocol “Bac-to-Bac Baculovirus Expression Systems” (Cat. Nos. 10359-016 and 10608-016). Passage 3 virus is used to infect SF9 cells to overexpress the recombinant Btk protein. The Btk protein is then purified to homogeneity using Ni-NTA column. The purity of the final protein preparation is greater than 95% based on the sensitive Sypro-Ruby staining. A solution of 50 μM ATP is prepared in water and adjusted to pH 7.4 with 1N NaOH. A quantity of 1.25 μL of compounds in 5% DMSO is transferred to a 96-well ½ area Costar polystyrene plate. Compounds are tested singly and with an 11-point dose-responsive curve (starting concentration is 10 μM; 1:2 dilution). A quantity of 18.75 μL of master mix minus enzyme (as a negative control) and master mix plus enzyme is transferred to appropriate wells in 96-well ½ area costar polystyrene plate. 5 μL of 50 μM ATP is added to that mixture in the 96-well ½ area Costar polystyrene plate for final ATP concentration of 10 μM. The reaction is allowed to incubate for 1 hour at room temperature. The reaction is stopped with 1X Lanthascreen TR-FRET dilution buffer containing 60 mM EDTA and 2 mM Tb-PY20 Ab. The plate is read using time-resolved fluorescence with a Perkin Elmer Envision using excitation filter 495 nm, emission filter 520 nm, and 2nd emission filter 565 nm. IC50 values are subsequently calculated.

Example 8

Ramos Cell Btk Assay

A generalized procedure for a standard cellular Btk Kinase Assay that can be used to test compounds disclosed in this application is as follows.

Ramos cells are incubated at a density of 0.5x10^7 cells/ml in the presence of test compound for 1 hr at 37 °C.
Cells are then stimulated by incubating with 10 μg/ml anti-human IgM F(ab)₂ for 5 minutes at 37 °C. Cells are pelleted, lysed, and a protein assay is performed on the cleared lysate. Equal protein amounts of each sample are subject to SDS-PAGE and western blotting with either anti-phosphoBtk(Tyr223) antibody (Cell Signaling Technology #3531) to assess Btk autophosphorylation or an anti-Btk antibody (BD Transduction Labs #611116) to control for total amounts of Btk in each lysate.

**Example 9**

**B-Cell Proliferation Assay**

A generalized procedure for a standard cellular B-cell proliferation assay that can be used to test compounds disclosed in this application is as follows.

**Example 10**

**T Cell Proliferation Assay**

A generalized procedure for a standard T cell proliferation assay that can be used to test compounds disclosed in this application is as follows.

**Example 11**

**CD86 Inhibition Assay**

A generalized procedure for standard assay for the inhibition of B cell activity that can be used to test compounds disclosed in this application is as follows.

**Example 12**

**B-ALL Cell Survival Assay**

The following is a procedure for a standard B-ALL cell survival study using an XTT readout to measure the number of viable cells. This assay can be used to test compounds disclosed in this application for their ability to inhibit the survival of B-ALL cells in culture. One human B-cell acute lymphoblastic leukemia line that can be used is SUP-B15, a human Pre-B-cell ALL line that is available from the ATCC.
SUP-B15 pre-B-ALL cells are plated in multiple 96-well microtiter plates in 100 μl of Iscove's media + 20% FBS at a concentration of 5 x 10^5 cells/ml. Test compounds are then added with a final conc. of 0.4% DMSO. Cells are incubated at 37°C with 5% CO2 for up to 3 days. After 3 days cells are split 1:3 into fresh 96-well plates containing the test compound and allowed to grow up to an additional 3 days. After each 24h period, 50 μl of an XTT solution (Roche) is added to one of the replicate 96-well plates and absorbance readings are taken at 2, 4 and 20 hours following manufacturer’s directions. The reading taken with an OD for DMSO only treated cells within the linear range of the assay (0.5-1.5) is then taken and the percentage of viable cells in the compound treated wells are measured versus the DMSO only treated cells.

Example 13

The compounds disclosed in the examples above were tested in the Btk biochemical assay described herein (Example 6 or 7) and certain of those compounds exhibited an IC_{50} value less than or equal to 1 micromolar. Certain of those compounds exhibited an IC_{50} value less than or equal to 100 nM. Certain of those compounds exhibited an IC_{50} value less than or equal to 10 nM.

Some of the compounds disclosed in synthetic Examples 1-5 were tested in the B-cell proliferation assay (as described in Example 9) and exhibited an IC_{50} value less than or equal to 10 micromolar. Certain of those compounds exhibited an IC_{50} value less than or equal to 1 micromolar. Certain of those compounds exhibited an IC_{50} value less than or equal to 5 micromolar when assayed under conditions described herein (as described in Example 10).

Certain of those compounds did not inhibit T-cell proliferation and had IC_{50} values greater than or equal to 5 micromolar when assayed under conditions described herein (as described in Example 10).

Certain compounds disclosed herein exhibited IC_{50} values for inhibition of T-cell proliferation that were at least 3-fold, and in some instances 5-fold, or even 10-fold greater than the IC_{50} values of those compounds for inhibition of B-cell proliferation.

Some of the compounds disclosed herein were tested in an assay for inhibition of B cell activity (under the conditions described in Example 11), and exhibited an IC_{50} value less than or equal to 10 micromolar. Certain of those compounds exhibited an IC_{50} value less than or equal to 1 micromolar. Certain of those compounds exhibited an IC_{50} value less than or equal to 500 nM in this assay.

Some of the compounds disclosed herein were tested in a B-cell leukemia cell survival assay (under the conditions described in Example 12), and exhibited an IC_{50} value less than or equal to 10 micromolar.

Some of the compounds disclosed in disclosed herein exhibited both biochemical and cell-based activity. For example, some of the compounds disclosed herein exhibited an IC_{50} value less than or equal to 10 micromolar in the Btk biochemical assay described herein (Example 6 or 7) and an IC_{50} value less than or equal to 10 micromolar in at least one of the cell-based assays (other than the T-cell assay) described herein (Examples 8, 9, 11 or 12). Certain of those compounds exhibited an TC_{50} value less than or equal to 1 micromolar in the Btk biochemical assay described herein (Example 6 or 7) and an IC_{50} value less than or equal to 10 micromolar in at least one of the cell-based assays (other than the T-cell assay) described herein (Examples 8, 9, 11 or 12).

Some of the compounds disclosed herein were tested in an assay for inhibition of B cell activity (under the conditions described in Example 11), and exhibited an IC_{50} value less than or equal to 10 micromolar. Certain of those compounds exhibited an IC_{50} value less than or equal to 1 micromolar. Certain of those compounds exhibited an IC_{50} value less than or equal to 10 micromolar in at least one of the cell-based assays (other than the T-cell assay) described herein (Examples 7, 8, 10 or 11).

For claim construction purposes, it is not intended that the claims set forth hereinafter be construed in any way narrower than the literal language thereof, and it is thus not intended that exemplary embodiments from the specification be read into the claims. Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. In the foregoing and in the examples, all temperatures are set forth uncorrected in degrees Celsius and, all parts and percentages are by weight, unless otherwise indicated. The preceding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceding examples. From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention.

Claims

1. A compound chosen from compounds of Formula 1:
and pharmaceutically acceptable salts, solvates, chelates, non-covalent complexes, and mixtures thereof, wherein

R is chosen from aryl, heteroaryl and

in which;

aryl encompasses 5- and 6-membered carbocyclic aromatic rings; bicyclic ring systems wherein at least one ring is carbocyclic and aromatic; and tricyclic ring systems wherein at least one ring is carbocyclic and aromatic; and wherein aryl includes 5- and 6-membered carbocyclic aromatic rings fused to a 5- to 7-membered heterocycloalkyl ring containing 1 or more heteroatoms chosen from N, O, and S; hetero-aryl encompasses 5- to 7-membered aromatic, monocyclic rings containing one or more heteroatoms chosen from N, O, and S, with the remaining ring atoms being carbon; and bicyclic heterocycloalkyl rings containing one or more heteroatoms chosen from N, O, and S, with the remaining ring atoms being carbon and wherein at least one heteroatom is present in an aromatic ring; and wherein heteroaryl includes a 5- to 7-membered heterocycloalkyl, aromatic ring fused to a 5- to 7-membered cycloalkyl ring; R5 is chosen from hydrogen, hydroxy, alkyl groups having one to four carbons, sulfonyl, amino, alkoxy groups having one to four carbons, alkyl groups having one to four carbons substituted with one or more halo, alkoxy groups having one to four carbons substituted with one or more halo, alkyl groups having one to four carbons substituted with hydroxy, heterocycloalkyl, and heteroaryl; and X is chosen from N and CH;

R21 and R22 are independently chosen from hydrogen, alkyl groups having one to four carbons, halo, and hydroxy;

R16 is chosen from hydrogen, cyano, cycloalkyl, and alkyl groups having one to four carbons; and alkyl groups having one to four carbons substituted with a group chosen from alkoxy, amino, and acyl;

L is chosen from C0-C4alkylene, -O- C0-C4alkylene, -(C0-C4alkylene)(SO)-, -(C0-C4alkylene)(SO2)-, and -(C0-C4alkylene)(C=O)-; and

G is chosen from hydrogen, halo, hydroxy, alkoxy, nitro, alkyl, -NR7R8 wherein R7 and R8 are independently chosen from hydrogen, acyl, and (C1-C6)alkyl; or wherein R7 and R8, together with the nitrogen to which they are bound, form a 5- to 7-membered nitrogen containing heterocycloalkyl which optionally further includes one
or two additional heteroatoms chosen from N, O, and S, carbamimidoyl, heterocycloalkyl, cycloalkyl, aryl, heteroaryl, 4-acyl-piperazin-1-yl, 4-alkyl groups having one to four carbons-piperazin-1-yl, 4-alkyl groups having one to four carbons-piperidin-1-yl, 4-hydroxy-4-alkyl groups having one to four carbons-piperidin-1-yl, 3-oxo-piperazin-1-yl, 4-alkyl groups having one to four carbons-homopiperazin-1-yl.

2. The compound of claim 1 wherein R is 4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl.

3. The compound of claim 1 wherein the compound of Formula 1 is chosen from compounds of Formula 2:

![Chemical Structure](image)

(Formula 2)

wherein

R₅ is chosen from hydrogen, hydroxy, alkyl groups having one to four carbons, sulfonyl, amino, alkoxy groups having one to four carbons, alkyl groups having one to four carbons substituted with one or more halo, alkoxy groups having one to four carbons substituted with one or more halo, alkyl groups having one to four carbons substituted with hydroxy, heterocycloalkyl, and heteroaryl; and X is chosen from N and CH.

4. The compound of any one of claims 1 to 3, wherein L is a covalent bond or -(C=O)-.

5. The compound of any one of claims 1 to 4 wherein G is chosen from hydrogen, hydroxy, -NR₇R₈ wherein R₇ and R₈ are independently chosen from hydrogen, acyl, and (C₁-C₆)alkyl; or wherein R₇ and R₈, together with the nitrogen to which they are bound, form 5- to 7-membered nitrogen containing heterocycloalkyl which optionally further includes one or two additional heteroatoms chosen from N, O, and S, 5,6-dihydro-8H-imidazo[1,2-a]pyrazin-7-yl, alkoxy groups having one to four carbons, and 1H-tetrazol-5-yl.

6. The compound of any one of claims 1 to 5 wherein R₄ is chosen from methyl, trifluoromethyl, difluoromethyl, methoxy, trifluoromethoxy, difluoromethoxy, and fluoro.

7. The compound of any one of claims 1 to 6 wherein R₂₂ is chosen from hydrogen and alkyl groups having one to four carbons, R₁₆ is chosen from hydrogen and alkyl groups having one to four carbons, and R₂₁ is chosen from hydrogen and alkyl groups having one to four carbons.

8. The compound of claim 3 wherein R₅ is chosen from hydrogen, piperidinyl, and alkyl groups having one to four carbons.
9. The compound of claim 1 wherein the compound of Formula 1 is chosen from:
10. A pharmaceutical composition, comprising a compound of any one of claims 1 to 9, together with at least one pharmaceutically acceptable vehicle chosen from carriers, adjuvants, and excipients.

11. A compound according to any one of claims 1 to 9 or a pharmaceutical composition according to claim 10 for use in the treatment of a disease responsive to inhibition of Btk activity.

12. A compound according to claim 11 wherein the disease responsive to inhibition of Btk activity is chosen from cancer, preferably B-cell lymphoma or leukemia, allergic disorders, autoimmune diseases, inflammatory diseases, and acute inflammatory reactions.

13. A compound according to any one of claims 1 to 9 or a pharmaceutical composition according to claim 10 for increasing sensitivity of cancer cells to chemotherapy, wherein the administered amount of said compound or pharmaceutical composition is sufficient to increase the sensitivity of cancer cells to the chemotherapeutic agent in a patient undergoing chemotherapy.

14. An in vitro method for inhibiting ATP hydrolysis or for inhibiting B-cell activity, the method comprising contacting cells expressing Btk with a compound of any one of claims 1 to 9 in an amount sufficient to detectably decrease the level of ATP hydrolysis in vitro or an amount sufficient to detectably decrease B-cell activity in vitro.

15. An in vitro method for determining the presence of Btk in a sample, comprising contacting the sample with a compound of any one of claims 1 to 9 under conditions that permit detection of Btk activity, detecting a level of Btk activity in
16. Use of a compound of any one of claims 1 to 9 or a pharmaceutical composition according to claim 10 in the manufacture of a medicament for the treatment of a disease responsive to inhibition of Btk activity.

17. Use of a compound of claim 16 for the treatment of cancer, autoimmune diseases, inflammatory diseases, acute inflammatory reactions or allergic disorders.

18. Use of a compound of any one of claims 1 to 9 or a pharmaceutical composition according to claim 10 in the manufacture of a medicament for increasing sensitivity of cancer cells to chemotherapy in a patient undergoing chemotherapy.

Patentansprüche

1. Verbindung ausgewählt aus Verbindungen der Formel 1:

![Chemical Structure](image)

(Formel 1)

und pharmazeutisch verträgliche Salze, Solvate, Chelate, nicht-kovalente Komplexe und Mischungen davon, worin

R ausgewählt ist aus Aryl, Heteroaryl und

![Chemical Structure](image)

in welchen:

Aryl umfasst 5- und 6-gliedrige carbocyclische aromatische Ringe; bicyclische Ringsysteme, wobei mindestens ein Ring carbocyclisch und aromatisch ist; und tricyclische Ringsysteme, wobei mindestens ein Ring carbocyclisch und aromatisch ist; und wobei Aryl 5- und 6-gliedrige carbocyclische aromatische Ringe umfasst, die mit
einem 5- bis 7-gliedrigen Heterocycloalkyl-Ring verschmolzen sind, der mindestens 1 Heteroatom, ausgewählt aus N, O und S, umfasst; Heteroaryl umfasst 5- bis 7-gliedrige aromatische, monocyclische Ringe, die mindestens ein Heteroatom, ausgewählt aus N, O und S, enthalten, wobei die verbleibenden Ringatome Kohlenstoff sind; und bicyclische Heterocycloalkyl-Ringe, die mindestens ein Heteroatom, ausgewählt aus N, O und S, enthalten, wobei die verbleibenden Ringatome Kohlenstoff sind und wobei mindestens ein Heteroatom in einem aromatischen Ring vorhanden ist; und wobei Heteroaryl einen 5- bis 7-gliedrigen aromatischen Heterocycloalkyl-Ring beinhaltet, der mit einem 5- bis 7-gliedrigen Cycloalkyl-Ring verschmolzen ist; R₅ ausgewählt ist aus Wasserstoff, Hydroxy, Alkylgruppen mit ein bis vier Kohlenstoffen, Sulfonyl, Amino, Alkoxygruppen mit ein bis vier Kohlenstoffen, Alkylgruppen mit ein bis vier Kohlenstoffen, die mit mindestens einem Halogen substituiert sind, Alkoxygruppen mit ein bis vier Kohlenstoffen, die mit mindestens einem Halogen substituiert sind, Alkylgruppen mit ein bis vier Kohlenstoffen, die mit Hydroxy, Heterocycloalkyl und Heteroaryl substituiert sind; und
X ausgewählt ist aus N und CH;
G ausgewählt ist aus Wasserstoff, Halogen, Hydroxy, Alkoxyl, Nitro, Alkyl, -NR₇R₈, wobei R₇ und R₈ unabhängig ausgewählt sind aus Wasserstoff, Acyln und (C₁-C₆)Alkyl; oder wobei R₇ und R₈, zusammen mit dem Stickstoff, an den sie gebunden sind, einen 5- bis 7-gliedrigen Stickstoff bilden, der Heterocycloalkyl enthält, welches wahlweise weiterhin ein oder zwei zusätzliche Heteroatome enthält, ausgewählt aus N, O, und S, Carbamimidoyl, Heterocycloalkyl, Cycloalkyl, Aryl, Heteroaryl, 4-Acyl-piperazin-1-yl, 4-Alkylgruppen mit ein bis vier Kohlenstoff-piperazin-1-yl, 4-Alkylgruppen mit ein bis vier Kohlenstoff-piperidin-1-yl, 3-Oxo-piperazin-1-yl, 4-Alkylgruppen mit ein bis vier Kohlenstoff-homopiperazin-1-yl.

2. Verbindung gemäß Anspruch 1, wobei R
4,5,6,7-Tetrahydrobenzo[b]thiophen-2-yl ist.

3. Verbindung gemäß Anspruch 1, wobei die Verbindung der Formel 1 ausgewählt ist aus Verbindungen der Formel 2:
wobei

R₅ ausgewählt ist aus Wasserstoff, Hydroxy, Alkylgruppen mit ein bis vier Kohlenstoffen, Sulfonyl, Amino, Alkoxygruppen mit ein bis vier Kohlenstoffen, Alkylgruppen mit ein bis vier Kohlenstoffen, die mit mindestens einem Halogen substituiert sind, Alkoxygruppen mit ein bis vier Kohlenstoffen, die mit mindestens einem Halogen substituiert sind, Alkylgruppen mit ein bis vier Kohlenstoffen, die mit Hydroxy, Heterocycloalkyl und Heteroaryl substituiert sind; und

X ausgewählt ist aus N und CH.

4. Verbindung gemäß einem der Ansprüche 1 bis 3, wobei L eine kovalente Bindung oder -(C=O)-ist.

5. Verbindung gemäß einem der Ansprüche 1 bis 4, wobei G ausgewählt ist aus Wasserstoff, Hydroxy, -NR₇R₈ wobei R₇ und R₈ unabhängig ausgewählt sind aus Wasserstoff, Acyl, und (C₁-C₆)Alkyl; oder wobei R₇ und R₈, zusammen mit dem Stickstoff, an den sie gebunden sind, einen 5- bis 7-gliedrigen Heterocycloalkyl-Ring bilden, weicher Stickstoff enthält, weicher wahlweise weiterhin ein oder zwei zusätzliche Heteroatome enthält, ausgewählt aus N, O, und S, 5,6-Dihydro-8H-imidazo[1,2-a]pyrazin-7-yl, Alkoxygruppen mit ein bis vier Kohlenstoffen und 1H-Tetrazol-5-yl.

6. Verbindung gemäß einem der Ansprüche 1 bis 5, wobei R₄ ausgewählt ist aus Methyl, Trifluormethyl, Difluormethyl, Methoxy, Trifluormethoxy, Difluormethoxy und Fluor.


9. Verbindung gemäß Anspruch 1, wobei die Verbindung der Formel 1 ausgewählt ist aus:
10. Pharmazeutische Zusammensetzung, die eine Verbindung gemäß einem der Ansprüche 1 bis 9 umfasst, zusammen mit mindestens einem pharmazeutisch verträglichen Vehiculum, ausgewählt aus Trägersubstanzen, Adjuvanzien und Hilfsstoffen.

11. Verbindung gemäß einem der Ansprüche 1 bis 9 oder eine pharmazeutische Zusammensetzung gemäß Anspruch 10 zur Verwendung bei der Behandlung einer auf Inhibition der Btk-Aktivität ansprechenden Erkrankung.


13. Verbindung gemäß einem der Ansprüche 1 bis 9 oder eine pharmazeutische Zusammensetzung gemäß Anspruch 10 zur Erhöhung der Empfindlichkeit von Krebszellen gegenüber Chemotherapie, wobei die verabreichte Menge der Verbindung oder pharmazeutischen Zusammensetzung ausreichend ist, um in einem Patienten, der sich einer Chemotherapie unterzieht, die Empfindlichkeit von Krebszellen gegenüber dem Chemo-Therapeutikum zu erhöhen.


Revendications

1. Composé choisi parmi les composés de formule 1 :

(Formule 1)

et sels, solvates, chélates, complexes non covalents, et mélanges pharmaceutiquement acceptables de ceux-ci, où

R est choisi parmi un aryle, un hétéroaryle et


(dans lequel :

aryl englobe les cycles aromatiques carbocycliques à 5 et 6 chaînons ; les systèmes de cycle bicyclique dans lesquels au moins un cycle est carbocyclique et aromatique ; et les systèmes de cycle tricyclique dans lesquels au moins un cycle est carbocyclique et aromatique ; et où aryle inclut les cycles aromatiques carbocycliques à 5 et 6 chaînons fusionnés à un cycle hétérocycloalkyle à 5 à 7 chaînons contenant 1 ou plusieurs hétéroatomes choisis parmi N, O et S ;
hétéro-aryle englobe les cycles monocycliques aromatiques à 5 à 7 chaînons contenant un ou plusieurs hétéroatomes choisis parmi N, O et S, le reste des atomes du cycle étant du carbone ; et les cycles hétérocycloalkyle bicycliques contenant un ou plusieurs hétéroatomes choisis parmi N, O et S, le reste des atomes de cycle étant du carbone et où au moins un hétéroatome est présent dans un cycle aromatique ; et où hétéroaryle inclut un cycle aromatique hétérocycloalkyle à 5 à 7 chaînons fusionné à un cycle cycloalkyle à 5 à 7 chaînons ;
R₅ est choisi parmi un hydrogène, un hydroxy, les groupes alkyle comportant un à quatre carbones, un sulfonyle, un amino, les groupes alcoxy comportant un à quatre carbones, les groupes alcoxy comportant un à quatre carbones substitués par un ou plusieurs halogéno, les groupes alcoxy comportant un à quatre carbones substitués par un ou plusieurs halogéno, les groupes alkyle comportant un à quatre carbones substitués par un hydroxy, un hétérocycloalkyle et un hétéroaryle ; et
X est choisi parmi N et CH ;
R₄ est choisi parmi hydrogène, les groupes alkyle comportant un à quatre carbones, les groupes alcoxy comportant un à quatre carbones, halogéno, et hydroxy ;
R₂, et R₂₂ sont indépendamment choisis parmi un hydrogène et les groupes alkyle comportant un à quatre carbones ;
R₁₆ est choisi parmi un hydrogène, un cyano, un cycloalkyle, et les groupes alkyle comportant un à quatre
carbones ; et les groupes alkyle comportant un à quatre carbones substitués par un groupe choisi parmi un alcoxy, un amino et un acyle ;
L est choisi parmi un C₀-C₄alkyle, un -O-C₀-C₄alkyle, un -(C₀-C₄alkyle) (SO) -, un -
(C₀-C₄alkyle)(SO₂)- ; et un - (C₀-C₄alkyle)(C=O)- ; et
G est choisi parmi un hydrogène, un halogéno, un hydroxy, un alcoxy, un nitro, un alkyle, -NR₇R₈ dans lequel
R₇ et R₈ sont indépendamment choisis parmi un hydrogène, un acyle, et un (C₁-C₆) alkyle ; ou dans lequel R₇
et R₈, conjointement avec l’azote auquel il sont liés, forment un hétérocycloalkyle à 5 à 7 chaînons contenant
de l’azote qui inclut facultativement en outre un ou deux hétéroatomes additionnels choisis parmi N, O et S, un
carbamimidoyle, un hétérocycloalkyle, un cycloalkyle, un aryle, un hétéroaryle, un 4-acyl-pipérazin-1-yle, les
groupes 4-alkyle comportant un à quatre carbones-pipérazin-1-yle, les groupes 4-alkyle comportant un à quatre
carbons-pipéridin-1-yle, les groupes 4-hydroxy-4-alkyle comportant un à quatre carbones-pipéridin-1-yle, 3-
oxo-pipérazin-1-yle, les groupes 4-alkyle comportant un à quatre carbones-homopipérazin-1-yle.

2. Composé selon la revendication 1, dans lequel R est
le 4,5,6,7-tétrahydrobenzo[b]thiophèn-2-yle.

3. Composé selon la revendication 1, dans lequel le composé de formule I est choisi parmi les composés de formule 2

   (Formule 2)

   dans lequel

   R₅ est choisi parmi un hydrogène, un hydroxy, les groupes alkyle comportant un à quatre carbones, un sulfonyle,
   un amino, les groupes alcoxy comportant un à quatre carbones, les groupes alkyle comportant un à quatre
carbones substitués par un ou plusieurs halogéno, les groupes alcoxy comportant un à quatre carbones subst-
titués par un ou plusieurs halogéno, les groupes alcoxy comportant un à quatre carbones substitués par un
hydroxy, un hétérocycloalkyle, et un hétéroaryle ; et
X est choisi parmi N et CH.

4. Composé selon l’une quelconque des revendications 1 à 3, dans lequel L est une liaison covalente ou -(C=O)-.

5. Composé selon l’une quelconque des revendications 1 à 4, dans lequel G est choisi parmi un hydrogène,
   un hydroxy,
   -NR₇R₈ dans lequel R₇ et R₈ sont indépendamment choisis parmi un hydrogène, un acyle, et un (C₁-C₆)alkyle ; ou
   dans lequel R₇ et R₈, conjointement avec l’azote auquel ils sont liés, forment un hétérocycloalkyle à 5 à 7 chaînons
   contenant de l’azote qui inclut facultativement en outre un ou deux hétéroatomes additionnels choisis parmi N, O et S,
   le 5,6-dihydro-8H-imidazo[1,2-al]pyrazin-7-yle,
   les groupes alcoxy comportant un à quatre carbones, et le 1H-tétrazol-5-yle.

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6. Composé selon l’une quelconque des revendications 1 à 5, dans lequel R₄ est choisi parmi un méthyle, un trifluorométhyle, un difluorométhyle, un méthoxy, un trifluorométhoxy, un difluorométhoxy et un fluoro.

7. Composé selon l’une quelconque des revendications 1 à 6, dans lequel R₂₂ est choisi parmi un hydrogène et les groupes alkyle comportant un à quatre carbones, R₁₆ est choisi parmi un hydrogène et les groupes alkyle comportant un à quatre carbones, et R₂₁ est choisi parmi un hydrogène et les groupes alkyle comportant un à quatre carbones.

8. Composé selon la revendication 3, dans lequel R₅ est choisi parmi un hydrogène, un pipéridinyle, et les groupes alkyle comportant un à quatre carbones.

9. Composé selon la revendication 1, dans lequel le composé de formule 1 est choisi parmi :
10. Composition pharmaceutique comprenant un composé de l’une quelconque des revendications 1 à 9, conjointement avec au moins un véhicule pharmaceutiquement acceptable choisi parmi les supports, les adjuvants et les excipients.

11. Composé selon l’une quelconque des revendications 1 à 9 ou composition pharmaceutique selon la revendication 10, pour son utilisation dans le traitement d’une maladie réactive à une inhibition d’activité de Btk.

12. Composé selon la revendication 11, dans lequel la maladie réactive à l’inhibition d’activité de Btk est choisie parmi le cancer, de préférence un lymphome ou une leucémie à cellules B, des troubles allergiques, des maladies auto-immunes, des maladies inflammatoires, et des réactions inflammatoires aiguës.

13. Composé selon l’une quelconque des revendications 1 à 9 ou composition pharmaceutique selon la revendication 10, permettant d’augmenter la sensibilité de cellules cancéreuses à une chimiothérapie, dans lequel ou laquelle la quantité administrée dudit composé ou de ladite composition pharmaceutique est suffisante pour augmenter la sensibilité de cellules cancéreuses à l’agent chimiothérapeutique chez un patient subissant une chimiothérapie.


15. Méthode in vitro permettant de déterminer la présence de Btk dans un échantillon, comprenant la mise en contact de l’échantillon avec un composé de l’une quelconque des revendications 1 à 9 dans des conditions qui permettent la détection d’activité de Btk, la détection d’un niveau d’activité de Btk dans l’échantillon, et de là, la détermination de la présence ou de l’absence de Btk dans l’échantillon.

16. Utilisation d’un composé de l’une quelconque des revendications 1 à 9 ou d’une composition pharmaceutique selon la revendication 10, dans la fabrication d’un médicament destiné au traitement d’une maladie réactive à l’inhibition d’activité de Btk.

17. Utilisation d’un composé de la revendication 16 pour le traitement du cancer, de maladies auto-immunes, de maladies inflammatoires, de réactions inflammatoires aiguës ou de troubles allergiques.

18. Utilisation d’un composé de l’une quelconque des revendications 1 à 9 ou d’une composition pharmaceutique selon la revendication 10, dans la fabrication d’un médicament destiné à augmenter la sensibilité des cellules cancéreuses à une chimiothérapie chez un patient subissant une chimiothérapie.
REFERENCES CITED IN THE DESCRIPTION

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