These compounds are useful as JAK3 kinase inhibitors.

Title: PYRAZOLE[1,5a]PYRIDINE DERIVATIVES

Abstract: Pyrazolo[1,5-a]pyridine derivatives of formula I, wherein the meaning for R1, R2 and R3 is as disclosed in the description. These compounds are useful as JAK3 kinase inhibitors.
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Pyrazolo[1,5-a]pyridine derivatives

Field of the invention

The present invention relates to a new series of pyrazolo[1,5-a]pyridine derivatives, as well as to processes for their preparation, to pharmaceutical compositions comprising them and to their use in therapy.

Background of the invention

The Janus kinases (JAKs) are cytoplasmic protein tyrosine kinases that play pivotal roles in pathways that modulate cellular functions in the lymphohematopoietic system that are critical for cell proliferation and cell survival. JAKs are involved in the initiation of cytokine-triggered signaling events by activating through tyrosine phosphorylation the signal transducers and activators of transcription (STAT) proteins. JAK/STAT signaling has been implicated in the mediation of many abnormal immune responses such as transplant rejection and autoimmune diseases, as well as in solid and hematologic malignancies such as leukemias and lymphomas and in myeloproliferative disorders, and has thus emerged as an interesting target for drug invention.

Four members of the JAK family have been identified so far: JAK1, JAK2, JAK3 and Tyk2. Unlike JAK1, JAK2 and Tyk2, whose expression is ubiquitous, JAK3 is mainly found in hematopoietic cells. JAK3 is associated in a non-covalent manner with the γc subunit of the receptors of IL-2, IL-4, IL-7, IL-9, IL-13 and IL-15. These cytokines play an important role in the proliferation and differentiation of T lymphocytes. JAK3-deficient mouse T cells do not respond to IL-2. This cytokine is fundamental in the regulation of T lymphocytes. In this regard, it is known that antibodies directed against the IL-2 receptor are able to prevent transplant rejection. In patients with X severe combined immunodeficiency (X-SCID), very low levels of JAK3 expression as well as genetic defects in the γc subunit of the receptor have been identified, which indicates that immunosuppression is a consequence of an alteration in the JAK3 signaling pathway.
Animal studies have suggested that JAK3 not only plays a critical role in T and B lymphocyte maturation, but also that JAK3 is required to maintain lymphocyte function. Modulation of the immunological activity through this new mechanism can prove useful in the treatment of T cell proliferative disorders such as transplant rejection and autoimmune diseases.

JAK3 has also been shown to play an important role in mast cells, because antigen-induced degranulation and mediator release have been found to be substantially reduced in mast cells from JAK3 deficient mice. JAK3 deficiency does not affect mast cell proliferation nor IgE receptor expression levels. On the other hand, JAK3-/- and JAK3+/- mast cells contain the same intracellular mediators. Therefore, JAK3 appears to be essential in the IgE-induced release of mediators in mast cells and its inhibition would be, thus, an effective treatment for allergic reactions.


Accordingly, it would be desirable to provide novel compounds that are capable of inhibiting JAK/STAT signaling pathways, and in particular which are capable of inhibiting JAK3 activity, and which are good drug candidates. Compounds should exhibit good activity in in vitro and in vivo pharmacological assays, good oral absorption when administered by the oral route, as well as be metabolically stable and exhibit a favourable pharmacokinetic profile. Moreover, compounds should not be toxic and exhibit few side effects.

Description of the invention

One aspect of the invention relates to a compound of formula I
or a salt thereof, wherein:

- **R**₁ represents hydrogen, C₅₋₆ alkyl, haloC₅₋₆ alkyl, hydroxyC₅₋₆ alkyl,
- **R**₂ represents hydrogen, C₅₋₆ alkyl, halogen, -CN, -CONR₅₋₆R₄, -COR₅, -CO₂R₅, -OR₄, -SO₂R₅,
- **R**₇ represents -SO₂R₄, -NR₅₋₆R₄, -NR₆COR₅, -NR₆CONR₅₋₆R₄, -NR₆CO₂R₅, -NR₆SO₂R₅ or Cy-i, wherein Cy-i is optionally substituted with one or more **R**₈;
- **R**₃ represents -CN, -CONR₅₋₆R₄, -COR₅, -CO₂R₅, -OR₄, -SO₂R₅,
- **R**₁₀ represents C₅₋₆ alkyl, haloC₅₋₆ alkyl, hydroxyC₅₋₆ alkyl, Cy-i, wherein Cy-i is optionally substituted with one or more **R**₁₀;
- **R**₉ represents -CN, -CONR₅₋₆R₄, -COR₅, -CO₂R₅, -OR₄, -SO₂R₅,
- **R**₂ and **R**₃ can be bonded completing, together with the N atom, a Cy₄ group, wherein Cy₄ is optionally substituted with one or more **R**₁₂;
- each **R**₄ independently represents hydrogen or **R**₅;
- each **R**₅ independently represents C₅₋₆ alkyl, haloC₅₋₆ alkyl, Cy-C₅₋₆ alkyl, hydroxyC₅₋₆ alkyl, cyanoC₅₋₆ alkyl, Cy-Cy-i, wherein Cy-i is optionally substituted with one or more **R**₆;
- **R**₆ represents hydrogen or Cy-C₅₋₆ alkyl;
- each **R**₇ independently represents -CN, -CONR₅₋₆R₄, -COR₅, -CO₂R₅, -OR₄, -SO₂R₅,
- **R**₈ represents -SO₂R₄, -NR₅₋₆R₄, -NR₆COR₅, -NR₆CONR₅₋₆R₄, -NR₆CO₂R₅, -NR₆SO₂R₅ or Cy-i, wherein Cy-i is optionally substituted with one or more **R**₈;
- each **R**₁₀ independently represents hydrogen or **R**₁₀.
Rn - C1-4 alkyl or Cy5, wherein Cy5 is optionally substituted with one or more Ri3; R11 represents halogen, -CN, -CONR14 R14, -COR15, -CO2 R15, -OR14, -OCONR14 R14, -SO2 R15, -SO2 NR14 R14, -NR14 R14, -NR6 COR14, -NR6 CONR14 R14, -NR6 CO2 R15, -NR6 SO2 R15 or Cy5, wherein Cy5 is optionally substituted with one or more R13; each R12 independently represents C1-4 alkyl, haloC1-4 alkyl, hyd HOXyC1-4 alkyl, R11 - C1-4 alkyl, or R12 represents any of the meanings described for R11; each R13 independently represents C1-4 alkyl, haloC1-4 alkyl, C1^alkOXYC1-4 alkyl, hyd HOXyC1-4 alkyl, cyanoC1-4 alkyl, halogen, -CN, -CONR16 R16, -COR17, -CO2 R17, -OR16, -OCONR16 R16, -SO2 R17, -SO2 NR16 R16, -NR16 R16, -NR6 COR16, -NR6 CONR16 R16, -NR6 CO2 R17 or -NR6 SO2 R17; each R14 independently represents hydrogen or R15; each R15 independently represents C1-4 alkyl, haloC1-4 alkyl, C1^alkOXYC1-4 alkyl, hyd HOXyC1-4 alkyl, cyanoC1-4 alkyl, Cy5 - C1-4 alkyl or Cy5, wherein Cy5 is optionally substituted with one or more R13; each R16 independently represents hydrogen or R17; each R17 independently represents C1-4 alkyl, haloC1-4 alkyl, C1^alkOXYC1-4 alkyl, hyd HOXyC1-4 alkyl or cyanoC1-4 alkyl; Cy1 represents a 3- to 7-membered monocyclic carbocyclic ring that is saturated, partially unsaturated or aromatic, and which optionally contains from 1 to 3 heteroatoms independently selected from N, S and O, wherein said ring is bonded to the rest of the molecule through any available C or N atom, and wherein one or more C or S ring atoms are optionally oxidized forming CO, SO or SO2 groups; Cy2 represents a 3- to 7-membered monocyclic carbocyclic ring that is saturated, partially unsaturated or aromatic, and which optionally contains from 1 to 3 heteroatoms independently selected from N, S and O, wherein said ring is bonded to the rest of the molecule through any available C atom, and wherein one or more C or S ring atoms are optionally oxidized forming CO, SO or SO2 groups; Cy3 represents a 3- to 7-membered monocyclic or 8- to 12-membered bicyclic carbocyclic ring that is saturated, partially unsaturated or aromatic, and which optionally contains from 1 to 4 heteroatoms independently selected from N, S and O, wherein said ring is bonded to the rest of the molecule through any
available C atom, and wherein one or more C or S ring atoms are optionally oxidized forming CO, SO or SO₂ groups;

Cy₄ represents a 3- to 7-membered monocyclic heterocyclic ring that is saturated or partially unsaturated, which is optionally fused to a 5- or 6-membered carbocyclic or heterocyclic ring that is saturated, partially unsaturated or aromatic, wherein Cy₄ optionally contains from 1 to 4 heteroatoms in total independently selected from N, S and O; and wherein one or more C or S atoms of Cy₄ are optionally oxidized forming CO, SO or SO₂ groups; and

Cy₅ represents a 3- to 7-membered monocyclic or 8- to 12-membered bicyclic carbocyclic ring that is saturated, partially unsaturated or aromatic, and which optionally contains from 1 to 4 heteroatoms independently selected from N, S and O, wherein said ring is bonded to the rest of the molecule through any available C or N atom, and wherein one or more C or S ring atoms are optionally oxidized forming CO, SO or SO₂ groups.

The present invention also relates to the salts and solvates of the compounds of formula I.

Some compounds of formula I can have chiral centers that can give rise to various stereoisomers. The present invention relates to each of these stereoisomers and also mixtures thereof.

The compounds of formula I are JAK, particularly JAK3, kinase inhibitors and therefore can be useful for the treatment or prevention of any disease mediated by this kinase.

Thus, another aspect of the invention relates to a compound of formula I

or a salt thereof, wherein:
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R\textsubscript{i} represents hydrogen, d\textsubscript{4}alkyl, haloC\textsubscript{i-4}alkyl, hydroxyC\textsubscript{i-4}alkyl, R\textsubscript{7}C\textsubscript{i-4}alkyl, halogen, -CN, -CONR\textsubscript{4}R\textsubscript{4}, -COR\textsubscript{5}, -CO\textsubscript{2}R\textsubscript{5}, -OR\textsubscript{4}, -SO\textsubscript{2}R\textsubscript{5}, -SO\textsubscript{2}NR\textsubscript{4}R\textsubscript{4}, -NR\textsubscript{4}COR\textsubscript{4}, -NR\textsubscript{6}CONR\textsubscript{4}R\textsubscript{4}, -NR\textsubscript{6}CO\textsubscript{2}R\textsubscript{5}, -NR\textsubscript{6}SO\textsubscript{2}R\textsubscript{5} or Cy\textsubscript{i}, wherein Cy\textsubscript{i} is optionally substituted with one or more R\textsubscript{9};

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R\textsubscript{2} represents hydrogen, C\textsubscript{i-4}alkyl haloC\textsubscript{i-4}alkyl, hydroxyC\textsubscript{i-4}alkyl, R\textsubscript{7}C\textsubscript{i-4}alkyl or Cy\textsubscript{2}, wherein Cy\textsubscript{2} is optionally substituted with one or more R\textsubscript{8};

R\textsubscript{3} represents C\textsubscript{i-4}alkyl, haloC\textsubscript{i-4}alkyl, hydroxyC\textsubscript{i-4}alkyl, Rn-C\textsubscript{i-4}alkyl, -CONR\textsubscript{9}R\textsubscript{9}, -COR\textsubscript{10}, -CO\textsubscript{2}R\textsubscript{i-0}, -SO\textsubscript{2}R\textsubscript{i-0}, -SO\textsubscript{2}NR\textsubscript{9}R\textsubscript{9} or Cy\textsubscript{3}, wherein Cy\textsubscript{3} is optionally substituted with one or more Ri\textsubscript{2};

or R\textsubscript{2} and R\textsubscript{3} can be bonded completing, together with the N atom, a Cy\textsubscript{4} group, wherein Cy\textsubscript{4} is optionally substituted with one or more Ri\textsubscript{2};

each R\textsubscript{4} independently represents hydrogen or R\textsubscript{5};

each R\textsubscript{5} independently represents Ci\textsubscript{4}alkyl, haloC\textsubscript{i-4}alkyl, Ci\textsubscript{i-4}alkoxyC\textsubscript{i-4}alkyl, hydroxyC\textsubscript{i-4}alkyl, cyanoC\textsubscript{i-4}alkyl, Cyi-C\textsubscript{i-4}alkyl or Cyi, wherein Cyi is optionally substituted with one or more R\textsubscript{6};

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R\textsubscript{6} represents hydrogen or Ci\textsubscript{4}alkyl;

R\textsubscript{7} represents -CN, -CONR\textsubscript{4}R\textsubscript{4}, -COR\textsubscript{5}, -CO\textsubscript{2}R\textsubscript{5}, -OR\textsubscript{4}, -SO\textsubscript{2}R\textsubscript{5}, -SO\textsubscript{2}NR\textsubscript{4}R\textsubscript{4}, -NR\textsubscript{4}COR\textsubscript{4}, -NR\textsubscript{6}CONR\textsubscript{4}R\textsubscript{4}, -NR\textsubscript{6}CO\textsubscript{2}R\textsubscript{5}, -NR\textsubscript{6}SO\textsubscript{2}R\textsubscript{5} or Cy\textsubscript{i}, wherein Cy\textsubscript{i} is optionally substituted with one or more R\textsubscript{8};

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each R\textsubscript{8} independently represents Ci\textsubscript{4}alkyl, haloC\textsubscript{i-4}alkyl, Ci\textsubscript{i-4}alkoxyC\textsubscript{i-4}alkyl, hydroxyC\textsubscript{i-4}alkyl, cyanoC\textsubscript{i-4}alkyl, halogen or hydroxyl;

each R\textsubscript{9} independently represents hydrogen or Ri\textsubscript{1};

each Ri\textsubscript{1} independently represents Ci\textsubscript{4}alkyl, haloC\textsubscript{i-4}alkyl, hydroxyC\textsubscript{i-4}alkyl, Rn-C\textsubscript{i-4}alkyl or Cy\textsubscript{5}, wherein Cy\textsubscript{5} is optionally substituted with one or more Ri\textsubscript{3};

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Rn represents halogen, -CN, -CONR\textsubscript{i}R\textsubscript{i}, -COR\textsubscript{i}, -CO\textsubscript{2}R\textsubscript{i}, -OR\textsubscript{i}, -OCONR\textsubscript{i}R\textsubscript{i}, -SO\textsubscript{2}R\textsubscript{i}, -SO\textsubscript{2}NR\textsubscript{i}R\textsubscript{i}, -NR\textsubscript{i}COR\textsubscript{i}, -NR\textsubscript{6}CONR\textsubscript{i}R\textsubscript{i}, -NR\textsubscript{6}CO\textsubscript{2}R\textsubscript{i}, -NR\textsubscript{6}SO\textsubscript{2}R\textsubscript{i} or Cy\textsubscript{5}, wherein Cy\textsubscript{5} is optionally substituted with one or more Ri\textsubscript{3};

each Ri\textsubscript{2} independently represents Ci\textsubscript{4}alkyl, haloC\textsubscript{i-4}alkyl, hydroxyC\textsubscript{i-4}alkyl, Rn-C\textsubscript{i-4}alkyl, or Ri\textsubscript{2} represents any of the meanings described for Rn;

each Ri\textsubscript{3} independently represents Ci\textsubscript{4}alkyl, haloC\textsubscript{i-4}alkyl, Ci\textsubscript{i-4}alkoxyC\textsubscript{i-4}alkyl, hydroxyC\textsubscript{i-4}alkyl, cyanoC\textsubscript{i-4}alkyl, halogen, -CN, -CONR\textsubscript{6}R\textsubscript{6}, -COR\textsubscript{7}, -CO\textsubscript{2}R\textsubscript{7}, -OR\textsubscript{6}, -OCONR\textsubscript{6}R\textsubscript{6}, -SO\textsubscript{2}R\textsubscript{7}, -SO\textsubscript{2}NR\textsubscript{6}R\textsubscript{6}, -NR\textsubscript{6}COR\textsubscript{6}. 

each \( R_{14} \) independently represents hydrogen or \( R_{15} \); each \( R_{15} \) independently represents \( C_{1-4} \)alkyl, halo\( C_{1-4} \)alkyl, \( C_{1} \)\(^{-}\)alkO\( xyC_{1-4} \)alkyl, \( \text{hyd} \)T\( OxyC_{1-4} \)alkyl, cyano\( C_{1-4} \)alkyl, \( C_{2-4} \)alkyl or \( C_{4} \), wherein \( C_{4} \) is optionally substituted with one or more \( R_{13} \); each \( R_{16} \) independently represents hydrogen or \( R_{17} \); each \( R_{17} \) independently represents \( C_{1-4} \)alkyl, halo\( C_{1-4} \)alkyl, \( C_{1} \)\(^{-}\)alkO\( xyC_{1-4} \)alkyl, \( \text{hyd} \)T\( OxyC_{1-4} \)alkyl or cyano\( C_{1-4} \)alkyl;

\( C_{3} \) represents a 3- to 7-membered monocyclic carbocyclic ring that is saturated, partially unsaturated or aromatic, and which optionally contains from 1 to 3 heteroatoms independently selected from N, S and O, wherein said ring is bonded to the rest of the molecule through any available C or N atom, and wherein one or more C or S ring atoms are optionally oxidized forming CO, SO or \( SO_{2} \) groups;

\( C_{4} \) represents a 3- to 7-membered monocyclic or 8- to 12-membered bicyclic carbocyclic ring that is saturated, partially unsaturated or aromatic, and which optionally contains from 1 to 4 heteroatoms independently selected from N, S and O, wherein said ring is bonded to the rest of the molecule through any available C atom, and wherein one or more C or S ring atoms are optionally oxidized forming CO, SO or \( SO_{2} \) groups;

\( C_{5} \) represents a 3- to 7-membered monocyclic heterocyclic ring that is saturated or partially unsaturated, which is optionally fused to a 5- or 6-membered carbocyclic or heterocyclic ring that is saturated, partially unsaturated or aromatic, wherein \( C_{5} \) optionally contains from 1 to 4 heteroatoms in total independently selected from N, S and O; and wherein one or more C or S atoms of \( C_{4} \) are optionally oxidized forming CO, SO or \( SO_{2} \) groups; and

\( C_{6} \) represents a 3- to 7-membered monocyclic or 8- to 12-membered bicyclic carbocyclic ring that is saturated, partially unsaturated or aromatic, and
which optionally contains from 1 to 4 heteroatoms independently selected from N, S and O, wherein said ring is bonded to the rest of the molecule through any available C or N atom, and wherein one or more C or S ring atoms are optionally oxidized forming CO, SO or SO₂ groups;

Another aspect of the invention relates to a pharmaceutical composition which comprises a compound of formula I or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable excipients.

Another aspect of the present invention relates to the use of a compound of formula I or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment or prevention of a disease mediated by JAKs, particularly JAK3. More preferably, the disease mediated by JAKs, particularly JAK3 is at least one disease selected from transplant rejection, immune, autoimmune or inflammatory diseases, neurodegenerative diseases, or proliferative disorders. In a further preferred embodiment, the disease mediated by JAKs, particularly JAK3 is selected from transplant rejection or immune, autoimmune or inflammatory diseases.

Another aspect of the present invention relates to the use of a compound of formula I or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment or prevention of at least one disease selected from transplant rejection, immune, autoimmune or inflammatory diseases, neurodegenerative diseases, or proliferative disorders. In a preferred embodiment, the disease is selected from transplant rejection or immune, autoimmune or inflammatory diseases.

Another aspect of the present invention relates to the use of a compound of formula I or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment or prevention of a disease selected from transplant rejection, rheumatoid arthritis, psoriatic arthritis, psoriasis, type I diabetes, complications from diabetes, multiple sclerosis, systemic lupus erythematosus, atopic dermatitis, mast cell-mediated allergic reactions, leukemias, lymphomas, and thromboembolic and allergic complications associated with leukemias and lymphomas.

Another aspect of the present invention relates to a compound of formula I
or a pharmaceutically acceptable salt thereof for use in the treatment or prevention of a disease mediated by JAKs, particularly JAK3. More preferably, the disease mediated by JAKs, particularly JAK3 is at least one disease selected from transplant rejection, immune, autoimmune or inflammatory diseases, neurodegenerative diseases, or proliferative disorders. In a further preferred embodiment, the disease mediated by JAKs, particularly JAK3 is selected from transplant rejection or immune, autoimmune or inflammatory diseases.

Another aspect of the present invention relates to a compound of formula I or a pharmaceutically acceptable salt thereof for use in the treatment or prevention of at least one disease selected from transplant rejection, immune, autoimmune or inflammatory diseases, neurodegenerative diseases, or proliferative disorders. In a preferred embodiment, the disease is selected from transplant rejection or immune, autoimmune or inflammatory diseases.

Another aspect of the present invention relates to a compound of formula I or a pharmaceutically acceptable salt thereof for use in the treatment or prevention of a disease selected from transplant rejection, rheumatoid arthritis, psoriatic arthritis, psoriasis, type I diabetes, complications from diabetes, multiple sclerosis, systemic lupus erythematosus, atopic dermatitis, mast cell-mediated allergic reactions, leukemias, lymphomas, and thromboembolic and allergic complications associated with leukemias and lymphomas.

Another aspect of the present invention relates to the use of a compound of formula I or a pharmaceutically acceptable salt thereof for the treatment or prevention of a disease mediated by JAKs, particularly JAK3. More preferably, the disease mediated by JAKs, particularly JAK3 is at least one disease selected from transplant rejection, immune, autoimmune or inflammatory diseases, neurodegenerative diseases, or proliferative disorders. In a further preferred embodiment, the disease mediated by JAKs, particularly JAK3 is selected from transplant rejection or immune, autoimmune or inflammatory diseases.

Another aspect of the present invention relates to the use of a compound of formula I or a pharmaceutically acceptable salt thereof for the treatment or prevention of at least one disease selected from transplant rejection, immune, autoimmune or inflammatory diseases, neurodegenerative diseases, or proliferative disorders. In a preferred embodiment, the disease is selected from
transplant rejection or immune, autoimmune or inflammatory diseases.

Another aspect of the present invention relates to the use of a compound of formula I or a pharmaceutically acceptable salt thereof for the treatment or prevention of a disease selected from transplant rejection, rheumatoid arthritis, psoriatic arthritis, psoriasis, type I diabetes, complications from diabetes, multiple sclerosis, systemic lupus erythematosus, atopic dermatitis, mast cell-mediated allergic reactions, leukemias, lymphomas, and thromboembolic and allergic complications associated with leukemias and lymphomas.

Another aspect of the present invention relates to a method of treating or preventing a disease mediated by JAKs, particularly JAK3, in a subject in need thereof, especially a human being, which comprises administering to said subject a compound of formula I or a pharmaceutically acceptable salt thereof. More preferably, the disease mediated by JAKs, particularly JAK3 is at least one disease selected from transplant rejection, immune, autoimmune or inflammatory diseases, neurodegenerative diseases, or proliferative disorders. In a further preferred embodiment, the disease mediated by JAKs, particularly JAK3 is selected from transplant rejection or immune, autoimmune or inflammatory diseases.

Another aspect of the present invention relates to a method of treating or preventing at least one disease selected from transplant rejection, immune, autoimmune or inflammatory diseases, neurodegenerative diseases, or proliferative disorders in a subject in need thereof, especially a human being, which comprises administering to said subject a compound of formula I or a pharmaceutically acceptable salt thereof. In a preferred embodiment, the disease is selected from transplant rejection or immune, autoimmune or inflammatory diseases.

Another aspect of the present invention relates to a method of treating or preventing a disease selected from transplant rejection, rheumatoid arthritis, psoriatic arthritis, psoriasis, type I diabetes, complications from diabetes, multiple sclerosis, systemic lupus erythematosus, atopic dermatitis, mast cell-mediated allergic reactions, leukemias, lymphomas, and thromboembolic and allergic complications associated with leukemias and lymphomas in a subject in need thereof, especially a human being, which comprises administering to said subject
a compound of formula I or a pharmaceutically acceptable salt thereof.

Another aspect of the present invention relates to a process for the preparation of a compound of formula I as defined above, which comprises:

(a) reacting a compound of formula VIII with a compound of formula IX

\[
\begin{align*}
\text{VIII} & : \quad \text{R}_1 \quad \text{R}_2 \quad \text{R}_3 \\
\text{IX} & : \quad \text{R}_2 \quad \text{R}_3 \quad \text{NH}
\end{align*}
\]

wherein \( \text{R}_1, \text{R}_2 \) and \( \text{R}_3 \) have the meaning described in claim 1 and \( \text{X} \) represents halogen; or

(b) converting, in one or a plurality of steps, a compound of formula XII into a compound of formula I

\[
\begin{align*}
\text{XII} & : \quad \text{R}_1 \\
\text{XN} & : \quad \text{NH}_2
\end{align*}
\]

wherein \( \text{R}_1 \) has the meaning described in claim 1; or

(c) converting, in one or a plurality of steps, a compound of formula I into another compound of formula I.

In the above definitions, the term \( \text{C}_{1-4} \) alkyl, as a group or part of a group, means a straight or branched alkyl chain which contains from 1 to 4 carbon atoms and includes the groups methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl and tert-butyl.

A \( \text{C}_{1-4} \) alkoxy group, as a group or part of a group, means a group of formula \( -\text{OC}_{1-4} \) alkyl, wherein the \( \text{C}_{1-4} \) alkyl moiety has the same meaning as previously described. Examples include methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy and tert-butoxy.

Halogen or its abbreviation halo means fluoro, chloro, bromo or iodo.

A \( \text{C}_{1-4} \) alkoxy\( \text{C}_{1-4} \) alkyl group means a group resulting from the replacement of one or more hydrogen atoms from a \( \text{C}_{1-4} \) alkyl group with one or more \( \text{C}_{1-4} \) alkoxy groups as defined above, which can be the same or different. Examples include,
among others, the groups methoxymethyl, ethoxymethyl, propoxymethyl, isopropoxymethyl, butoxymethyl, isobutoxymethyl, sec-butoxymethyl, tert-butoxymethyl, dimethoxymethyl, 1-methoxyethyl, 2-methoxyethyl, 2-ethoxyethyl, 1,2-diethoxyethyl, 1-butoxyethyl, 2-sec-butoxyethyl, 3-methoxypropyl, 2-butoxypropyl, 1-methoxy-2-ethoxypropyl, 3-tert-butoxypropyl and 4-methoxybutyl.

A haloCi\textsubscript{4} alkyl group means a group resulting from the replacement of one or more hydrogen atoms from a Ci\textsubscript{4} alkyl group with one or more halogen atoms (i.e. fluoro, chloro, bromo or iodo), which can be the same or different. Examples include, among others, the groups trifluoromethyl, fluoromethyl, 1-chloroethyl, 2-chloroethyl, 1-fluoroethyl, 2-fluoroethyl, 2-bromoethyl, 2-iodoethyl, 2,2,2-trifluoroethyl, pentfluorooethyl, 3-fluoropropyl, 3-chloropropyl, 2,2,3,3-tetrafluoropropyl, 2,2,3,3,3-pentafluoropropyl, heptafluoropropyl, 4-fluorobutyl and nonafluorobutyl.

A hydroxyCi\textsubscript{4} alkyl group means a group resulting from the replacement of one or more hydrogen atoms from a Ci\textsubscript{4} alkyl group with one or more hydroxy groups. Examples include, among others, the groups hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 1,2-dihydroxyethyl, 3-hydroxypropyl, 2-hydroxypropyl, 1-hydroxypropyl, 2,3-dihydroxypropyl, 4-hydroxybutyl, 3-hydroxybutyl, 2-hydroxybutyl and 1-hydroxybutyl.

A cyanoCi\textsubscript{4} alkyl group means a group resulting from the replacement of one or more hydrogen atoms from a Ci\textsubscript{4} alkyl group with one or more cyano groups. Examples include, among others, the groups cyanomethyl, dicyanomethyl, 1-cyanoethyl, 2-cyanoethyl, 3-cyanopropyl, 2,3-dicyanopropyl and 4-cyanobutyl.

A CyrCi\textsubscript{4} alkyl group means a group resulting from the replacement of one hydrogen atom from a Ci\textsubscript{4} alkyl group with one Cyi group. Examples include, among others, the groups (morpholin-4-yl)methyl, 2-(morpholin-4-yl)ethyl, 3-(morpholin-4-yl)propyl, 4-(morpholin-4-yl)butyl, (piperazin-i -yl)methyl, (4-methylpiperazin-1 -yl)methyl, 2-(4-methylpiperazin-1 -yl)ethyl, 3-(4-methylpiperazin-1 -yl)propyl, 4-(4-methylpiperazin-1 -yl)butyl, (4-ethylpiperazin-1 -yl)methyl, (4-propylpiperazin-1 -yl)methyl, (4-butylpiperazin-1 -yl)methyl, (1,1-dioxothiomorpholin-4-yl)methyl, 2-(1,1-dioxothiomorpholin-4-yl)ethyl, 3-(1,1-dioxothiomorpholin-4-yl)propyl and 4-(1,1-dioxothiomorpholin-4-yl)butyl.
A Cy₅-Ci₄alkyl group means a group resulting from the replacement of one hydrogen atom from a Ci₄alkyl group with one Cy₅ group. Examples include, among others, the groups (morpholin-4-yl)methyl, 2-(morpholin-4-yl)ethyl, 3-(morpholin-4-yl)propyl, 4-(morpholin-4-yl)butyl, (indoliny1-1-yl)methyl, 2-(indoliny1-1-yl)ethyl, 3-(indoliny1-1-yl)propyl, 4-(indoliny1-1-yl)butyl, (pyridin-1-yl)methyl, (4-methylpyridin-1-yl)methyl, 2-(4-methylpyridin-1-yl)ethyl, 3-(4-methylpyridin-1-yl)propyl, 4-(4-methylpyridin-1-yl)butyl, (4-ethylpyridin-1-yl)methyl, (4-propylpyridin-1-yl)methyl, (4-butylpyridin-1-yl)methyl, (1,1-dioxothiomorpholin-4-yl)methyl, 2-(1,1-dioxothiomorpholin-4-yl)ethyl, 3-(1,1-dioxothiomorpholin-4-yl)propyl and 4-(1,1-dioxothiomorpholin-4-yl)butyl.

A R₇-Ci₄alkyl group means a group resulting from the replacement of one hydrogen atom from a Ci₄alkyl group with one R₇ group.

A RIRCi₄alkyl group means a group resulting from the replacement of one hydrogen atom from a Ci₄alkyl group with one Rn group.

A Cyᵢ group refers to a 3- to 7-membered monocyclic carbocyclic or heterocyclic ring. When heterocyclic, it contains from 1 to 3 heteroatoms independently selected from N, S and O. Cyᵢ is saturated, partially unsaturated or aromatic, and is bonded to the rest of the molecule through any available C or N atom. When Cyᵢ is saturated or partially unsaturated, one or more C or S atoms of said ring are optionally oxidized forming CO, SO or SO₂ groups. Cyᵢ is optionally substituted as disclosed above in the definition of a compound of formula I, said substituents can be the same or different and can be placed on any available position of the ring system. Examples of Cyᵢ group include, among others, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, azetidinyl, aziridinyl, oxirany1, oxetany1, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, oxazolidinyl, pyrazolidinyl, pyrrolidinyl, thiazolidinyl, dioxanyl, morpholinyl, thiomorpholinyl, 1,1-dioxothiomorpholinyl, piperazinyl, homopiperazinyl, piperidinyl, pyrany1, tetrahydropyranyl, homopiperidinyl, oxazin1, oxazolinyl, pyrrolinyl, thiazolinyl, pyrazolinyl, imidazolinyl, isoxazolinyl, isothiazolinyl, 2-oxo-pyrrolidinyl, 2-oxo-piperidinyl, 4-oxo-piperidinyl, 2-oxo-piperazinyl, 2-oxo-1,2-dihydropyridinyl, 2-oxo-1,2-dihydropyrazinyl, 2-oxo-1,2-dihydroprymidinyl, 3-oxo-2,3-dihydropyrazidazyl, phenyl, naphthy1, thienyl, fury1, pyrroly1, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, 1,3,4-oxadiazolyl,
1,3,4-thiadiazolyl, 1,2,4-oxadiazolyl, 1,2,4-thiadiazolyl, pyridyl, pyrazinyl, pyrimidinyl and pyridazinyl.

A Cy₂ group refers to a 3- to 7-membered monocyclic carbocyclic or heterocyclic ring. When heterocyclic, it contains from 1 to 3 heteroatoms independently selected from N, S and O. Cy₂ is saturated, partially unsaturated or aromatic, and is bonded to the rest of the molecule through any available C atom. When Cy₂ is saturated or partially unsaturated, one or more C or S atoms of said ring are optionally oxidized forming CO, SO or SO₂ groups. Cy₂ is optionally substituted as disclosed above in the definition of a compound of formula I, said substituents can be the same or different and can be placed on any available position of the ring system. Examples of Cy₂ group include, among others, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, azetidinyl, aziridinyl, oxiranyl, oxetanyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, oxazolidinyl, pyrazolidinyl, pyrrolidinyl, thiazolidinyl, dioxanyl, morpholinyl, thiomorpholinyl, 1,1-dioxothiomorpholinyl, piperazinyl, homopiperazinyl, piperidinyl, pyranyl, tetrahydropyranyl, homopiperdinyl, oxazinyl, oxazolinyl, pyrrolinyl, thiazolinyl, pyrazolinyl, imidazolinyl, isoxazolinyl, isothiazolinyl, 2-oxo-pyrrolidinyl, 2-oxo-piperidinyl, 4-oxo-piperazinyl, 2-oxo-1,2-dihydropyridinyl, 2-oxo-1,2-dihydropyrazinyl, 2-oxo-1,2-dihydropyrimidinyl, 3-oxo-2,3-dihydropyridazyl, phenyl, naphthyl, thienyl, furyl, pyrrolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, 1,3,4-oxadiazolyl, 1,3,4-thiadiazolyl, 1,2,4-oxadiazolyl, 1,2,4-thiadiazolyl, pyridyl, pyrazinyl, pyrimidinyl and pyridazinyl.

A Cy₃ group refers to a 3- to 7-membered monocyclic or 8- to 12-membered bicyclic carbocyclic or heterocyclic ring. When heterocyclic, it contains from 1 to 4 heteroatoms independently selected from N, S and O. Bicyclic rings may be formed either by two rings fused through two adjacent C or N atoms, or through two non-adjacent C or N atoms forming a bridged ring, or else they can be formed by two rings bonded through a single common C atom forming a spiro ring. Cy₃ is saturated, partially unsaturated or aromatic, and is bonded to the rest of the molecule through any available C atom. In Cy₃ one or more C or S atoms of a saturated or partially unsaturated ring are optionally oxidized forming CO, SO or SO₂ groups. Cy₃ is optionally substituted as disclosed above in the definition of a
compound of formula I; if substituted, said substituents can be the same or different and can be placed on any available position of the ring system. Examples of Cy₃ include, among others, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, azetidinyl, aziridinyl, oxiranyl, oxetanyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, oxazolidinyl, pyrrolidinyl, thiazolidinyl, dioxanyl, morpholinyl, thiomorpholinyl, 1,1-dioxothiomorpholinyl, piperazinyl, homopiperazinyl, piperidinyl, pyranyl, tetrahydropyranyl, homopipethidinyl, oxazinyl, oxazolinyl, pyrazolidinyl, pyrrolidinyl, thiazolidinyl, imidazolinyl, isoxazolinyl, isothiazolinyl, 2-oxo-pyrrolidinyl, 2-oxo-pipethidinyl, 2-oxo-piperazinyl, 2-oxo-1,2-dihydropyridinyl, 2-oxo-1,2-dihydropyrazinyl, 2-oxo-1,2-dihydropyrimidinyl, 3-oxo-2,3-dihydropyridazyl, phenyl, naphthyl, thiényl, furyl, pyrrolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetraazolyl, 1,3,4-oxadiazyolyl, 1,3,4-thiadiazyolyl, 1,2,4-oxadiazolyl, 1,2,4-thiadiazolyl, phenyl, naphthyl, thienyl, pyrrolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetraazolyl, 1,3,4-oxadiazyolyl, 1,3,4-thiadiazyolyl, 1,2,4-oxadiazolyl, 1,2,4-thiadiazolyl, benzimidazolyl, benzoxazolyl, benzofuranyl, isobenzofuranyl, indolyl, isoindolyl, benzo[b]thiophenyl, benzo[b]thiazolyl, quinolinyl, isoquinolinyl, phtalazinyl, quinoxalinyl, cinolinyl, naphthyridinyl, indazolyl, imidazopyridinyl, pyrrolopyridinyl, thienopyridinyl, imidazopyrimidinyl, imidazopyrazinyl, imidazopyridazinyl, pyrazolopyrazinyl, pyrazolopyridinyl, pyrazolopyrimidinyl, benzol[1,3]dioxolyl, phtalimidyl, 1-oxo-1,3-dihydroisobenzofuranyl, 1,3-dioxo-1,3-dihydroisobenzofuranyl, 2-oxo-2,3-dihydro-1H-indolyl, 1-oxo-2,3-dihydro-1H-indolyl, perhydroquinolinyl, 1-oxo-perhydroquinolinyl, 1-oxo-1,2-dihydroisquinolinyl, 4-oxo-3,4-dihydroquinazolinyl, 2-aza-bicyclo[2.2.1]heptanyl, 5-aza-bicyclo[2.1.1]hexanyl, 2/-/spiro[benzofuran-3,4'-piperidinyl], 3H-spiro[isobenzofuran-1,4'-piperidinyl], 1-oxo-2,8-diazaaspiro[4.5]decanyland 1-oxo-2,7-diazaaspiro[4.5]decanyland

A Cy₄ group refers to a 3- to 7-membered monocyclic heterocyclic ring, which is saturated or partially unsaturated. Cy₄ is optionally fused to a 5- or 6-membered carbocyclic or heterocyclic ring that is saturated, partially unsaturated or aromatic. Cy₄ contains from 1 to 4 heteroatoms in total independently selected from N, S and O. In Cy₄ one or more C or S atoms of a saturated or partially unsaturated ring are optionally oxidized forming CO, SO or SO₂ groups. Cy₄ is optionally substituted as disclosed above in the definition of a compound of
formula I; if substituted, said substituents can be the same or different and can be placed on any available position of the ring system. Examples of Cy₄ include, among others, azepanyl, aziridinyl, azetidinyl, 1,4-diazepanyl, pyrrolidinyl, imidazolidinyl, isoxazolidinyl, oxazolidinyl, pyrazolidinyl, thiazolidinyl, isothiazolidinyl, imidazolinyl, pyrrolinyl, pyrazolinyl, piperidinyl, homopiperidinyl, morpholinyl, thiomorpholinyl, 1,1-dioxothiomorpholinyl, piperezinyl, homopiperazinyl, 2-oxo-azepanyl, 2-oxo-azetidinyl, 2-oxo-1,4-diazepanyl, 2-oxopyrrolidinyl, 2-oxo-piperazinyl, 2-oxo-pipehdinyl, 3-oxo-pipehdinyl, 4-oxo-piperidinyl, 2-oxo-imidazolidinyl, 2-oxo-oxazolidinyl, 2-oxo-1,2-dihydropyridinyl, 2-oxo-1,2-dihydropyrazinyl, 2-oxo-1,2-dihydropyrimidinyl, 3-oxo-2,3-dihydropyridazinyl, 1,2,3,6-tetrahydropyridinyl, perhydroisoquinolinyl, 1-oxo-1,2-dihydroisoquinolinyl, 4-oxo-3,4-dihydroquinazolinyl, 5-aza-bicyclo[2.1.1]hexanyl, 2-aza-bicyclo[2.2.1]heptanyl, 6-aza-bicyclo[3.2.1]octanyl, octahydro-pyrrolo[1,2-a]pyrazinyl, 2/-/-spiro[benzofuran-3,4'-pipehdinyl], 3/-/-spiro[isobenzofuran-1,4'-piperidinyl], 2,8-diazaspiro[4.5]decan-1 -onyl, 2,7-diazaspiro[4.5]decan-1 -onyl, 2-aza-bicyclo[2.2.1]heptan-6-onyl and 6-aza-bicyclo[3.2.1]octan-7-onyl

A Cy₅ group refers to a 3- to 7-membered monocyclic or 8- to 12-membered bicyclic carbocyclic or heterocyclic ring. When heterocyclic, it contains from 1 to 4 heteroatoms independently selected from N, S and O. Bicyclic rings may be formed either by two rings fused through two adjacent C or N atoms, or through two non-adjacent C or N atoms forming a bridged ring, or else they can be formed by two rings bonded through a single common C atom forming a spiro ring. Cy₅ is saturated, partially unsaturated or aromatic, and is bonded to the rest of the molecule through any available C or N atoms. In Cy₅ one or more C or S atoms of a saturated or partially unsaturated ring are optionally oxidized forming CO, SO or SO₂ groups. Cy₅ is optionally substituted as disclosed above in the definition of a compound of formula I; if substituted, said substituents can be the same or different and can be placed on any available position of the ring system. Examples of Cy₅ include, among others, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, azetidinyl, aziridinyl, oxiranyl, oxetany, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, oxazolidinyl, pyrazolidinyl, pyrrolidinyl, thiazolidinyl, dioxanyl, morpholinyl, thiomorpholinyl, 1,1-dioxothiomorpholinyl, piperezinyl, homopiperazinyl, piperidinyl, pyranyl, tetrahydropyranyl, homopipehdinyl, oxazinyl,
oxazolinyl, pyrrolinyl, thiazolinyl, pyrazolinyl, imidazolyl, isoxazolinyl, isothiazolinyl, 2-oxo-pyrrolidinyl, 2-oxo-piperidinyl, 2-oxo-piperazinyl, 2-oxo-1,2-dihydropyridinyl, 2-oxo-1,2-dihydropyrazinyl, 2-oxo-1,2-dihydropyrimidinyl, 3-oxo-2,3-dihydropyridazyl, phenyl, naphthyl, thi enyl, furyl, pyrrol, thiazol, isothiazol, oxazol, isoxazol, imidazol, pyrazol, 1,2,3-triazol, 1,2,4-triazol, tetrazol, 1,3,4-oxadia zol, 1,3,4-thiadiazol, 1,2,4-oxadia zol, 1,2,4-thiadiazol, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, benzimidazol, benzoxazol, benzofuranyl, isobenzofuranyl, indol, isoindol, benzothiophen, benzothiazol, quinolin, isoquinolin, phtalazin, quinazol, quinoxalin, cinolin, naphthyridin, indazol, imidazopyridin, pyrrolopyridin, thi enopyridin, imidazopyrimidin, imidazopyrazin, imidazopyridazin, pyrazolopyrazin, pyrazolopyrimidin, benzo[1,3]dioxol, phtalimidy, 1-oxo-1,3-dihydroisobenzofuranyl, 1,3-dioxo-1,3-dihydroisobenzofuranyl, 2-oxo-2,3-dihydro-1/-indol, 1-oxo-2,3-dihydro-1 H-is oindol, perhydroquinolin, 1-oxo-perhydrosoquinolin, 1-oxo-1,2-dihydrosoquinolin, 4-oxo-3,4-dihydroquinazol, 2-aza-bicyclo[2.2.1]heptanyl, 5-aza-bicyclo[2.1.1]hexanyl, 2/-/spiro[benzofuran-3,4'-piperidin], 3H-spiro[isobenzofuran-1,4-piperidin], 1-oxo-2,8-diazaspiro[4.5]decanyl and 1-oxo-2,7-diazaspiro[4.5]decanyl.

In the above definitions of C3 and C5 when the examples listed refer to a bicycle in general terms, all possible dispositions of the atoms are included. Thus, for example, the term pyrazolopyridin can include groups such as 1H-pyrazol[3,4-c>][pyridin, 1H-pyrazol[1,5-a][pyridin, 1H-pyrazol[3,4-c][pyridin, 1H-pyrazol[4,3-c][pyridin, and 1H-pyrazol[4,3-c>][pyridin, the term imidazopyrazin can include groups such as 1H-imidazo[4,5-c>][pyrazin, imidazo[1,2-a][pyrazin, and imidazo[1,5-a][pyrazin, and the term pyrazolopyrimidin can include groups such as 1H-pyrazol[3,4-c][pyrimidin, 1H-pyrazol[4,3-c>][pyrimidin], pyrazol[1,5-a][pyrimidin, and pyrazol[1,5-c][pyrimidin.

When in the definitions used throughout the present specification for cyclic groups the examples given refer to a radical of a ring in general terms, for example pyridyl, thi enyl or indol, all the available bonding positions are included, unless a limitation is indicated in the corresponding definition for said cyclic group,
for example that the ring is bonded through a C atom in C\textsubscript{y2} and C\textsubscript{y3}, in which case such limitation applies. Thus for example, in the definitions of C\textsubscript{yi} and C\textsubscript{y5}, which do not include any limitation regarding the bonding position, the term piperidinyl includes 1-piperidinyl, 2-pipehdinyl, 3-piperidinyl and 4-pipehdinyl; and pyrrolidinyl includes 1-pyrrolidinyl, 2-pyrrolidinyl and 3-pyrrolidinyl.

The expression "optionally substituted with one or more" means that a group can be substituted with one or more, preferably with 1, 2, 3 or 4 substituents, more preferably with 1, 2 or 3 substituents, and still more preferably with 1 or 2 substituents, provided that said group has enough positions susceptible of being substituted. The substituents can be the same or different and can be placed on any available position.

When a non-aromatic ring is present as a substituent of a non-aromatic ring, it can replace one hydrogen atom, or it can replace two hydrogen atoms on the same C atom thus forming a spiro ring. Likewise, when a non-aromatic ring is present as a substituent of an alkyl group, it can either replace one hydrogen atom, or it can replace two hydrogen atoms and share one C atom of said alkylgroup, forming groups such as the ones shown below:

When in the definition of a substituent two or more groups with the same numbering are indicated (e.g. \(-\text{CONR}_{4}R_{4}, -\text{NR}_{4}R_{4}, -\text{NR}_{6}\text{CONR}_{6}R_{6}, \text{etc.}\) ), this does not mean that they must be the same. Each of them is independently selected from the list of possible meanings given for said group, and therefore they can be the same or different.

For the sake of clarity, throughout the present specification, the presence or absence of the term "independently selected from" or "independently represents" in a definition of a group or particular embodiment should not be considered as imposing any restrictions into said definition. All terms should be given their broadest possible meaning within the definition provided, which means that unless the contrary is explicitly mentioned, no limitation that two groups should be identical should be read into any definition of any term.

Throughout the present specification, by the term "treatment" is meant
eliminating, reducing or ameliorating the cause or the effects of a disease. For purposes of this invention treatment includes, but is not limited to, alleviation, amelioration or elimination of one or more symptoms of the disease; diminishment of the extent of the disease; stabilized (i.e. not worsening) state of disease; delay or slowing of disease progression; amelioration or palliation of the disease state; and remission of the disease (whether partial or total).

As used herein, "prevention" refers to preventing the occurrence of a disease in a subject that is predisposed to or has risk factors but does not yet display symptoms of the disease. Prevention includes also preventing the recurrence of a disease in a subject that has previously suffered said disease.

The invention thus relates to the compounds of formula I as defined above.

In another embodiment, the invention relates to the compounds of formula I wherein Ri represents hydrogen, Ci-alkyl, haloCi-alkyl, hydroxyCi-alkyl, R7-C1-alkyl, halogen, -CN, -CONR4R4, -CO2R5, -OR4 or -NR6COR4.

In another embodiment, the invention relates to the compounds of formula I wherein Ri represents hydrogen, Ci-alkyl, haloCi-alkyl, hydroxyCi-alkyl, R7-C1-alkyl, halogen or -CN.

In another embodiment, the invention relates to the compounds of formula I wherein Ri represents hydrogen or -CN.

In another embodiment, the invention relates to the compounds of formula I wherein Ri represents hydrogen.

In another embodiment, the invention relates to the compounds of formula I wherein Ri represents-CN.

In another embodiment, the invention relates to the compounds of formula I wherein R7 in Ri represents -CN, -CONR4R4, -CO2R5, -OR4 or -NR6COR4.

In another embodiment, the invention relates to the compounds of formula I wherein:

R2 represents hydrogen, C1-alkyl, haloC1-alkyl, hydroxyC1-alkyl, R7-C1-alkyl or Cy2, wherein Cy2 is optionally substituted with one or more R8, and

R3 represents C1-alkyl, haloC1-alkyl, hydroxyC1-alkyl, R1rCi-alkyl, -CONR9R9, -COR10, -CO2Ri0, -SO2Ri0, -SO2NRiRi or Cy3, wherein Cy3 is optionally substituted with one or more Ri2.

In another embodiment, the invention relates to the compounds of formula I
wherein \( R_2 \) represents hydrogen, \( \text{C}_4 \text{alkyl} \), \( \text{haloC}_4 \text{alkyl} \), \( \text{hydroxyC}_4 \text{alkyl} \) or \( \text{R}_7-\text{C}_4 \text{alkyl} \).

In another embodiment, the invention relates to the compounds of formula I wherein \( R_2 \) represents hydrogen, \( \text{C}_4 \text{alkyl} \), \( \text{haloC}_4 \text{alkyl} \) or \( \text{hydroxyC}_4 \text{alkyl} \).

In another embodiment, the invention relates to the compounds of formula I wherein \( R_2 \) represents hydrogen or \( \text{C}_4 \text{alkyl} \), preferably hydrogen, methyl or ethyl.

In another embodiment, the invention relates to the compounds of formula I wherein \( R_3 \) represents hydroxy\( \text{C}_4 \text{alkyl} \), \( \text{Rn-C}_4 \text{alkyl} \) or \( \text{C}_y \text{y}_3 \), wherein \( \text{C}_y \text{y}_3 \) is optionally substituted with one or more \( \text{Ri}_2 \).

In another embodiment, the invention relates to the compounds of formula I wherein \( R_3 \) represents \( \text{C}_y \text{y}_3 \), wherein \( \text{C}_y \text{y}_3 \) is optionally substituted with one or more \( \text{Ri}_2 \).

In another embodiment, the invention relates to the compounds of formula I wherein \( \text{C}_y \text{y}_3 \) represents a 3- to 7-membered saturated monocyclic carbocyclic ring, which optionally contains 1 or 2 heteroatoms independently selected from N, S and O, wherein said ring is bonded to the rest of the molecule through any available C atom, wherein one or more C or S ring atoms are optionally oxidized forming CO, SO or \( \text{SO}_2 \) groups, and wherein \( \text{C}_y \text{y}_3 \) is optionally substituted with one or more \( \text{Ri}_2 \).

In another embodiment, the invention relates to the compounds of formula I wherein \( \text{C}_y \text{y}_3 \) represents a 5- or 6-membered saturated monocyclic carbocyclic ring, which optionally contains 1 or 2 heteroatoms independently selected from N, S and O, wherein said ring is bonded to the rest of the molecule through any available C atom, wherein one or more C or S ring atoms are optionally oxidized forming CO, SO or \( \text{SO}_2 \) groups, and wherein \( \text{C}_y \text{y}_3 \) is optionally substituted with one or more \( \text{Ri}_2 \).

In another embodiment, the invention relates to the compounds of formula I wherein \( \text{C}_y \text{y}_3 \) represents cyclohexyl, 2-piperidinyl, 3-piperidinyl or 4-piperidinyl, wherein \( \text{C}_y \text{y}_3 \) is optionally substituted with one or more \( \text{Ri}_2 \).

In another embodiment, the invention relates to the compounds of formula I wherein \( \text{C}_y \text{y}_3 \) represents cyclohexyl, 3-piperidinyl or 4-piperidinyl, wherein \( \text{C}_y \text{y}_3 \) is optionally substituted with one or more \( \text{Ri}_2 \).
wherein \( \text{Cy}_3 \) represents cyclohexyl or 3-piperidinyl, wherein \( \text{Cy}_3 \) is optionally substituted with one or more \( \text{Ri}_2 \).

In another embodiment, the invention relates to the compounds of formula I wherein \( \text{Cy}_3 \) represents cyclohexyl, which is optionally substituted with one or more \( \text{Ri}_2 \).

In another embodiment, the invention relates to the compounds of formula I wherein \( \text{Cy}_3 \) represents 3-piperidinyl, which is optionally substituted with one or more \( \text{Ri}_2 \).

In another embodiment, the invention relates to the compounds of formula I wherein \( \text{Cy}_3 \) represents 4-piperidinyl, which is optionally substituted with one or more \( \text{Ri}_2 \).

In another embodiment, the invention relates to the compounds of formula I wherein:

\[
\text{R}_3 \text{ represents } \text{Cy}_3; \text{ and} \\
\text{Cy}_3 \text{ represents a group of formula } \text{Cy}_3a \text{ or } \text{Cy}_3b:
\]

\[
\text{Cy}_3a \\
\text{Cy}_3b
\]

wherein \( \text{Ri}_{2a} \) represents \(-\text{CORi}_5\); and

wherein additionally \( \text{Cy}_3a \) and \( \text{Cy}_3b \) are independently optionally substituted with one or more \( \text{Ri}_2 \).

In another embodiment, the invention relates to the compounds of formula I wherein:

\[
\text{R}_3 \text{ represents } \text{Cy}_3; \text{ and} \\
\text{Cy}_3 \text{ represents a group of formula } \text{Cy}_3a \text{ or } \text{Cy}_3b; \text{ wherein } \text{Ri}_{2a} \text{ represents } -\text{CORi}_{15}; \text{ and} \\
\text{wherein additionally } \text{Cy}_3a \text{ and } \text{Cy}_3b \text{ are independently optionally substituted with one or more } \text{Ri}_2 \text{ groups independently selected from } \text{C}_1-4 \text{ alkyl, haloC}_1-4 \text{ alkyl, hydroxyC}_1-4 \text{ alkyl and Rn-C}_1-4 \text{ alkyl.}
\]

In another embodiment, the invention relates to the compounds of formula I
wherein:

R\textsubscript{3} represents C\textsubscript{y}\textsubscript{3};

C\textsubscript{y}\textsubscript{3} represents a group of formula C\textsubscript{y}\textsubscript{3a} or C\textsubscript{y}\textsubscript{3b}; wherein R\textsubscript{i2a} represents -COR\textsubscript{15}; and

wherein additionally C\textsubscript{y}\textsubscript{3a} and C\textsubscript{y}\textsubscript{3b} are independently optionally substituted with one or more R\textsubscript{i2} groups independently selected from Ci\textsubscript{-4}alkyl, haloCi\textsubscript{-4}alkyl, hydroxyCi\textsubscript{-4}alkyl and Rn-Ci\textsubscript{-4}alkyl;

R\textsubscript{i4} represents hydrogen; and

R\textsubscript{i5} represents Ci\textsubscript{-4}alkyl or cyanoCi\textsubscript{-4}alkyl, preferably cyanomethyl.

In another embodiment, the invention relates to the compounds of formula I wherein:

R\textsubscript{3} represents C\textsubscript{y}\textsubscript{3};

C\textsubscript{y}\textsubscript{3} represents a group of formula C\textsubscript{y}\textsubscript{3a} or C\textsubscript{y}\textsubscript{3b}; wherein R\textsubscript{i2a} represents -COR\textsubscript{15}; and

R\textsubscript{i4} represents hydrogen; and

R\textsubscript{i5} represents Ci\textsubscript{-4}alkyl or cyanoCi\textsubscript{-4}alkyl, preferably cyanomethyl.

In another embodiment, the invention relates to the compounds of formula I wherein:

R\textsubscript{3} represents C\textsubscript{y}\textsubscript{3};

C\textsubscript{y}\textsubscript{3} represents a group of formula C\textsubscript{y}\textsubscript{3a}; wherein R\textsubscript{i2a} represents -COR\textsubscript{i5}; and

wherein additionally C\textsubscript{y}\textsubscript{3a} is optionally substituted with one or more R\textsubscript{i2}.

In another embodiment, the invention relates to the compounds of formula I wherein:

R\textsubscript{3} represents C\textsubscript{y}\textsubscript{3};

C\textsubscript{y}\textsubscript{3} represents a group of formula C\textsubscript{y}\textsubscript{3b}; and

wherein additionally C\textsubscript{y}\textsubscript{3b} is optionally substituted with one or more R\textsubscript{i2}. 
In another embodiment, the invention relates to the compounds of formula I wherein:

R$_3$ represents Cy$_3$; and

Cy$_3$ represents a group of formula Cy$_{3a}$ wherein R$_{12a}$ represents -COR$_i$$_5$.

In another embodiment, the invention relates to the compounds of formula I wherein:

R$_3$ represents Cy$_3$; and

Cy$_3$ represents a group of formula Cy$_{3b}$.

In another embodiment, the invention relates to the compounds of formula I wherein:

R$_3$ represents Cy$_3$;

Cy$_3$ represents a group of formula Cy$_{3a}$ wherein R$_{12a}$ represents -COR$_i$$_5$; and

R$_{15}$ represents Ci$_{4}$alkyl or cyanoCi$_{4}$alkyl, preferably cyanomethyl.

In another embodiment, the invention relates to the compounds of formula I wherein:

R$_1$ represents hydrogen or -CN; and

R$_2$ represents hydrogen, Ci$_{4}$alkyl, haloCi$_{4}$alkyl, hydroxyCi$_{4}$alkyl or R$_7$-Ci$_{4}$alkyl.

In another embodiment, the invention relates to the compounds of formula I wherein:

R$_1$ represents -CN; and

R$_2$ represents hydrogen, Ci$_{4}$alkyl, haloCi$_{4}$alkyl, hydroxyCi$_{4}$alkyl or R$_7$-Ci$_{4}$alkyl.

In another embodiment, the invention relates to the compounds of formula I wherein:

R$_1$ represents hydrogen or -CN; and

R$_2$ represents hydrogen, Ci$_{4}$alkyl, haloCi$_{4}$alkyl or hydroxyCi$_{4}$alkyl.

In another embodiment, the invention relates to the compounds of formula I wherein:

R$_1$ represents -CN; and

R$_2$ represents hydrogen, Ci$_{4}$alkyl, haloCi$_{4}$alkyl or hydroxyCi$_{4}$alkyl.
wherein:

R_i represents hydrogen or -CN; and

R_2 represents hydrogen or C_i-4 alkyl, preferably hydrogen, methyl or ethyl.

In another embodiment, the invention relates to the compounds of formula I

wherein:

R_i represents -CN; and

R_2 represents hydrogen or C_i-4 alkyl, preferably hydrogen, methyl or ethyl.

In another embodiment, the invention relates to the compounds of formula I

wherein:

R_i represents hydrogen or -CN; and

R_3 represents C_y3, wherein C_y3 is optionally substituted with one or more R_i2.

In another embodiment, the invention relates to the compounds of formula I

wherein:

R_i represents -CN; and

R_3 represents C_y3, wherein C_y3 is optionally substituted with one or more R_i2.

In another embodiment, the invention relates to the compounds of formula I

wherein:

R_i represents hydrogen or -CN;

R_2 represents hydrogen, C_i-4 alkyl, haloC_i-4 alkyl, hydroxyC_i-4 alkyl or R_7-C_i-4 alkyl; and

R_3 represents C_y3, wherein C_y3 is optionally substituted with one or more R_i2.

In another embodiment, the invention relates to the compounds of formula I

wherein:

R_i represents -CN;

R_2 represents hydrogen, C_i-4 alkyl, haloC_i-4 alkyl, hydroxyC_i-4 alkyl or R_7-C_i-4 alkyl; and

R_3 represents C_y3, wherein C_y3 is optionally substituted with one or more R_i2.

In another embodiment, the invention relates to the compounds of formula I

wherein:
R\textsubscript{i} represents hydrogen or -CN;
R\textsubscript{2} represents hydrogen or Ci\textsubscript{4}alkyl, preferably hydrogen, methyl or ethyl;
and
R\textsubscript{3} represents Cy\textsubscript{3}, wherein Cy\textsubscript{3} is optionally substituted with one or more

In another embodiment, the invention relates to the compounds of formula I wherein:
R\textsubscript{i} represents -CN;
R\textsubscript{2} represents hydrogen or Ci\textsubscript{4}alkyl, preferably hydrogen, methyl or ethyl;
and
R\textsubscript{3} represents Cy\textsubscript{3}, wherein Cy\textsubscript{3} is optionally substituted with one or more

In another embodiment, the invention relates to the compounds of formula I wherein:
R\textsubscript{i} represents hydrogen or -CN;
R\textsubscript{2} represents hydrogen, Ci\textsubscript{4}alkyl, haloCi\textsubscript{4}alkyl, hydroxyCi\textsubscript{4}alkyl or R\textsubscript{7}Ci\textsubscript{4}alkyl;
R\textsubscript{3} represents Cy\textsubscript{3}, and
Cy\textsubscript{3} represents a 5- or 6-membered saturated monocyclic carbocyclic ring, which optionally contains 1 or 2 heteroatoms independently selected from N, S and O, wherein said ring is bonded to the rest of the molecule through any available C atom, and wherein one or more C or S ring atoms are optionally oxidized forming CO, SO or SO\textsubscript{2} groups, wherein Cy\textsubscript{3} is optionally substituted with one or more Ri\textsubscript{2}.

In another embodiment, the invention relates to the compounds of formula I wherein:
R\textsubscript{i} represents -CN;
R\textsubscript{2} represents hydrogen, Ci\textsubscript{4}alkyl, haloCi\textsubscript{4}alkyl, hydroxyCi\textsubscript{4}alkyl or R\textsubscript{7}Ci\textsubscript{4}alkyl;
R\textsubscript{3} represents Cy\textsubscript{3}; and
Cy\textsubscript{3} represents a 5- or 6-membered saturated monocyclic carbocyclic ring, which optionally contains 1 or 2 heteroatoms independently selected from N, S and O, wherein said ring is bonded to the rest of the molecule through any
available C atom, wherein one or more C or S ring atoms are optionally oxidized forming CO, SO or SO₂ groups, and wherein Cy₃ is optionally substituted with one or more Ri₂.

In another embodiment, the invention relates to the compounds of formula I wherein:

- Ri represents hydrogen or -CN;
- R₂ represents hydrogen or C₁₋₄ alkyl, preferably hydrogen, methyl or ethyl;
- R₃ represents Cy₃, and
- Cy₃ represents a 5- or 6-membered saturated monocyclic carbocyclic ring, which optionally contains 1 or 2 heteroatoms independently selected from N, S and O, wherein said ring is bonded to the rest of the molecule through any available C atom, wherein one or more C or S ring atoms are optionally oxidized forming CO, SO or SO₂ groups, and wherein Cy₃ is optionally substituted with one or more Ri₂.

In another embodiment, the invention relates to the compounds of formula I wherein:

- Ri represents -CN;
- R₂ represents hydrogen or C₁₋₄ alkyl, preferably hydrogen, methyl or ethyl;
- R₃ represents Cy₃, and
- Cy₃ represents a 5- or 6-membered saturated monocyclic carbocyclic ring, which optionally contains 1 or 2 heteroatoms independently selected from N, S and O, wherein said ring is bonded to the rest of the molecule through any available C atom, wherein one or more C or S ring atoms are optionally oxidized forming CO, SO or SO₂ groups, and wherein Cy₃ is optionally substituted with one or more Ri₂.

In another embodiment, the invention relates to the compounds of formula I wherein:

- Ri represents hydrogen or -CN;
- R₂ represents hydrogen, C₁₋₄ alkyl, haloC₁₋₄ alkyl, hydroxyC₁₋₄ alkyl or R₇-C₁₋₄ alkyl;
- R₃ represents Cy₃, and
- Cy₃ represents cyclohexyl, 3-piperidinyl or 4-piperdinyl, wherein Cy₃ is optionally substituted with one or more Ri₂.
In another embodiment, the invention relates to the compounds of formula I wherein:

R\textsubscript{i} represents -CN;

R\textsubscript{2} represents hydrogen, C\textsubscript{i}-4 alkyl, haloC\textsubscript{i}-4 alkyl, hydroxyC\textsubscript{i}-4 alkyl or R\textsubscript{7}-Ci.

R\textsubscript{3} represents Cy\textsubscript{3}; and

Cy\textsubscript{3} represents cyclohexyl, 3-piperidinyl or 4-piperdinyl, wherein Cy\textsubscript{3} is optionally substituted with one or more R\textsubscript{i}.2.

In another embodiment, the invention relates to the compounds of formula I wherein:

R\textsubscript{i} represents hydrogen or -CN;

R\textsubscript{2} represents hydrogen or C\textsubscript{i}-4 alkyl, preferably hydrogen, methyl or ethyl;

R\textsubscript{3} represents Cy\textsubscript{3}; and

Cy\textsubscript{3} represents cyclohexyl, 3-piperidinyl or 4-piperdinyl, wherein Cy\textsubscript{3} is optionally substituted with one or more R\textsubscript{i}.2.

In another embodiment, the invention relates to the compounds of formula I wherein:

R\textsubscript{i} represents hydrogen or -CN;

R\textsubscript{2} represents hydrogen, C\textsubscript{i}-4 alkyl, haloC\textsubscript{i}-4 alkyl, hydroxyC\textsubscript{i}-4 alkyl or R\textsubscript{7}-Ci.

R\textsubscript{3} represents Cy\textsubscript{3}; and

Cy\textsubscript{3} represents cyclohexyl, optionally substituted with one or more R\textsubscript{i}.2.

In another embodiment, the invention relates to the compounds of formula I wherein:

R\textsubscript{i} represents -CN;

R\textsubscript{2} represents hydrogen, C\textsubscript{i}-4 alkyl, haloC\textsubscript{i}-4 alkyl, hydroxyC\textsubscript{i}-4 alkyl or R\textsubscript{7}-Ci.

R\textsubscript{3} represents Cy\textsubscript{3}; and

Cy\textsubscript{3} represents cyclohexyl, optionally substituted with one or more R\textsubscript{i}.2.
$C_{1-4}$ alkyl;

$R_3$ represents $C_y 3$; and

$C_y 3$ represents cyclohexyl, optionally substituted with one or more $R_{i2}$.  

In another embodiment, the invention relates to the compounds of formula I

wherein:

$R_i$ represents hydrogen or -CN;

$R_2$ represents hydrogen or $C_{i-4}$ alkyl, preferably hydrogen, methyl or ethyl;

$R_3$ represents $C_y 3$; and

$C_y 3$ represents cyclohexyl, optionally substituted with one or more $R_{i2}$.  

In another embodiment, the invention relates to the compounds of formula I

wherein:

$R_i$ represents -CN;

$R_2$ represents hydrogen, $C_{i-4}$ alkyl, halo$C_{i-4}$ alkyl, hydroxy$C_{i-4}$ alkyl or $R_7$-$C_{i-4}$ alkyl;

$R_3$ represents $C_y 3$; and

$C_y 3$ represents 3-piperidinyl or 4-pipehdinyl, wherein $C_y 3$ is optionally substituted with one or more $R_{i2}$.  

In another embodiment, the invention relates to the compounds of formula I

wherein:

$R_i$ represents -CN;

$R_2$ represents hydrogen, $C_{i-4}$ alkyl, halo$C_{i-4}$ alkyl, hydroxy$C_{i-4}$ alkyl or $R_7$-$C_{i-4}$ alkyl;

$R_3$ represents $C_y 3$; and

$C_y 3$ represents 3-piperidinyl or 4-pipehdinyl, wherein $C_y 3$ is optionally substituted with one or more $R_{i2}$.  

In another embodiment, the invention relates to the compounds of formula I
wherein:
R_i represents hydrogen or -CN;
R_2 represents hydrogen or C_1-4 alkyl, preferably hydrogen, methyl or ethyl;
R_3 represents C_3y;
and
C_3y represents 3-piperidinyl or 4-piperidinyl, wherein C_3y is optionally substituted with one or more R_i.

In another embodiment, the invention relates to the compounds of formula I wherein:
R_i represents -CN;
R_2 represents hydrogen or C_1-4 alkyl, preferably hydrogen, methyl or ethyl;
R_3 represents C_3y;
and
C_3y represents 3-piperidinyl or 4-piperidinyl, wherein C_3y is optionally substituted with one or more R_i.

In another embodiment, the invention relates to the compounds of formula I wherein:
R_i represents hydrogen or -CN;
R_2 represents hydrogen, C_1-4 alkyl, haloC_1-4 alkyl, hydroxyC_1-4 alkyl, or R_7-C_1-4 alkyl;
R_3 represents C_3y;
and
C_3y represents 3-piperidinyl, optionally substituted with one or more R_i.

In another embodiment, the invention relates to the compounds of formula I wherein:
R_i represents -CN;
R_2 represents hydrogen, C_1-4 alkyl, haloC_1-4 alkyl, hydroxyC_1-4 alkyl, or R_7-C_1-4 alkyl;
R_3 represents C_3y;
and
C_3y represents 3-piperidinyl, optionally substituted with one or more R_i.

In another embodiment, the invention relates to the compounds of formula I wherein:
R_i represents hydrogen or -CN;
R_2 represents hydrogen or C_1-4 alkyl, preferably hydrogen, methyl or ethyl;
R_3 represents C_3y;
and
C_3y represents 3-piperidinyl, optionally substituted with one or more R_i.
In another embodiment, the invention relates to the compounds of formula I wherein:

R_i represents -CN;
R_2 represents hydrogen or C_{1-4} alkyl, preferably hydrogen, methyl or ethyl;
R_3 represents Cy_3; and
Cy_3 represents 3-piperidinyl, optionally substituted with one or more R_i_2.

In another embodiment, the invention relates to the compounds of formula I wherein:

R_i represents hydrogen or -CN, preferably -CN;
R_2 represents hydrogen or C_{1-4} alkyl, preferably hydrogen, methyl or ethyl;
R_3 represents Cy_3; and
Cy_3 represents a group of formula Cy_{3a} or Cy_{3b}; wherein R_i_2 represents
-CONR_{4-i_4}, -CORi_5, -CO_2Ri_5, -SO_2Ri_5, -SO_2NRi_4Ri_4 or Cy_5, wherein Cy_5 is
optionally substituted with one or more R_3; and

wherein additionally Cy_{3a} and Cy_{3b} are independently optionally substituted with
one or more R_i_2.

In another embodiment, the invention relates to the compounds of formula I wherein:

R_i represents hydrogen or -CN, preferably -CN;
R_2 represents hydrogen or C_{1-4} alkyl, preferably hydrogen, methyl or ethyl;
R_3 represents Cy_3; and
Cy_3 represents a group of formula Cy_{3a} or Cy_{3b}; wherein R_i_2 represents
-COR_{15}; and
wherein additionally Cy_{3a} and Cy_{3b} are independently optionally substituted with
one or more R_i_2.

In another embodiment, the invention relates to the compounds of formula I wherein:

R_i represents hydrogen or -CN, preferably -CN;
R_2 represents hydrogen or C_{1-4} alkyl, preferably hydrogen, methyl or ethyl;
R_3 represents Cy_3; and
Cy_3 represents a group of formula Cy_{3a} or Cy_{3b}; wherein R_i_2 represents
-COR_{15}; and
wherein additionally Cy_{3a} and Cy_{3b} are independently optionally substituted with
one or more Ri₂ groups independently selected from Cᵳ₄alkyl, haloCᵳ₄alkyl, hydroxyCᵳ₄alkyl and Rn-Cᵳ₄alkyl.

In another embodiment, the invention relates to the compounds of formula I wherein:

Rᵳ₁ represents hydrogen or -CN, preferably -CN;
R₂ represents hydrogen or C₁₄alkyl, preferably hydrogen, methyl or ethyl;
R₃ represents Cy₃;
Cy₃ represents a group of formula Cy₃ᵃ or Cy₃ᵇ; wherein Ri₂ᵃ represents -COR₁₅;

wherein additionally Cy₃ᵃ and Cy₃ᵇ are independently optionally substituted with one or more Ri₂ groups independently selected from Cᵳ₄alkyl, haloCᵳ₄alkyl, hydroxyCᵳ₄alkyl and Rn-Cᵳ₄alkyl;
Rᵳ₄ represents hydrogen; and
Rᵳ₅ represents Cᵳ₄alkyl or cyanoCᵳ₄alkyl, preferably cyanomethyl.

In another embodiment, the invention relates to the compounds of formula I wherein:

Rᵳ₁ represents hydrogen or -CN;
R₂ represents hydrogen or C₁₄alkyl, preferably hydrogen, methyl or ethyl;
R₃ represents Cy₃;
Cy₃ represents a group of formula Cy₃ᵃ or Cy₃ᵇ; wherein Ri₂ᵃ represents -COR₁₅.

In another embodiment, the invention relates to the compounds of formula I wherein:

Rᵳ₁ represents -CN;
R₂ represents hydrogen or C₁₄alkyl, preferably hydrogen, methyl or ethyl;
R₃ represents Cy₃;
Cy₃ represents a group of formula Cy₃ᵃ or Cy₃ᵇ; wherein Ri₂ᵃ represents -COR₁₅.

In another embodiment, the invention relates to the compounds of formula I wherein:

Rᵳ₁ represents hydrogen or -CN;
R₂ represents hydrogen or C₁₄alkyl, preferably hydrogen, methyl or ethyl;
R₃ represents Cy₃;
Cy₃ represents a group of formula Cy₃a or Cy₃b; wherein R₁₂a represents 
-COR₁₅;
Rᵢ₄ represents hydrogen; and
Rᵢ₅ represents Cᵢ₄alkyl or cyanoCᵢ₄alkyl, preferably cyanomethyl.

In another embodiment, the invention relates to the compounds of formula I

wherein:
Rᵢ represents -CN;
R₂ represents hydrogen or Cᵢ₄alkyl, preferably hydrogen, methyl or ethyl;
R₃ represents Cy₃;

Cy₃ represents a group of formula Cy₃a or Cy₃b; wherein R₁₂a represents 
-COR₁₅;
Rᵢ₄ represents hydrogen; and
Rᵢ₅ represents Cᵢ₄alkyl or cyanoCᵢ₄alkyl, preferably cyanomethyl.

In another embodiment, the invention relates to the compounds of formula I

wherein:
Rᵢ represents hydrogen or -CN, preferably -CN;
R₂ represents hydrogen, Cᵢ₄alkyl, haloCᵢ₄alkyl, hydroxyCᵢ₄alkyl, or R₇-Cᵢ₄alkyl;
R₃ represents Cy₃;

Cy₃ represents a group of formula Cy₃a; wherein R₁₂a represents 
-CORᵢ₄ᵢ₄, -CORᵢ₅ᵢ₅, -CO₂ᵢ₅ᵢ₅, -SO₂ᵢ₅ᵢ₅, -SO₂ᵢ₅ᵢ₄ᵢ₄ᵣᵣᵣᵣ or Cy₅, wherein Cy₅ is 
only optionally substituted with one or more Rᵢ₃; and

wherein additionally Cy₃a is optionally substituted with one or more Rᵢ₂.

In another embodiment, the invention relates to the compounds of formula I

wherein:
Rᵢ represents hydrogen or -CN;
R₂ represents hydrogen or Cᵢ₄alkyl, preferably hydrogen, methyl or ethyl;
R₃ represents Cy₃;

Cy₃ represents a group of formula Cy₃a; wherein R₁₂a represents 
-CORᵢ₄ᵣᵣᵣᵣ, -CORᵢ₅ᵢ₅, -CO₂ᵢ₅ᵢ₅, -SO₂ᵢ₅ᵢ₅, -SO₂ᵢ₅ᵣᵣᵣᵣᵣᵣᵣᵣᵣᵣᵣᵣᵣᵣ or Cy₅, wherein Cy₅ is 
only optionally substituted with one or more Rᵢ₃; and

wherein additionally Cy₃a is optionally substituted with one or more Rᵢ₂.
wherein:

- **R\textsubscript{i}** represents -CN;
- **R\textsubscript{2}** represents hydrogen or C\textsubscript{\small{1-4}} alkyl, preferably hydrogen, methyl or ethyl;
- **R\textsubscript{3}** represents Cy\textsubscript{3};

- Cy\textsubscript{3} represents a group of formula Cy\textsubscript{3a}; wherein R\textsubscript{2a} represents -CONR\textsubscript{14}R\textsubscript{14}, -COR\textsubscript{15}, -CO\textsubscript{2}R\textsubscript{15}, -SO\textsubscript{2}R\textsubscript{15}, -SO\textsubscript{2}NR\textsubscript{14}R\textsubscript{14} or Cy\textsubscript{5}, wherein Cy\textsubscript{5} is optionally substituted with one or more R\textsubscript{13}; and

- wherein additionally Cy\textsubscript{3a} is optionally substituted with one or more R\textsubscript{12}.

In another embodiment, the invention relates to the compounds of formula I wherein:

- **R\textsubscript{1}** represents hydrogen or -CN, preferably -CN;
- **R\textsubscript{2}** represents hydrogen, C\textsubscript{\small{1-4}} alkyl, haloC\textsubscript{\small{1-4}} alkyl, hydroxyC\textsubscript{\small{1-4}} alkyl, or R\textsubscript{7}-C\textsubscript{\small{1-4}} alkyl;
- **R\textsubscript{3}** represents Cy\textsubscript{3};

- Cy\textsubscript{3} represents a group of formula Cy\textsubscript{3a}; wherein R\textsubscript{2a} represents -CONR\textsubscript{14}R\textsubscript{14}, -COR\textsubscript{15}, -CO\textsubscript{2}R\textsubscript{15}, -SO\textsubscript{2}R\textsubscript{15}, -SO\textsubscript{2}NR\textsubscript{14}R\textsubscript{14} or Cy\textsubscript{5}, wherein Cy\textsubscript{5} is optionally substituted with one or more R\textsubscript{13}; and

- wherein additionally Cy\textsubscript{3a} is optionally substituted with one or more R\textsubscript{12} groups independently selected from C\textsubscript{\small{1-4}} alkyl, haloC\textsubscript{\small{1-4}} alkyl, hyd TOxyC\textsubscript{\small{1-4}} alkyl and R\textsubscript{11}-C\textsubscript{\small{1-4}} alkyl.

In another embodiment, the invention relates to the compounds of formula I wherein:

- **R\textsubscript{1}** represents hydrogen or -CN;
- **R\textsubscript{2}** represents hydrogen or C\textsubscript{\small{1-4}} alkyl, preferably hydrogen, methyl or ethyl;
- **R\textsubscript{3}** represents Cy\textsubscript{3};

- Cy\textsubscript{3} represents a group of formula Cy\textsubscript{3a}; wherein R\textsubscript{2a} represents -CONR\textsubscript{14}R\textsubscript{14}, -COR\textsubscript{15}, -CO\textsubscript{2}R\textsubscript{15}, -SO\textsubscript{2}R\textsubscript{15}, -SO\textsubscript{2}NR\textsubscript{14}R\textsubscript{14} or Cy\textsubscript{5}, wherein Cy\textsubscript{5} is optionally substituted with one or more R\textsubscript{13}; and

- wherein additionally Cy\textsubscript{3a} is optionally substituted with one or more R\textsubscript{12} groups independently selected from C\textsubscript{\small{1-4}} alkyl, haloC\textsubscript{\small{1-4}} alkyl, hyd TOxyC\textsubscript{\small{1-4}} alkyl and R\textsubscript{11}-C\textsubscript{\small{1-4}} alkyl.

In another embodiment, the invention relates to the compounds of formula I wherein:
R_i represents -CN;
R_2 represents hydrogen or C_{1-4} alkyl, preferably hydrogen, methyl or ethyl;
R_3 represents Cy_3;
Cy_3 represents a group of formula Cy_{3a}; wherein R_{i2a} represents

-CONR_{14}R_{14}, -COR_{15}, -CO_{2}R_{15}, -SO_{2}R_{15}, -SO_{2}NR_{14}R_{14} or Cy_5, wherein Cy_5 is optionally substituted with one or more R_{13}; and

wherein additionally Cy_{3a} is optionally substituted with one or more R_{i12} groups independently selected from C_{1-4}alkyl, haloC_{1-4}alkyl, hydTOxyc_{1-4}alkyl and R_{11}-C_{1-4}alkyl.

In another embodiment, the invention relates to the compounds of formula I wherein:

R_1 represents hydrogen or -CN, preferably -CN;
R_2 represents hydrogen, C_{1-4} alkyl, haloC_{1-4}alkyl, hydroxyC_{1-4}alkyl or R_7C_{1-4}alkyl;
R_3 represents Cy_3;
Cy_3 represents a group of formula Cy_{3a}; wherein R_{i12a} represents -COR_{15}; and

wherein additionally Cy_{3a} is optionally substituted with one or more R_{i12}.

In another embodiment, the invention relates to the compounds of formula I wherein:

R_1 represents hydrogen or -CN, preferably -CN;
R_2 represents hydrogen, C_{1-4} alkyl, haloC_{1-4}alkyl, hydroxyC_{1-4}alkyl, or R_7C_{1-4}alkyl;
R_3 represents Cy_3;
Cy_3 represents a group of formula Cy_{3a}; wherein R_{i12a} represents -COR_{15}; and

wherein additionally Cy_{3a} is optionally substituted with one or more R_{i12} groups independently selected from C_{1-4}alkyl, haloC_{1-4}alkyl, hydTOxyc_{1-4}alkyl and R_{11}-C_{1-4}alkyl.

In another embodiment, the invention relates to the compounds of formula I wherein:

R_1 represents hydrogen or -CN;
R_2 represents hydrogen or C_{1-4} alkyl, preferably hydrogen, methyl or ethyl;
R₃ represents Cᵧ₃;
Cᵧ₃ represents a group of formula Cᵧ₃a; wherein R₁₂a represents -CORᵢ₅;
and
wherein additionally Cᵧ₃a is optionally substituted with one or more Rᵢ₂.

In another embodiment, the invention relates to the compounds of formula I wherein:
Rᵢ represents -CN;
R₂ represents hydrogen or Ci₋₄alkyl, preferably hydrogen, methyl or ethyl;
R₃ represents Cᵧ₃;
Cᵧ₃ represents a group of formula Cᵧ₃a; wherein Rᵢ₂a represents -CORᵢ₅;
and
wherein additionally Cᵧ₃a is optionally substituted with one or more Rᵢ₂.

In another embodiment, the invention relates to the compounds of formula I wherein:
Rᵢ represents hydrogen or -CN;
R₂ represents hydrogen or Ci₋₄alkyl, preferably hydrogen, methyl or ethyl;
R₃ represents Cᵧ₃;
Cᵧ₃ represents a group of formula Cᵧ₃a; wherein Rᵢ₂a represents -CORᵢ₅;
and
wherein additionally Cᵧ₃a is optionally substituted with one or more Rᵢ₂ groups independently selected from Ci₋₄alkyl, haloCi₋₄alkyl, hydroxyCi₋₄alkyl and Rn-Ci₋₄alkyl.

In another embodiment, the invention relates to the compounds of formula I wherein:
Rᵢ represents -CN;
R₂ represents hydrogen or C₁₋₄alkyl, preferably hydrogen, methyl or ethyl;
R₃ represents Cᵧ₃;
Cᵧ₃ represents a group of formula Cᵧ₃a; wherein Rᵢ₂a represents -CORᵢ₅;
and
wherein additionally Cᵧ₃a is optionally substituted with one or more Rᵢ₂ groups independently selected from Ci₋₄alkyl, haloCi₋₄alkyl, hydroxyCi₋₄alkyl and Rn-Ci₋₄alkyl.
wherein:
R\textsubscript{i} represents hydrogen or -CN, preferably -CN;
R\textsubscript{2} represents hydrogen, C\textsubscript{i-4}alkyl, haloC\textsubscript{i-4}alkyl, hydroxyC\textsubscript{i-4}alkyl, or R\textsubscript{7}-C\textsubscript{i-4}alkyl;
R\textsubscript{3} represents Cy\textsubscript{3};
Cy\textsubscript{3} represents a group of formula Cy\textsubscript{3a}; wherein R\textsubscript{i2a} represents -COR\textsubscript{i5}; whereby additionally Cy\textsubscript{3a} is optionally substituted with one or more R\textsubscript{i2} groups independently selected from C\textsubscript{i-4}alkyl, haloC\textsubscript{i-4}alkyl, hydroxyC\textsubscript{i-4}alkyl and Rn-C\textsubscript{i-4}alkyl; and
R\textsubscript{i5} represents C\textsubscript{i-4}alkyl or cyanoC\textsubscript{i-4}alkyl, preferably cyanomethyl.
In another embodiment, the invention relates to the compounds of formula I

wherein:
R\textsubscript{i} represents hydrogen or -CN, preferably -CN;
R\textsubscript{2} represents hydrogen, C\textsubscript{i-4}alkyl, preferably hydrogen, methyl or ethyl;
R\textsubscript{3} represents Cy\textsubscript{3};
Cy\textsubscript{3} represents a group of formula Cy\textsubscript{3a}; wherein R\textsubscript{i2a} represents -COR\textsubscript{i5}; whereby additionally Cy\textsubscript{3a} is optionally substituted with one or more R\textsubscript{i2} groups independently selected from C\textsubscript{i-4}alkyl, haloC\textsubscript{i-4}alkyl, hydroxyC\textsubscript{i-4}alkyl and Rn-C\textsubscript{i-4}alkyl; and
R\textsubscript{i5} represents C\textsubscript{i-4}alkyl or cyanoC\textsubscript{i-4}alkyl, preferably cyanomethyl.
In another embodiment, the invention relates to the compounds of formula I

wherein:
R\textsubscript{i} represents -CN;
R\textsubscript{2} represents hydrogen or C\textsubscript{i-4}alkyl, preferably hydrogen, methyl or ethyl;
R\textsubscript{3} represents Cy\textsubscript{3};
Cy\textsubscript{3} represents a group of formula Cy\textsubscript{3a}; wherein R\textsubscript{i2a} represents -COR\textsubscript{i5}; whereby additionally Cy\textsubscript{3a} is optionally substituted with one or more R\textsubscript{i2} groups independently selected from C\textsubscript{i-4}alkyl, haloC\textsubscript{i-4}alkyl, hydroxyC\textsubscript{i-4}alkyl and Rn-C\textsubscript{i-4}alkyl; and
R\textsubscript{i5} represents C\textsubscript{i-4}alkyl or cyanoC\textsubscript{i-4}alkyl, preferably cyanomethyl.
In another embodiment, the invention relates to the compounds of formula I
wherein additionally Cy\textsubscript{3a} is optionally substituted with one or more Ri\textsubscript{2}; and

R\textsubscript{i5} represents Ci\textsubscript{-4}alkyl or cyanoCi\textsubscript{-4}alkyl, preferably cyanomethyl.

In another embodiment, the invention relates to the compounds of formula I

wherein:

5   Ri represents hydrogen or -CN;
R\textsubscript{2} represents hydrogen or C\textsubscript{1-4}alkyl, preferably hydrogen, methyl or ethyl;
R\textsubscript{3} represents Cy\textsubscript{3};
Cy\textsubscript{3} represents a group of formula Cy\textsubscript{3a}, wherein R\textsubscript{i2a} represents -COR\textsubscript{i5};

wherein additionally Cy\textsubscript{3a} is optionally substituted with one or more Ri\textsubscript{2} groups independently selected from Ci\textsubscript{-4}alkyl, haloCi\textsubscript{-4}alkyl, hydroxyCi\textsubscript{-4}alkyl and Rn-Ci\textsubscript{-4}alkyl; and

Ri\textsubscript{5} represents Ci\textsubscript{-4}alkyl or cyanoCi\textsubscript{-4}alkyl, preferably cyanomethyl.

In another embodiment, the invention relates to the compounds of formula I

wherein:

15  Ri represents -CN;
R\textsubscript{2} represents hydrogen or C\textsubscript{1-4}alkyl, preferably hydrogen, methyl or ethyl;
R\textsubscript{3} represents Cy\textsubscript{3};
Cy\textsubscript{3} represents a group of formula Cy\textsubscript{3a}, wherein R\textsubscript{i2a} represents -COR\textsubscript{i5};

wherein additionally Cy\textsubscript{3a} is optionally substituted with one or more Ri\textsubscript{2} groups independently selected from Ci\textsubscript{-4}alkyl, haloCi\textsubscript{-4}alkyl, hydroxyCi\textsubscript{-4}alkyl and Rii-Ci\textsubscript{-4}alkyl; and

Ri\textsubscript{5} represents Ci\textsubscript{-4}alkyl or cyanoCi\textsubscript{-4}alkyl, preferably cyanomethyl.

In another embodiment, the invention relates to the compounds of formula I

wherein:

25  Ri represents hydrogen or -CN;
R\textsubscript{2} represents hydrogen or C\textsubscript{1-4}alkyl, preferably hydrogen, methyl or ethyl;
R\textsubscript{3} represents Cy\textsubscript{3}; and
Cy\textsubscript{3} represents a group of formula Cy\textsubscript{3a}, wherein R\textsubscript{i2a} represents -COR\textsubscript{i5}.

In another embodiment, the invention relates to the compounds of formula I

wherein:

30  Ri represents -CN;
R\textsubscript{2} represents hydrogen or C\textsubscript{1-4}alkyl, preferably hydrogen, methyl or ethyl;
R\textsubscript{3} represents Cy\textsubscript{3}; and
Cy₃ represents a group of formula Cy₃ₐ; wherein R₁₂ₐ represents -CORᵢ₅.
In another embodiment, the invention relates to the compounds of formula I wherein:

Rᵢ represents hydrogen or -CN;
R₂ represents hydrogen or Ci₄₋₅ alkyl, preferably hydrogen, methyl or ethyl;
R₃ represents Cy₃;
Cy₃ represents a group of formula Cy₃ₐ; wherein R₁₂ₐ represents -CORᵢ₅;
and
Rᵢ₅ represents Ci₄₋₅ alkyl or cyanoCi₄₋₅ alkyl, preferably cyanomethyl.

In another embodiment, the invention relates to the compounds of formula I wherein:

Rᵢ represents hydrogen or -CN;
R₂ represents hydrogen or Ci₄₋₅ alkyl, preferably hydrogen, methyl or ethyl;
R₃ represents Cy₃; and
Cy₃ represents a group of formula Cy₃ₐ; wherein R₁₂ₐ represents -CORᵢ₅;
and
Rᵢ₅ represents Ci₄₋₅ alkyl or cyanoCi₄₋₅ alkyl, preferably cyanomethyl.

In another embodiment, the invention relates to the compounds of formula I wherein:

Rᵢ represents hydrogen or -CN;
R₂ represents hydrogen or Ci₄₋₅ alkyl, preferably hydrogen, methyl or ethyl;
R₃ represents Cy₃; and
Cy₃ represents a group of formula Cy₃ₐ.
In another embodiment, the invention relates to the compounds of formula I wherein:

Rᵢ represents hydrogen or -CN;
R₂ represents hydrogen or Ci₄₋₅ alkyl, preferably hydrogen, methyl or ethyl;
R₃ represents Cy₃; and
Cy₃ represents a group of formula Cy₃ₐ;
R$_3$ represents Cy$_3$;
Cy$_3$ represents a group of formula Cy$_{3b}$; and
R$_i$$_4$ represents hydrogen.

In another embodiment, the invention relates to the compounds of formula I wherein:

R$_i$ represents -CN;
R$_2$ represents hydrogen or C$_i$-$4$ alkyl, preferably hydrogen, methyl or ethyl;
R$_3$ represents Cy$_3$;
Cy$_3$ represents a group of formula Cy$_{3b}$; and
R$_i$$_4$ represents hydrogen.

Furthermore, the present invention covers all possible combinations of the particular and preferred embodiments described above.

In another embodiment, the invention relates to a compound of formula I or a salt thereof selected from the list of compounds described in the examples 1 to 16.

In another embodiment, the invention relates to a compound of formula I selected from:

$^\text{trans}$-5-cyano-3-[6-(4-hydroxycyclohexylamino)pyridin-2-yl]pyrazolo[1,5-a]pyridine,
$^\text{trans}$-5-cyano-3-[6-(4-hydroxycyclohexyl-$\Lambda$-methylamino)pyridin-2-yl]pyrazolo[1,5-a]pyridine,
$\text{trans}$-5-cyano-3-[6-(4-hydroxycyclohexylamino)pyridin-2-yl]pyrazolo[1,5-a]pyridine,
5-cyano-3-[6-(4-hydroxycyclohexylamino)pyridin-2-yl]pyrazolo[1,5-a]pyridine,
5-cyano-3-[6-(4-hydroxycyclohexyl-$\Lambda$-amino)pyridin-2-yl]pyrazolo[1,5-a]pyridine,

(1R,2R)-5-cyano-3-[6-(1-(2-cyanoacetyl)piperidin-3-ylamino)pyridin-2-yl]pyrazolo[1,5-a]pyridine,

(1R,2R)-5-cyano-3-[6-(1-(2-cyanoacetyl)piperidin-3-ylamino)pyridin-2-yl]pyrazolo[1,5-a]pyridine,

or a salt thereof.

In another embodiment, the invention relates to a compound of formula I selected from:
^rans-5-cyano-3-[6-(4-hydroxycyclohexyl-N-methylamino)pyridin-2-yl]pyrazolo[1,5-a]pyridine,
^rans-5-cyano-3-[6-(N-ethyl-N-(4-hydroxycyclohexyl)amino)pyridin-2-yl]pyrazolo[1,5-a]pyridine,
5-cyano-3-[6-(1-(2-cyanoacetyl)piperidin-3-ylamino)pyridin-2-yl]pyrazolo[1,5-a]pyridine,
(/?)^-5-cyano-3-[6-(1 -(2-cyanoacetyl)piperidin-3-ylamino)pyridin-2-yl]pyrazolo[1,5-a]pyridine, and
(/?)^-5-cyano-3-[6-( \Lambda\text{-methyl-1} -(2-cyanoacetyl)piperidin-3-ylamino)pyridin-2-yl]pyrazolo[1,5-a]pyridine,
or a salt thereof.

In another embodiment, the invention relates to a compound of formula 1, which provides more than 50% inhibition of JAK3 activity at 10 \( \mu \text{M} \), more preferably at 1 \( \mu \text{M} \) and still more preferably at 0.1 \( \mu \text{M} \), in a JAK3 assay such as the one described in example 17.

In an additional embodiment, the invention relates to a compound of formula 1, which provides more than 50% inhibition of JAK2 activity at 10 \( \mu \text{M} \), more preferably at 1 \( \mu \text{M} \), and still more preferably at 0.5 \( \mu \text{M} \), in a JAK2 assay such as the one described in example 18.

The compounds of the present invention contain one or more basic nitrogens and may, therefore, form salts with organic or inorganic acids. Examples of these salts include: salts with inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, nitric acid, perchloric acid, sulfuric acid or phosphoric acid; and salts with organic acids such as methanesulfonic acid, thfluoromethanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, fumaric acid, oxalic acid, acetic acid, maleic acid, ascorbic acid, citric acid, lactic acid, tartaric acid, malonic acid, glycolic acid, succinic acid and propionic acid, among others. Some of the compounds of the present invention may contain one or more acidic protons and, therefore, they may also form salts with bases. Examples of these salts include: salts with inorganic cations such as sodium, potassium, calcium, magnesium, lithium, aluminium, zinc, etc; and salts formed with pharmaceutically acceptable amines such as ammonia, alkylamines, hydroxylalkylamines, lysine, arginine, \( \Lambda\text{-methylglucamine}, \) procaine
and the like.

There is no limitation on the type of salt that can be used, provided that these are pharmaceutically acceptable when they are used for therapeutic purposes. The term pharmaceutically acceptable salt represents those salts which are, according to medical judgment, suitable for use in contact with the tissues of humans and other mammals without undue toxicity, irritation, allergic response and the like. Pharmaceutically acceptable salts are well known in the art.

The salts of a compound of formula I can be obtained during the final isolation and purification of the compounds of the invention or can be prepared by treating a compound of formula I with a sufficient amount of the desired acid or base to give the salt in the conventional manner. The salts of the compounds of formula I can be converted into other salts of the compounds of formula I by ion exchange using ionic exchange resins.

The compounds of formula I and their salts may differ in some physical properties but they are equivalent for the purposes of the present invention. All salts of the compounds of formula I are included within the scope of the invention.

The compounds of the present invention may form complexes with solvents in which they are reacted or from which they are precipitated or crystallized. These complexes are known as solvates. As used herein, the term solvate refers to a complex of variable stoichiometry formed by a solute (a compound of formula I or a salt thereof) and a solvent. Examples of solvents include pharmaceutically acceptable solvents such as water, ethanol and the like. A complex with water is known as a hydrate. Solvates of compounds of the invention (or salts thereof), including hydrates, are included within the scope of the invention.

The compounds of formula I may exist in different physical forms, i.e. amorphous and crystalline forms. Moreover, the compounds of the invention may have the ability to crystallize in more than one form, a characteristic which is known as polymorphism. Polymorphs can be distinguished by various physical properties well known in the art such as X-ray diffraction pattern, melting point or solubility. All physical forms of the compounds of formula I, including all polymorphic forms ("polymorphs") thereof, are included within the scope of the invention.

Some of the compounds of the present invention may exist as several
diastereoisomers and/or several optical isomers. Diastereoisomers can be separated by conventional techniques such as chromatography or fractional crystallization. Optical isomers can be resolved by conventional techniques of optical resolution to give optically pure isomers. This resolution can be carried out on any chiral synthetic intermediate or on products of formula I. Optically pure isomers can also be individually obtained using enantiospecific synthesis. The present invention covers all individual isomers as well as mixtures thereof (for example racemic mixtures or mixtures of diastereomers), whether obtained by synthesis or by physically mixing them.

The compounds of formula I can be obtained by following the processes described below. As it will be obvious to one skilled in the art, the exact method used to prepare a given compound may vary depending on its chemical structure. Moreover, in some of the processes described below it may be necessary or advisable to protect the reactive or labile groups with conventional protecting groups. Both the nature of these protecting groups and the procedures for their introduction and removal are well known in the art (see for example Greene T.W. and Wuts P.G.M, "Protecting Groups in Organic Synthesis", John Wiley & Sons, 3rd edition, 1999). As an example, as protecting group of an amino function the tert-butoxycarbonyl (BOC) group can be used. Whenever a protecting group is present, a later deprotection step will be required, which can be performed under standard conditions in organic synthesis, such as those described in the above-mentioned reference.

Unless otherwise stated, in the methods described below the meanings of the different substituents are the meanings described above with regard to a compound of formula I.

In general, compounds of formula I can be obtained by the method described in Scheme 1:
Scheme 1

wherein R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub> have the meaning previously described in relation with a compound of formula I; X represents halogen; and A represents iodine, 2,4-dinitrophenolate, p-toluensulphonate or 2,4,6-trimethylbencenosulphonate.

Step a may be carried out by the reaction of a compound of formula II with aminosulfonic acid in the presence of a H<sub>2</sub>SO<sub>4</sub> aqueous solution; and of a base such as K<sub>2</sub>CO<sub>3</sub>, NaOH or KOH; in a solvent such as dichloromethane, tetrahydrofurane, water, ethanol, methanol, isopropanol or acetonithle; and heating preferably at reflux to obtain a compound of formula III.

Alternatively, step a may be carried out by the reaction of a compound of formula II with 2,4-dinitrophenylhydroxylamine, o-(p-toluensulfonyl)hydroxylamine, or o-(mesitylsulfonyl)hydroxylamine (obtained in situ from methyl N-mesitylsulfonyloxyacetimidate in the presence of a 70% HClO<sub>4</sub> aqueous solution; in a solvent such as dioxane; and cooling preferably at -5 °C); in the presence of a solvent such as dichloromethane; and heating preferably from 0 °C to room temperature to obtain a compound of formula III.
In step b the reaction of a compound of formula III with ethyl propiolate may be carried out under \( \text{O}_2 \) atmosphere; in the presence of a base such as \( \text{K}_2\text{CO}_3 \), NaOH or KOH; in a solvent such as N,N-dimethylformamide, dimethylsulfoxide, dichloromethane or toluene; and at room temperature to obtain a compound of formula IV.

Step c may be carried out by the reaction of a compound of formula IV with an acid such as \( \text{H}_2\text{SO}_4 \), polyphosphoric acid, HCl, HBr, or HI and water in 1:1 proportion, heating preferably between 120 °C and 50 °C to obtain a compound of formula V.

Step d may be carried out by the reaction of a compound of formula V with N-bromosuccinimide (NBS) in the presence of benzoyl peroxide or azobisisobutyronitrile (AIBN); and of a solvent such as dichloromethane or carbon tetrachloride; and at room temperature to obtain a compound of formula VI.

In step e the reaction between a compound of formula VI with a compound of formula VII may be carried out using the conditions described in the literature for Suzuki’s coupling reactions. For example, the reaction may be carried out in the presence of a Pd catalyst such as \( \text{Pd(PPh}_3\text{)}_4 \); in the presence of a base such as \( \text{K}_2\text{CO}_3 \); in a mixture of solvents such as a dimethoxyethane and water; and heating preferably at 85 °C to obtain a compound of formula VIII.

When \( \text{X} \) represents fluorine, step f may be carried out by the reaction of a compound of formula VIII with an amine of formula IX in the presence of a base such as diisopropylethylamine, thetylamine or \( \text{K}_2\text{CO}_3 \), in a solvent such as N-methylpyrrolidone, N,N-dimethylformamide, dimethylsulfoxide, dimethylamide or pyridine, and heating preferably at 190 °C to obtain a compound of formula I.

When \( \text{X} \) represents chlorine, bromine or iodine, step f may be carried out by the reaction of a compound of formula VIII with an amine of formula IX using the conditions described in the literature for Buchwald’s coupling reactions. For example, the reaction may be carried out in the presence of a Pd catalyst such as \( \text{Pd}_2(\text{dba})_3 \), and of a phosphine such as 2-dicyclohexylphosphino-2',4',6'-trisopropyl-biphenyl (X-Phos®), in the presence of a base such as \( \text{K}_2\text{CO}_3 \), in a solvent such as ethyl-butanol, and heating preferably at 100 °C to obtain a compound of formula I.
Alternatively, a compound of formula VIII can be obtained by the method described in Scheme 2:

\[
\begin{align*}
X & \quad \xrightarrow{a} \quad \text{XI} \\
& \quad \text{III} \quad \xrightarrow{b} \quad \text{VIII}
\end{align*}
\]

Scheme 2

wherein \( R_1 \) has the meaning previously described in relation with a compound of formula I; \( X \) represents halogen; and \( A \) represents iodine, 2,4-dinitrophenolate, \( p \)-toluensulphonate or 2,4,6-thmethylbencenosulphonate.

In step a of scheme 2 the reaction of a compound of formula \( X \) with \( \text{thmethylsilylacetilene} \) may be carried out using the conditions described in the literature for Sonogashira’s coupling reactions. For example, the reaction may be carried out in the presence of a Pd catalyst such as \( \text{Pd(PPh}_3\text{)}_4 \), of \( \text{CuI} \), and of a base such as isopropylamine, and at room temperature to obtain a compound of formula XI after the \( \text{thmethylsilyl} \) group deprotection in the conditions described in the literature for deprotection reactions of silyl groups.

In step b the reaction of a compound of formula XI with a compound of formula III may be carried out in the presence of a base such as 1,8-diazabicyclo[5.4.0]undec-7-ene, \( \text{K}_2\text{CO}_3 \), diisopropylethylamine, thethylamine, \( \text{KOH} \), \( \text{Cs}_2\text{CO}_3 \), potassium tert-butoxide in a solvent such as acetonithle, tetrahydrofuran, \( \text{N-methylpyrrolidone} \), \( \text{N,N-dimethylformamide} \), ethanol or dimethylsulfoxide, at room temperature or heating preferably between 40 \( ^\circ \)C and 80 \( ^\circ \)C to obtain a compound of formula VIII.

Alternatively, a compound of formula I can be obtained by the method described in Scheme 3:

\[
\begin{align*}
\text{VIII} & \quad \xrightarrow{a} \quad \text{XII} \\
& \quad \text{b} \quad \text{I}
\end{align*}
\]

Scheme 3
wherein R₁, R₂ and R₃ have the meaning previously described in relation with a compound of formula I; and X represents halogen.

In step a of scheme 3 the reaction of a compound of formula VIII with diphenylmethanimine may be carried out using the conditions described in the literature for Buchwald’s coupling reactions. For example, the reaction may be carried out in the presence of a Pd catalyst such Pd₂(db₃)a₃; of a phosphine such as 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP); and of a base such as sodium tert-butoxide; in a solvent such as toluene; and heating preferably at reflux to obtain, after an acidic hydrolysis step in the presence of an acid such as HCl, an amine of formula XII.

Finally, in step b an amine of formula XII is converted into a compound of formula I in one or several steps using conversion reactions of amino groups well-known in organic chemistry under the standard experimental conditions. For a compound of formula I wherein R₂ is different than hydrogen, step b should be carried out two times. Said transformations include, for example:

- the substitution of a primary or secondary amine by treatment with an alkylating agent under standard conditions, or by reductive amination, i.e. by treatment with an aldehyde or a ketone in the presence of a reducing agent such as sodium cyanoborohydride or sodium thacetoxyborohydride;
- the conversion of an amine into a sulfonamide by reaction with a sulfonyl halide, such as sulfonyl chloride, optionally in the presence of catalytic amounts of a base such as 4-dimethylaminopyridine, in a suitable solvent such as dioxane, chloroform, dichloromethane or pyridine, optionally in the presence of a base such as thethylamine or pyridine;
- the conversion of an amine into an amide, carbamate or urea under standard conditions.

Furthermore, some compounds of the present invention can also be obtained from other compounds of formula I by appropriate conversion reactions of functional groups in one or several steps, using well-known reactions in organic chemistry under the standard experimental conditions. Said transformations can be carried out upon R₁, R₂ or R₃ groups and include, for example:

- the reduction of a nitro group to give an amino group, for example by treatment with hydrogen, hydrazine or formic acid in the presence of a suitable
catalyst such as Pd/C; or by treatment with sodium borohydride in the presence of NiCl₂, or SnCl₂;
the substitution of a primary or secondary amine by treatment with an alkylation agent under standard conditions, or by reductive amination, i.e. by treatment with an aldehyde or a ketone in the presence of a reducing agent such as sodium cyanoborohydride or sodium thacetoxyborohydride;
the conversion of an amine into a sulfonamide by reaction with a sulfonyl halide, such as sulfonyl chloride, optionally in the presence of catalytic amounts of a base such as 4-dimethylaminopyridine, in a suitable solvent such as dioxane, chloroform, dichloromethane or pyridine, optionally in the presence of a base such as thethylamine or pyridine;
the conversion of an amine into an amide, carbamate or urea under standard conditions;
the alkylation of an amide by treatment with an alkylation agent under basic conditions;
the conversion of an alcohol into an ether, ester or carbamate under standard conditions;
the partial or total oxidation of an alcohol to give ketones, aldehydes or carboxylic acids under standard oxidizing conditions;
the reduction of an aldehyde or a ketone to an alcohol by treatment with a reducing agent such as sodium borohydride;
the reduction of a carboxylic acid or a carboxylic acid derivative to an alcohol by treatment with a reducing agent such as diisobutylaluminium hydride or LiAlH₄;
the conversion of an alcohol into a halogen by reaction with SOCl₂, PBr₃, tetrabutylammonium bromide in the presence of P₂O₅ or PI₃;
the conversion of a halogen atom into an amine by reaction with an amine, optionally in the presence of a suitable solvent, and preferably heating;
the conversion of a primary amide into a -CN group or vice versa, under standard conditions.
Likewise, any of the aromatic rings of the compounds of the present invention can undergo electrophilic aromatic substitution reactions or nucleophilic aromatic substitution reactions, widely described in the literature.
Some of these interconversion reactions are explained in greater detail in the examples.

As it will be obvious to those skilled in the art, these interconversion reactions can be carried out upon the compounds of formula I as well as upon any suitable synthesis intermediate thereof.

The compounds of formula II and X are commercially available or can be prepared by well-known methods described in the literature starting from commercially available compounds using interconversion reactions such those described above for a compound of formula I, and can be protected with suitable protecting groups.

As mentioned above, the compounds of the present invention act by inhibiting JAK/STAT signaling pathways, particularly by inhibiting JAK3 activity. Therefore, the compounds of the invention are expected to be useful to treat or prevent diseases in which JAKs, particularly JAK3, play a role in mammals, including human beings. These diseases include, but are not limited to, transplant rejection; immune, autoimmune and inflammatory diseases; neurodegenerative diseases; and proliferative disorders (see e.g. O'Shea J.J. et al, Nat. Rev. Drug. Discov. 2004, 3(7):555-64; Cetkovic-Cvrlje M. et al, Curr. Pharm. Des. 2004, 10(1 5):1 767-84; Cetkovic-Cvrlje M. et al, Arch. Immunol. Ther. Exp. (Warsz), 2004, 52(2):69-82).

Acute or chronic transplant rejection reactions that can be treated or prevented with the compounds of the present invention include any kind of cell, tissue or organ xenotransplants or allografts, such as of heart, lung, liver, kidney, pancreas, uterus, joints, pancreatic islets, bone marrow, limbs, cornea, skin, hepatocytes, pancreatic beta cells, pluripotential cells, neuronal cells and myocardial cells, as well as graft-versus-host reactions (see e.g. Rousvoal G. et al, Transpl. Int. 2006, 19(1 2):1 014-21; Borie DC. et al, Transplantation 2005, 79(7):791 -801 ; Paniagua R. et al, Transplantation 2005, 80(9):1 283-92; Higuchi T. et al, J. Heart Lung Transplant. 2005, 24(1 0):1 557-64; Saemann MD. et al, Transpl Int. 2004, 17(9):481 -89; Silva Jr HT. et al, Drugs 2006, 66(1 3):1 665-1 684).

Immune, autoimmune and inflammatory diseases that can be treated or prevented with the compounds of the present invention include among others, rheumatic diseases (e.g. rheumatoid arthritis and psoriatic arthritis), autoimmune

Neurodegenerative diseases that can be treated or prevented with the compounds of the present invention include, among others, amyotrophic lateral sclerosis and Alzheimer's disease (see e.g. Trieu VN. et al, Biochem. Biophys. Res. Commun. 2000, 267(1):22-5).


It has been found that certain compounds of formula 1, besides inhibiting JAK3 activity, also inhibit JAK2 kinase to varying degrees, and therefore can also

Compounds of formula I that have been found to be particularly useful as JAK2 inhibitors include compounds of examples 1u, 1v, 2p, 9b, 11, 13, 14 and 15. These compounds thus can also be particularly useful, in addition to treating or preventing all the diseases mentioned in the preceding paragraphs, for the treatment or prevention of myeloproliferative disorders (MPD).

Thus, another aspect of the invention relates to a compound of formula I, or a pharmaceutically acceptable salt thereof, and particularly compounds of examples 1u, 1v, 2p, 9b, 11, 13, 14 and 15, for use in the treatment or prevention of a disease mediated by JAK2. More preferably, the disease mediated by JAK2 is a myeloproliferative disorder.

Another aspect of the present invention relates to the use of a compound of formula I, or a pharmaceutically acceptable salt thereof, and particularly compounds of examples 1u, 1v, 2p, 9b, 11, 13, 14 and 15, for the manufacture of a medicament for the treatment or prevention of a disease mediated by JAK2. More preferably, the disease mediated by JAK2 is a myeloproliferative disorder.

Another aspect of the invention relates to a compound of formula I, or a pharmaceutically acceptable salt thereof, and particularly compounds of examples 1u, 1v, 2p, 9b, 11, 13, 14 and 15, for use in the treatment or prevention of a myeloproliferative disorder. In a preferred embodiment, the myeloproliferative disorder is selected from polycythemia vera, essential thrombocytosis, idiopathic myelofibrosis, chronic myelogenous leukemia, hypereosinophilic syndrome, chronic neutrophilic leukemia, chronic myelomonocytic leukemia, myelofibrosis.
with myeloid metaplasia, chronic basophilic leukemia, chronic eosinophilic leukemia, systemic mastocytosis and myelodisplastic syndrome.

Another aspect of the invention relates to the use of a compound of formula I, or a pharmaceutically acceptable salt thereof, and particularly compounds of examples 1u, 1v, 2p, 9b, 11, 13, 14 and 15, for the manufacture of a medicament for the treatment or prevention of a myeloproliferative disorder. In a preferred embodiment, the myeloproliferative disorder is selected from polycythemia vera, essential thrombocytosis, idiopathic myelofibrosis, chronic myelogenous leukemia, hypereosinophilic syndrome, chronic neutrophilic leukemia, chronic myelomonocytic leukemia, myelofibrosis with myeloid metaplasia, chronic basophilic leukemia, chronic eosinophilic leukemia, systemic mastocytosis and myelodysplastic syndrome.

Biological assays that can be used to determine the ability of a compound to inhibit JAKs, particularly JAK3 and JAK2, are well known in the art. For example, a compound to be tested can be incubated in the presence of JAK3 or JAK2 to determine whether inhibition of JAK3 or JAK2 enzymatic activity occurs, as described in the assays of examples 17 and 18, respectively. Other in vitro useful assays that can be used to measure JAK3-inhibitory activity include cellular assays, for example IL-2-induced proliferation of human T lymphocytes. The immunosuppressive activity of the compounds of the invention can be tested using standard in vivo animal models for immune and autoimmune diseases, which are well known in the art. For example, the following assays can be used: delayed-type hypersensitivity (DTH) (see e.g. the method disclosed in Kudlacz E. et al, Am J. Transplant. 2004, 4(1):51-7, the contents of which are incorporated herein by reference), rheumatoid arthritis models such as collagen-induced arthritis (see e.g. the method disclosed in the assay of Holmdahl R et al, APMIS, 1989, 97(7):575-84, the contents of which are incorporated herein by reference), multiple sclerosis models such as experimental autoimmune encephalomyelitis (EAE) (see e.g. the method disclosed in Gonzalez-Rey et al, Am. J. Pathol. 2006, 168(4): 1179-88, the contents of which are incorporated herein by reference) and transplant rejection models (see e.g. the various animal models disclosed in the references listed above in relation to the treatment of transplant rejection, incorporated herein by reference). Biological assays that can be used to determine the toxicity profile of
the compounds of the invention are well known in the art. Several in vitro toxicity assays can be carried on such as a viability panel in different cell lines (e.g. HepG2).

For selecting active compounds against JAK3, testing at 10 µM must result in an activity of more than 50% inhibition of JAK3 activity in the test provided in example 17. More preferably, when tested in this assay compounds should exhibit more than 50% inhibition at 1 µM, and still more preferably, they should exhibit more than 50% inhibition at 0.1 µM.

For selecting active compounds for JAK2, testing at 10 µM must result in an activity of more than 50% inhibition of JAK2 activity in the test provided in example 18. More preferably, when tested in this assay compounds should exhibit more than 50% inhibition at 1 µM, and still more preferably, they should exhibit more than 50% inhibition at 0.5 µM.

The present invention also relates to a pharmaceutical composition that comprises a compound of the present invention (or a pharmaceutically acceptable salt or solvate thereof) and one or more pharmaceutically acceptable excipients. The excipients must be "acceptable" in the sense of being compatible with the other ingredients of the composition and not deleterious to the recipients thereof.

The compounds of the present invention can be administered in the form of any pharmaceutical formulation, the nature of which, as it is well known, will depend upon the nature of the active compound and its route of administration. Any route of administration may be used, for example oral, parenteral, nasal, ocular, rectal and topical administration.

Solid compositions for oral administration include tablets, granulates and capsules. In any case the manufacturing method is based on a simple mixture, dry granulation or wet granulation of the active compound with excipients. These excipients can be, for example, diluents such as lactose, microcrystalline cellulose, mannitol or calcium hydrogenphosphate; binding agents such as for example starch, gelatin or povidone; disintegrants such as sodium carboxymethyl starch or sodium croscarmellose; and lubricating agents such as for example magnesium stearate, stearic acid or talc. Tablets can be additionally coated with suitable excipients by using known techniques with the purpose of delaying their disintegration and absorption in the gastrointestinal tract and thereby provide a
sustained action over a longer period, or simply to improve their organoleptic
properties or their stability. The active compound can also be incorporated by
coating onto inert pellets using natural or synthetic film-coating agents. Soft gelatin
capsules are also possible, in which the active compound is mixed with water or
an oily medium, for example coconut oil, mineral oil or olive oil.

Powders and granulates for the preparation of oral suspensions by the
addition of water can be obtained by mixing the active compound with dispersing
or wetting agents; suspending agents and preservatives. Other excipients can also
be added, for example sweetening, flavoring and colouring agents.

Liquid forms for oral administration include emulsions, solutions,
suspensions, syrups and elixirs containing commonly used inert diluents, such as
purified water, ethanol, sorbitol, glycerol, polyethylene glycols (macrogols) and
propylene glycol. Said compositions can also contain coadjuvants such as wetting,
suspended, sweetening, flavoring agents, preservatives and buffers.

Injectable preparations, according to the present invention, for parenteral
administration, comprise sterile solutions, suspensions or emulsions, in an
aqueous or non-aqueous solvent such as propylene glycol, polyethylene glycol or
vegetable oils. These compositions can also contain coadjuvants, such as wetting,
emulsifying, dispersing agents and preservatives. They may be sterilized by any
known method or prepared as sterile solid compositions, which will be dissolved in
water or any other sterile injectable medium immediately before use. It is also
possible to start from sterile materials and keep them under these conditions
throughout all the manufacturing process.

For the rectal administration, the active compound can be preferably
formulated as a suppository on an oily base, such as for example vegetable oils or
solid semisynthetic glycehdes, or on a hydrophilic base such as polyethylene
glycols (macrogol).

The compounds of the invention can also be formulated for their topical
application for the treatment or prevention of pathologies occurring in zones or
organs accessible through this route, such as eyes, skin and the intestinal tract.
Formulations include creams, lotions, gels, powders, solutions and patches
wherein the compound is dispersed or dissolved in suitable excipients.

For the nasal administration or for inhalation, the compound can be
formulated as an aerosol and it can be conveniently released using suitable propellants.

The dosage and frequency of doses will depend upon the nature and severity of the disease to be treated, the age, the general condition and body weight of the patient, as well as the particular compound administered and the route of administration, among other factors. A representative example of a suitable dosage range is from about 0.01 mg/Kg to about 100 mg/Kg per day, which can be administered as a single or divided doses.

The following examples illustrate the scope of the invention.

Examples

The following abbreviations have been used in the examples:

15 AcN: acetonitrile
   BINAP: 2,2'-bis(diphenylfosfine)-1 ,1'-binaphthyl
   DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene
   DME: 1,2-dimethoxyethane
   DMF: N,N-dimethylformamide
20 EDC: N-[3-(dimethylamino)propyl]-/V-ethylcarbodiimide
   EDIPA: ethyl disopropylamine
   Et₂O: diethyl ether
   EtOAc: ethyl acetate
   EtOH: ethanol
25 HOBT: 1-hydroxybenzotriazole
   HPLC: high performance liquid chromatography
   KOtBu: potassium tert-butoxide
   LC-MS: liquid chromatography-mass spectroscopy
   MeOH: methanol
30 NaOtBu: sodium tert-butoxide
   NMP: N-methylpyrrolidone
   Pd₂(dba)₃: ths(dibenzylideneacetone)dipalladium(0)
   TBAF: tetrabutylammonium fluoride
TEA: triethylamine
THF: tetrahydrofuran
TMSI: 1-(trimethylsilyl)imidazole
t<sub>R</sub>: retention time
X-Phos: 2-dicyclohexylphosphino-2',4',6'-trisopropyl-biphenyl

LC-MS spectra have been performed using the following chromatographic methods:

**Method 1:** Waters Acquity UPLC BEH C<sub>18</sub> Column (1.7 µm, 2.1 x 50 mm), temperature 40 °C, flow rate: 0.5 mL/min, eluent: AcN(A) / Ammonium bicarbonate 10 mM (B), gradient: 0 min 10% A - 3.75 min 90% A.

**Method 2:** YMC Column, 3 µm (50 mm x 4.6), temperature: 30 °C, flow rate: 2.6 mL/min, eluent A = H<sub>2</sub>O (0.1 % HCOOH) B = AcN (0.1 % HCOOH), gradient: 0 min 5% B; 4.8 min 95% B; 6 min 95% B.

## REFERENCE EXAMPLE 1

3-(6-Fluoropyridin-2-yl)pyrazolo[1,5-a]pyridine

To a 3-bromopyrazolo[1,5-a]pyridine (2.40 g, 12.17 mmol) solution in DME (54 mL) under argon atmosphere, 6-fluoro-2-pyridylboronic acid (1.80 g, 12.77 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (1.40 g, 1.21 mmol) and a solution of K<sub>2</sub>CO<sub>3</sub> (3.70 g, 26.8 mmol) in H<sub>2</sub>O (7 mL) were added. The resulting mixture was heated at 85 °C for 5 h, cooled and concentrated to dryness. The crude product obtained was chromatographed over silica gel using hexane/EtOAc mixtures of increasing polarity as eluent, to afford 1.21 g of the desired compound (47% yield).

LC-MS (Method 2): t<sub>R</sub> = 3.00 min; m/z = 214 (MH<sup>+</sup>).

## REFERENCE EXAMPLE 2

2-Ethynyl-6-fluoropyridine

a) 6-Fluoro-2-(trimethylsilyletinyl)pyridine

To a 2-bromo-6-fluoropyridine (5.0 g, 28.4 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (1.64 g, 1.42 mmol),
CuI (0.27 g, 1.42 mmol) and EDIPA (5.3 ml, 36.9 mmol) solution in toluene (115 ml) under argon atmosphere, etinyltrimethylsilane (4.0 ml, 28.4 mmol) was added. The resulting mixture was stirred at room temperature for 18 h. The crude product obtained was filetered over Celite®. The filtated solution was diluted with a saturated aqueous solution of NH₄Cl and extracted three times with CH₂Cl₂. The organic layers were dried over Na₂SO₄ and concentrated to dryness. The crude product obtained was chromatographed over silica gel using hexane/CH₂Cl₂ mixtures of increasing polarity as eluent, to afford 5.28 g of the desired compound (96% yield)

**b) Title compound**

To a solution of the compound obtained in the previous section (5.28 g, 27.3 mmol) in Et₂O (70 ml) at -78 °C, a 1 M solution of TBAF in THF (7.93 ml, 7.93 mmol) was slowly added. The mixture was stirred at -78 °C for 1 h. Then, was diluted with EtOAc and washed three times with H₂O. The organic layer was dried over MgSO₄ and concentrated to dryness. The crude product obtained was chromatographed over silica gel using hexane/CH₂Cl₂ mixtures of increasing polarity as eluent, to afford 2.34 g of the desired compound (70% yield).

LC-MS (Method 2): tᵣ = 2.10 min; m/z = 122 (MH⁺).

Following a similar procedure to that described in reference example 2, but using the corresponding starting material, the following compound was obtained:

<table>
<thead>
<tr>
<th>Reference example</th>
<th>Name of the example</th>
<th>Starting material</th>
<th>HPLC Method</th>
<th>tᵣ (min)</th>
<th>m/z</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>6-Bromo-2-etylnpyridine</td>
<td>2,6-dibromopyridine</td>
<td>2</td>
<td>2.42</td>
<td>182</td>
</tr>
</tbody>
</table>

**REFERENCE EXAMPLE 3**

5-Cyano-3-(6-fluoropyridin-2-yl)pyrazolo[1,5-a]pyridine
a) 1-amino-4-cyanopyridinium 2,4,6-Trimethylbenzosulfonato

To a 4-cyanopyridine (0.72 g, 6.97 mmol) solution in CH₂Cl₂ (10 ml), at 0 °C, a solution of o-2,4,6-trimethylbenzosulfonylhydroxylamine (1.50 g, 6.97 mmol) in CH₂Cl₂ (20 ml) was slowly added. After the addition, the resulting solution was stirred at room temperature for 2 h. Et₂O (320 ml) was added. The precipitated was filtered and dried in a vacuum heater to afford 1.50 g of the desired compound (67% yield).

LC-MS (Method 2): tᵣ = 1.52 min; m/z = 120 (MH⁺).

b) Title compound

To a solution of the compound obtained in the previous section (1.45 g, 4.54 mmol) and the reference example 2 (0.50 g, 4.13 mmol) in AcN (20 ml) at 0 °C, a DBU (1.24 ml, 8.26 mmol) solution in AcN (7 ml) was slowly added. The resulting mixture was heated at 50 °C for 18 h. After that, was cooled and concentrated to dryness. The crude product obtained was chromatographed over silica gel using hexane/EtOAc mixtures of increasing polarity as eluent, to afford 0.48 g of the desired compound (45% yield).

LC-MS (Method 2): tᵣ = 3.03 min; m/z = 239 (MH⁺).

REFERENCE EXAMPLE 4

3-(6-Bromopyridin-2-yl)pyrazolo[1,5-a]pyridine

Following a similar procedure to that described in reference example 3 but using 1-aminopyridinium iodate instead of 1-amino-4-cyanopyridinium 2,4,6-thmethylbenzosulfonate, and the reference example 2a instead of the reference example 2, the desired compound was obtained (49 % yield).

LC-MS (Method 2): tᵣ = 3.45 min; m/z = 274 (MH⁺).

REFERENCE EXAMPLE 5

3-Amino-1-ethoxycarbonylpiperidine

a) 3-(tert-Butoxycarbonylamino)-1-ethoxycarbonylpiperidine
To a 3-te/t-butoxycarbonylaminopiperidine (500 mg, 2.49 mmol) solution in CH₂Cl₂ (15 ml) TEA (1.05 ml, 7.49 mmol) and ethyl chloroformiate (0.48 ml, 4.99 mmol) were added. The resulting mixture was stirred at room temperature for 12 h. After that, was concentrated to dryness, diluted with EtOAc and washed three times with H₂O. The organic layer was dried over Na₂SO₄ and concentrated to dryness, to afford the desired compound in quantitative yield.

b) Title compound

The compound obtained in the previous section and a 4 M solution of HCl in dioxane (8 ml) were mixed in a flask. The resulting mixture was stirred at room temperature for 2 h and concentrated to dryness. The crude product thus obtained was purified over a SCX-2 column, using MeOH/NH₃ mixtures of increasing polarity as eluent, to afford 379 mg of the desired compound (88% yield).

LC-MS (Method 2): tᵣ = 1.35 min; m/z = 173 (MH⁺).

REFERENCE EXAMPLE 6
frans-4-Ethylaminocyclohexanol

To a solution of frans-4-aminocyclohexanol hydrochloride (250 mg, 1.65 mmol) in MeOH (5 ml), a solution of KOH (200 mg, 3.56 mmol) and acetic acid (0.25 ml) in MeOH (5 ml) was added. After that, acetaldehyde (0.13 ml, 2.31 mmol) and NaBH₂CN (176 mg, 2.8 mmol) were added. The resulting mixture was stirred at room temperature for 18 h. After that, was concentrated to dryness and diluted with a 4 M solution of HCl in dioxane (5 ml), the volatile compounds were concentrated to dryness. The crude product obtained was chromatographed was purified over a SCX-2 column, using MeOH/NH₃ mixtures of increasing polarity as eluent, to afford 72 mg of the desired compound (30% yield)

LC-MS (Method 2): tᵣ = 0.535 min; m/z = 144 (MH⁺).

EXAMPLE 1
3-[6-(1-Hydroxymethylcyclopentylamino)pyridin-2-yl]pyrazolo[1,5-a]pyridine
To a solution of the reference example 1 (40 mg, 0.18 mmol) in NMP (1.5 mL), 1-hydroxymethylcyclopentylamine (173 mg, 1.50 mmol) and EDIPA (0.13 mL, 0.75 mmol) were added. The reaction mixture was heated at 190 °C for 6 days. After cooling, was diluted with EtOAc and washed three times with a NaHCO₃ saturated aqueous solution. The organic layer was dried over MgSO₄ and concentrated to dryness. The crude product thus obtained was chromatographed over silica gel using hexane/EtOAc mixtures of increasing polarity as eluent, to afford 30 mg of the title compound (52% yield).

LC-MS (Method 2): \( t_R = 1.77 \) min; \( m/z = 309 \) (MH⁺).

Following a similar procedure to that described in example 1, but using in each case the corresponding starting materials, the following compounds were obtained:

<table>
<thead>
<tr>
<th>Example</th>
<th>Name of the example</th>
<th>Starting material</th>
<th>HPLC Method</th>
<th>( t_R ) (min)</th>
<th>m/z</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>3-[6-(4-hydroxymethyl)piperidin-1-yl]pyridin-2-yl]pyrazolo[1,5-a]pyridine</td>
<td>4-hydroxymethyl piperidine</td>
<td>2</td>
<td>1.82</td>
<td>309</td>
</tr>
<tr>
<td>1b</td>
<td>3-[6-(3-hydroxycyclohexylamino)pyridin-2-yl]pyrazolo[1,5-a]pyridine</td>
<td>3-aminocyclohexanol</td>
<td>2</td>
<td>1.77</td>
<td>309</td>
</tr>
<tr>
<td>1c</td>
<td>trans-3-[6-(4-hydroxycyclohexyl-N-methylamino)pyridin-2-yl]pyrazolo[1,5-a]pyridine</td>
<td>trans-4-methylaminocyclohexanol</td>
<td>2</td>
<td>1.97</td>
<td>323</td>
</tr>
<tr>
<td>1d</td>
<td>3-[6-(1-ethoxycarbonylpiperidin-4-ylamino)pyridin-2-yl]pyrazolo[1,5-a]pyridine</td>
<td>4-amino-1-ethoxycarbonylpiperidine</td>
<td>2</td>
<td>2.73</td>
<td>351</td>
</tr>
<tr>
<td>1e</td>
<td>trans-3-[6-(4-aminocyclohexylamino)pyridin-2-yl]pyrazolo[1,5-a]pyridine</td>
<td>trans-1,4-diaminocyclohexane</td>
<td>2</td>
<td>0.97</td>
<td>308</td>
</tr>
<tr>
<td></td>
<td>Formula</td>
<td>Name</td>
<td>2</td>
<td>1.43</td>
<td>309</td>
</tr>
<tr>
<td>---</td>
<td>---------------------------------------------</td>
<td>-----------------------------------------------</td>
<td>----</td>
<td>------</td>
<td>-----</td>
</tr>
<tr>
<td>1f</td>
<td>trans-3-[6-(4-hydroxycyclohexylamino)pyridin-2-yl]pyrazolo[1,5-a]pyridine</td>
<td>trans-4-aminocyclohexanol hydrochloride</td>
<td>2</td>
<td>2.22</td>
<td>295</td>
</tr>
<tr>
<td>1g</td>
<td>3-[6-(tetrahydro-4H-piran-4-ylamino)pyridin-2-yl]pyrazolo[1,5-a]pyridine</td>
<td>4-aminotetrahydro-4H-pirane hydrochloride</td>
<td>2</td>
<td>3.73</td>
<td>307</td>
</tr>
<tr>
<td>1h</td>
<td>3-[6-(N-methylcyclohexylamino)pyridin-2-yl]pyrazolo[1,5-a]pyridine</td>
<td>N-cyclohexylmethyline</td>
<td>2</td>
<td>1.90</td>
<td>309</td>
</tr>
<tr>
<td>1i</td>
<td>3-[6-(3-hydroxymethylpiperidin-1-yl)pyridin-2-yl]pyrazolo[1,5-a]pyridine</td>
<td>3-hydroxymethylpiperidine</td>
<td>2</td>
<td>1.90</td>
<td>309</td>
</tr>
<tr>
<td>1j</td>
<td>3-[6-(1-methylpiperidin-4-ylamino)pyridin-2-yl]pyrazolo[1,5-a]pyridine</td>
<td>4-amino-1-methylpiperidine</td>
<td>2</td>
<td>1.02</td>
<td>308</td>
</tr>
<tr>
<td>1k</td>
<td>3-[6-(2,2,6,6-tetramethylpiperidin-4-ylamino)pyridin-2-yl]pyrazolo[1,5-a]pyridine</td>
<td>4-amino-2,2,6,6-tetramethylpiperidine</td>
<td>2</td>
<td>1.35</td>
<td>350</td>
</tr>
<tr>
<td>1l</td>
<td>3-[6-(2-phenylpropan-2-amino)pyridin-2-yl]pyrazolo[1,5-a]pyridine</td>
<td>2-phenylpropan-2-amine</td>
<td>2</td>
<td>2.48</td>
<td>329</td>
</tr>
<tr>
<td>1m</td>
<td>(S)-3-[6-(1-phenylethylamino)pyridin-2-yl]pyrazolo[1,5-a]pyridinea</td>
<td>(S)-1-phenylethylamine</td>
<td>1</td>
<td>2.53</td>
<td>315</td>
</tr>
<tr>
<td>1n</td>
<td>3-[6-(1-benzylamino)pyridin-2-yl]pyrazolo[1,5-a]pyridine</td>
<td>benzylamine</td>
<td>2</td>
<td>2.20</td>
<td>301</td>
</tr>
<tr>
<td>1o</td>
<td>(S)-3-[6-(1-cyclohexylethylamino)pyridin-2-yl]pyrazolo[1,5-a]pyridine</td>
<td>(S)-1-cyclohexylethylamine</td>
<td>2</td>
<td>2.58</td>
<td>321</td>
</tr>
<tr>
<td>1p</td>
<td>(S)-3-[6-(1-methoxypropan-2-ylamino)pyridin-2-yl]pyrazolo[1,5-a]pyridine</td>
<td>(S)-2-amino-1-methoxypropane</td>
<td>2</td>
<td>1.60</td>
<td>283</td>
</tr>
</tbody>
</table>
Following a similar procedure to that described in example 1, but using reference example 3 instead of reference example 1 and in each case the corresponding starting materials, the following compounds were obtained:

<table>
<thead>
<tr>
<th>Example</th>
<th>Name of the example</th>
<th>Starting material</th>
<th>HPLC Method</th>
<th>t_R (min)</th>
<th>m/z</th>
</tr>
</thead>
<tbody>
<tr>
<td>1u</td>
<td>trans-5-cyano-3-[6-(4-hydroxycyclohexylamino)pyridin-2-yl]pyrazolo[1,5-a]pyridine</td>
<td>trans-4-amino cyclohexanol hydrochloride</td>
<td>2</td>
<td>1.87</td>
<td>334</td>
</tr>
<tr>
<td>1v</td>
<td>trans-5-cyano-3-[6-(4-hydroxycyclohexyl-N-methylamino)pyridin-2-yl]pyrazolo[1,5-a]pyridine</td>
<td>trans-4-methylaminocyclohexanol</td>
<td>2</td>
<td>2.92</td>
<td>348</td>
</tr>
<tr>
<td>1w</td>
<td>trans-3-[6-(4-amino cyclohexylamino)pyridin-2-yl]-5-cyanopyrazolo[1,5-a]pyridine</td>
<td>trans-1,4-diaminocycloexane</td>
<td>2</td>
<td>1.42</td>
<td>333</td>
</tr>
<tr>
<td>1x</td>
<td>5-ciano-(S)-3-[6-(1-phenylethylamino)pyridin-2-yl]pyrazolo[1,5-a]pyridine</td>
<td>(S)-1-phenylethylamine</td>
<td>2</td>
<td>3.50</td>
<td>340</td>
</tr>
</tbody>
</table>

**EXAMPLE 2**

5-Cyano-3-[6-(4-hydroxybutylamino)pyridin-2-yl]pyrazolo[1,5-a]pyridine
To a solution of reference example 3 (40 mg, 0.17 mmol) in NMP (1.5 ml), 4-amino-1-butanol (45 mg, 0.50 mmol) and EDIPA (0.09 ml, 0.50 mmol) were added. The reaction mixture was heated at 140 °C for 1 h in a monomode microwave oven (250 W). After cooling, was diluted with EtOAc and washed three times with a NaHCO₃. The organic layer was dried over MgSO₄ and concentrated to dryness. The crude product thus obtained was chromatographed over silica gel using hexane/acetone mixtures of increasing polarity as eluent, to afford 21 mg of the title compound (41% yield).

LC-MS (Method 2): tᵱ = 2.47 min; m/z = 308 (MH⁺).

The following compounds were obtained following a similar procedure to that described in example 2, but using in each case the corresponding starting materials:

<table>
<thead>
<tr>
<th>Example</th>
<th>Name of the example</th>
<th>Starting material</th>
<th>HPLC Method</th>
<th>tᵱ (min)</th>
<th>m/z</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>5-cyano-3-[6-(N-methyl-(3-hydroxypropyl)amino)pyridin-2-yl]pyrazolo[1,5-a]pyridine</td>
<td>3-methylamino-1-propanol</td>
<td>2</td>
<td>2.68</td>
<td>308</td>
</tr>
<tr>
<td>2b</td>
<td>3-[6-(3-amino-cyclohexylamino)pyridin-2-yl]-5-cyanopyrazolo[1,5-a]pyridine</td>
<td>1,3-diaminocyclohexane</td>
<td>2</td>
<td>2.25</td>
<td>333</td>
</tr>
<tr>
<td>2c</td>
<td>5-cyano-3-[6-(N-methyl-N-(2-methylamino)ethylamino)pyridin-2-yl]pyrazolo[1,5-a]pyridine</td>
<td>N,N'-dimethylethan o-1,2-diamine</td>
<td>2</td>
<td>2.28</td>
<td>307</td>
</tr>
<tr>
<td>2d</td>
<td>5-cyano-3-[6-((1-ethoxycarbonyl)piperidin-3-ylamino)pyridin-2-yl]pyrazolo[1,5-a]pyridine</td>
<td>Reference example 5</td>
<td>2</td>
<td>3.13</td>
<td>391</td>
</tr>
<tr>
<td>2e</td>
<td>3-[6-(2-aminoethylamino)pyridin-2-yl]-5-cyanopyrazolo[1,5-a]pyridine</td>
<td>1,2-ethylendiamine</td>
<td>2</td>
<td>1.93</td>
<td>279</td>
</tr>
<tr>
<td></td>
<td>Chemical Structure</td>
<td>Molecular Formula</td>
<td>LogP</td>
<td>MW</td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>-----------------------------------------------------------------------------------</td>
<td>-------------------</td>
<td>------</td>
<td>-----</td>
<td></td>
</tr>
<tr>
<td>2f</td>
<td>(S)-5-cyano-3-[6-(2-hydroxymethyl)pyrrolidin-1-yl]pyridin-2-yl</td>
<td>pyrazolo[1,5-a]pyridine</td>
<td></td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(S)-2-hydroxymethyl pyrrolidine</td>
<td></td>
<td>3.87</td>
<td>320</td>
<td></td>
</tr>
<tr>
<td>2g</td>
<td>(R)-5-cyano-3-[6-(2-hydroxymethyl)pyrrolidin-1-yl]pyridin-2-yl</td>
<td>pyrazolo[1,5-a]pyridine</td>
<td></td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(R)-2-hydroxymethyl pyrrolidine</td>
<td></td>
<td>3.87</td>
<td>320</td>
<td></td>
</tr>
<tr>
<td>2h</td>
<td>5-cyano-3-[6-(3-hydroxy)pyrrolidin-1-yl]pyridin-2-yl</td>
<td>pyrazolo[1,5-a]pyridine</td>
<td></td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3-hydroxy pyrroldine</td>
<td></td>
<td>2.55</td>
<td>306</td>
<td></td>
</tr>
<tr>
<td>2i</td>
<td>5-cyano-3-[6-(3-(N,N-dimethylamino)pyrrolidin-1-yl)pyridin-2-yl</td>
<td>pyrazolo[1,5-a]pyridine</td>
<td></td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3-(N,N-dimethylamino)pyrrolidine</td>
<td></td>
<td>2.98</td>
<td>333</td>
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<tr>
<td>2k</td>
<td>5-cyano-3-[6-(N-ethyl-N-(4-hydroxybutyl)amino)pyridin-2-yl</td>
<td>pyrazolo[1,5-a]pyridine</td>
<td></td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4-ethylamino-1-butanol</td>
<td></td>
<td>3.03</td>
<td>336</td>
<td></td>
</tr>
<tr>
<td>2l</td>
<td>5-cyano-3-[6-(3-hydroxypropylamino)pyridin-2-yl</td>
<td>pyrazolo[1,5-a]pyridine</td>
<td></td>
<td>2</td>
<td></td>
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<tr>
<td></td>
<td>3-amino-1-propanol</td>
<td></td>
<td>2.33</td>
<td>294</td>
<td></td>
</tr>
<tr>
<td>2m(1)</td>
<td>3-[6-(3-aminopyrrolidin-1-yl)pyridin-2-yl</td>
<td>5-cyanopyrazolo[1,5-a]pyridine</td>
<td></td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3-(tert-butoxycarbonylamino)pyrroldine</td>
<td></td>
<td>2.30</td>
<td>305</td>
<td></td>
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<tr>
<td>2n</td>
<td>5-cyano-3-[6-(3-hydroxypiperidin-1-yl)pyridin-2-yl</td>
<td>pyrazolo[1,5-a]pyridine</td>
<td></td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3-hydroxypiperidine</td>
<td></td>
<td>2.65</td>
<td>320</td>
<td></td>
</tr>
<tr>
<td>2o</td>
<td>5-cyano-3-[6-(4-hydroxypiperidin-1-yl)pyridin-2-yl</td>
<td>pyrazolo[1,5-a]pyridine</td>
<td></td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4-hydroxypiperidine</td>
<td></td>
<td>2.53</td>
<td>320</td>
<td></td>
</tr>
<tr>
<td>2p</td>
<td>trans-5-cyano-3-[6-(N-ethyl-N-(4-hydroxycyclohexyl)amino)pyridin-2-yl</td>
<td>pyrazolo[1,5-a]pyridine</td>
<td></td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reference example 6</td>
<td></td>
<td>3.17</td>
<td>362</td>
<td></td>
</tr>
<tr>
<td>2q</td>
<td>3-[6-(3-acetylaminopiperidin-1-yl)pyridin-2-yl</td>
<td>5-cyanopyrazolo[1,5-a]pyridine</td>
<td></td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3-acetylaminopiperidine</td>
<td></td>
<td>2.50</td>
<td>361</td>
<td></td>
</tr>
</tbody>
</table>
Reaction performed at 100°C instead of at 140°C.

**EXAMPLE 3**

**trans-3-[6-(4-Acylaminocyclohexylamino)pyridin-2-yl]pyrazolo[1,5-a]pyridine**

To a solution of example 1e (65 mg, 0.21 mmol) in DMF (2 mL), acetic acid (0.013 mL, 0.23 mmol), EDC (45 mg, 0.023 mmol), HOBT (31 mg, 0.23 mol), and EDIPA (0.074 mL, 0.42 mmol) were added. The resulting mixture was stirred at room temperature for 18 h. The crude reaction thus obtained was concentrated to dryness, diluted with CH₂Cl₂ and washed three times with a NaHCO₃ saturated aqueous solution. The organic layer was dried over MgSO₄ and concentrated to dryness. The crude product thus obtained was chromatographed over silica gel using CH₂Cl₂/MeOH mixtures of increasing polarity as eluent, to afford 34 mg of the title compound (46% yield).

LC-MS (Method 2): tᵣ = 1.53 min; m/z = 350 (MH⁺).

**EXAMPLE 4**

**trans-3-[6-(4-Metanosulfonylaminocyclohexylamino)pyridin-2-yl]pyrazolo[1,5-a]pyridine**

To a solution of example 1e (65 mg, 0.21 mmol) and TEA (0.030 mL, 0.21 mmol) in DMF (2 mL) methanesulfonyl chloride (0.017 mL, 0.21 mmol) was added at 0 °C. The resulting mixture was stirred at 0 °C for 1 h, and after that at room temperature for 18 h. The crude product thus obtained was concentrated to dryness and chromatographed over silica gel using CH₂Cl₂/MeOH mixtures of increasing polarity as eluent, to afford 26 mg of the title compound (32% yield).

LC-MS (Method 2): tᵣ = 1.63 min; m/z = 386 (MH⁺).
To a solution of reference example 4 (50 mg, 0.18 mmol) in tert-butanol (2 mL), K$_2$CO$_3$ (55 mg, 0.40 mmol), X-Phos (8.70 mg, 0.018 mmol), Pd$_2$(dba)$_3$ (8.35 mg, 0.0092 mmol) and 1-(3-aminophenyl)pyrrolidin-2-one (35 mg, 0.20 mmol) were added at room temperature and under Ar atmosphere. The mixture was heated at 100 °C for 18 h. The reaction crude was diluted with MeOH and filtered over Celite®. The filtrated solution was concentrated to dryness and chromatographed over silica gel using hexane/EtOAc mixtures of increasing polarity as eluent, to afford 49 mg of the title compound (72% yield).

Following a similar procedure to that described in example 5, but using in each case the corresponding starting materials, the following compounds were obtained:

<table>
<thead>
<tr>
<th>Example</th>
<th>Name of the example</th>
<th>Starting material</th>
<th>HPLC method</th>
<th>$t_R$ (min)</th>
<th>m/z</th>
</tr>
</thead>
<tbody>
<tr>
<td>5a</td>
<td>3-[6-(N-cyclohexylamino)pyridin-2-yl]pyrazolo[1,5-a]pyridine</td>
<td>cyclohexylamine</td>
<td>2</td>
<td>2.22</td>
<td>293</td>
</tr>
<tr>
<td>5b</td>
<td>3-[6-(N-(2-methylcyclohexyl)amino)pyridin-2-yl]pyrazolo[1,5-a]pyridine</td>
<td>2-methylcyclohexylamine</td>
<td>2</td>
<td>2.90</td>
<td>307</td>
</tr>
<tr>
<td>5c</td>
<td>3-[6-(4-acetylaminophenylamino)pyridin-2-yl]pyrazolo[1,5-a]pyridine</td>
<td>N-(4-aminophenyl)acetamide</td>
<td>2</td>
<td>2.12</td>
<td>344</td>
</tr>
<tr>
<td>5d</td>
<td>3-[6-(3-acetylaminophenylamino)pyridin-2-yl]pyrazolo[1,5-a]pyridine</td>
<td>N-(3-aminophenyl)acetamide</td>
<td>2</td>
<td>2.12</td>
<td>344</td>
</tr>
</tbody>
</table>
EXAMPLE 6

3-[6-(3-Hydroxyphenyl-Λ-/methylamino)pyridin-2-yl]pyrazolo[1,5-a]pyridine

a) 3-[6-(Λ-/Methyl-3-methoxyphenylamino)pyridin-2-yl]pyrazolo[1,5-a]pyridine

Following a similar procedure to that described in example 5 but using Λ-/methyl-3-methoxyaniline instead of 1-(3-aminophenyl)pyrroolidin-2-one, the desired compound was obtained (73% yield).

LC-MS (Method 2): \( t_R = 3.98 \) min; \( m/z = 331 \) (MH+).

b) Title compound

To a solution of the compound obtained in the previous section (60 mg, 0.17 mmol) in CHCl₃ (3 mL), a BBr₃ 1.0 M solution in CH₂Cl₂ (0.35 mL, 0.35 mmol) was added. The reaction mixture was heated at 65 °C for 18 h. The crude of the reaction thus obtained was concentrated to dryness and chromatographed over silica gel using hexane/aceton mixtures of increasing polarity as eluent, affording 43 mg of the title compound (76% yield).

LC-MS (Method 2): \( t_R = 3.07 \) min; \( m/z = 317 \) (MH+).

EXAMPLE 7

3-[6-(N-Cyclopropylcarbonylamino)pyridin-2-yl]pyrazolo[1,5-a]pyridine

a) 3-[6-(N-Diphenylmethylenamino)pyridin-2-yl]pyrazolo[1,5-a]pyridine

To a solution of reference example 4 (118 mg, 0.43 mmol) in toluen (8.6 mL), NaO¹Bu (58 mg, 0.60 mmol), BINAP (21 mg, 0.034 mmol), Pd₂(dbq)₃ (15 mg, 0.017 mmol) and benzophenonimine (0.11 mL, 0.65 mmol) were added at room temperature and under Ar atmosphere. The reaction mixture was stirred at 85 °C for 7 h. The crude of the reaction thus obtained was concentrated to dryness and chromatographed over silica gel using hexane/EtOAc mixtures of increasing polarity as eluent, affording 130 mg of the desired compound (81% yield).
b) 3-(6-Aminopyridin-2-yl)pyrazolo[1,5-a]pyridine
To a solution of the compound obtained in the previous section (130 mg, 0.35 mmol) in MeOH (17 mL), hydroxylamine hydrochloride (120 mg, 1.73 mmol) and DIPEA (0.302 mL, 1.73 mmol) were added. The reaction mixture was stirred at room temperature for 18 h. The crude of the reaction was concentrated to dryness and chromatographed over silica gel using hexane/EtOAc mixtures of increasing polarity as eluent, affording 65 mg of the desired compound (89% yield).
LC-MS (Method 2): \( t_R = 1.14 \text{ min}; \ m/z = 211 \) (MH⁺).

c) Title compound
To a solution of the compound obtained in the previous section (19 mg, 0.09 mmol) in anhydrous THF (1 mL), TEA (0.018 mL, 0.135 mmol) was added, and then the chloride of the cyclopropanoic acid (0.010 mL, 0.113 mmol) was slowly added at 0 °C. The reaction mixture was stirred at room temperature for 4 days. The crude of the reaction thus obtained was concentrated to dryness and chromatographed over silica gel using CH₂CVMeOH mixtures of increasing polarity as eluent, affording 13 mg of the desired compound (50% yield).
LC-MS (Method 2): \( t_R = 2.73 \text{ min}; \ m/z = 279 \) (MH⁺).

EXAMPLE 8
(S)-3-[6-(1-Phenylethylamino)pyridin-2-yl]-5-hydroxymethylpyrazolo[1,5-a]pyridine

a) 1-Amino-4-ethoxycarbonylpyridinium 2,4-dinitrophenolate
To a solution of ethyl isocyanate (1 g, 6.62 mmol) in AcN (4.41 mL), O-(2,4-dinitrophenyl)hydroxylamine (1.45 g, 7.28 mmol) was added. The reaction mixture was stirred at 40 °C for 18 h. The crude of the reaction thus obtained was concentrated to dryness and extracted three times with Et₂O (3x15 mL). The solid thus obtained was filtered and dried, affording 1.58 g of the desired compound (58% yield).

b) 5-Ethoxycarbonyl-3-(6-fluoropyridin-2-yl)pyrazolo[1,5-a]pyridine
Following a similar procedure to that described in section b of reference example 3, but using the compound obtained in previous section instead of 1-amino-4-cyanopyridinium2,4,6-thmethylbencenosulfonate, the desired compound was obtained (64% yield).

5

LC-MS (Method 2): \( t_R = 3.48 \text{ min} \); \( m/z = 286 \ (\text{MH}^+) \).

c) 5-Carboxy-S-C\(\Theta\)fluoropyridin^-yOpyrazololl ,5-a]pyridine
To a solution of the compound obtained in the previous section (50 mg, 0.175 mmol) in a mixture DME/H\(\text{}_2\text{O} \ 2:1 \ (1.5 \text{ mL})\), LiOH-H\(\text{}_2\text{O} \ (22 \text{ mg, 0.526 mmol})\) was added. The reaction mixture was stirred at room temperature for 18 h. The crude of the reaction thus obtained was diluted with EtOAc and extracted three times with a NaHCO\(_3\). The aqueous layer was acidified to pH=1 with a HCl 1N aqueous solution, and extracted three times with CH\(\text{}_2\text{Cl}_2 \ (3 \times 10 \text{ mL})\). The combined organic layers were dried over Na\(_2\)SO\(_4\) and concentrated to dryness, affording 41 mg of the desired compound (91% yield).

LC-MS (Method 2): \( t_R = 2.48 \text{ min} \); \( m/z = 258 \ (\text{MH}^+) \).

d) (S)-5-Carboxy-3-[6-(1 -phenylethylamino)pyridin-2-yl]pyrazolo[1 ,5-au]pyridine
Following a similar procedure to that described in example 1, but using the compound obtained in the previous section instead reference example 1, and (S)-1-phenylethylamine instead of 1-hydroxymethylcyclopentylamine, the desired compound was obtained (100% yield).

e) (S)-S-(\Theta(1 -Phenylethylamino)pyridin-2-yl)-S-methoxycarbonylpyrazolo[i ,S-au]pyridine
To a solution of the compound obtained in the previous section (57 mg, 0.16 mmol) in MeOH (5 mL), SOCl\(_2 \ (0.0023 \text{ mL, 0.032 mmol})\) was added. The reaction mixture was stirred The reaction mixture was stirred at room temperature for 18 h. The crude of the reaction thus obtained was concentrated to dryness, diluted with a NaHCO\(_3\) saturated aqueous solution and extracted with CH\(\text{}_2\text{Cl}_2 \ (3 \times 5 \text{ mL})\). The combined organic layers were dried over Na\(_2\)SO\(_4\) and the solvent was evaporated to dryness, affording 28 mg of the desired compound (46% yield).
f) Title compound

To a solution of the compound obtained in the previous section (28 mg, 0.075 mmol) in anhydrous THF (2 ml), at 0 °C and under Ar atmosphere LiAlH₄ (5 mg, 0.15 mmol) was added. The reaction mixture was stirred at room temperature for 18 h. The crude of the reaction was diluted with EtOAc and washed with a sodium tartrate saturated aqueous solution (3 x 10 mL). The combined organic layers were dried over Na₂SO₄ and the solvent was evaporated to dryness. The crude of the reaction thus obtained was chromatographed over silica gel using hexane/EtOAc mixtures of increasing polarity as eluent, affording 9.5 mg of the title compound (36% yield).

LC-MS (Method 2): t<sub>R</sub> = 1.90 min; m/z = 345 (MH⁺).

EXAMPLE 9

3-[6-(Piperidin-4-ylamino)pyridin-2-yl]pyrazolo[1,5-a]pyridine

a) 3-[6-(1-Ethoxycarbonylpiperidin-4-ylamino)pyridin-2-yl]pyrazolo[1,5-a]pyridine

Following a similar procedure to that described in example 1, but using 1-ethoxycarbonyl-4-aminopiperidine, the desired compound was obtained (49% yield).

LC-MS (Method 2): t<sub>R</sub> = 2.00 min; m/z = 366 (MH⁺).

b) Title compound

To a solution of the compound obtained in previous section (127 mg, 0.350 mmol) in EtOH (3 mL) a NaOH 1 N aqueous solution (2 mL) was added and the mixture thus obtained was heated at 100 °C for 18 h. The reaction crude was cooled, concentrated to dryness and chromatographed over silica gel using CH₂Cl₂/MeOH mixtures of increasing polarity, obtaining 73 mg of the title compound (70% yield).

LC-MS (Method 2): t<sub>R</sub> = 1.02 min; m/z = 294 (MH⁺).

Following a similar procedure to that described in example 9, but using in each
case the corresponding starting materials, the following compounds were obtained:

<table>
<thead>
<tr>
<th>Example</th>
<th>Name of the example</th>
<th>Starting material</th>
<th>HPLC method</th>
<th>t_R (min)</th>
<th>m/z</th>
</tr>
</thead>
<tbody>
<tr>
<td>9a(1)</td>
<td>3-[6-(piperidin-4-ylamino)pyridin-2-yl]-5-carboxypyrazolo[1,5-a]pyridine</td>
<td>Reference example 3</td>
<td>2</td>
<td>1.40</td>
<td>338</td>
</tr>
<tr>
<td>9b(2)</td>
<td>5-cyano-3-[6-(piperidin-4-ylamino)pyridin-2-yl]pyrazolo[1,5-a]pyridine</td>
<td>Reference example 3</td>
<td>2</td>
<td>1.98</td>
<td>319</td>
</tr>
</tbody>
</table>

(1) Before purification, the crude product was acidified with a HCl 4M solution in dioxane (2 ml).

(2) obtained as example 11 section c.

EXAMPLE 10

3-[6-(1-Acetyl)piperidin-4-yl]pyridin-2-yl]pyrazolo[1,5-a]pyridine

To a solution of example 9 (60 mg, 0.204 mmol) in DMF (2 ml) acetic acid (0.014 ml, 0.245 mmol), EDC (46 mg, 0.245 mmol), HOBr (33 mg, 0.245 mmol) and EDIPA (0.071 ml, 0.408 mmol) were added. The mixture thus obtained was stirred at room temperature for 18 h. After that, the solvent was concentrated to dryness and the resulting crude reaction was partitioned between CH₂Cl₂ and a NaHCO₃ saturated aqueous solution. The layers were separated and the aqueous layer was extracted twice with CH₂Cl₂. The combined organic layers were dried over MgSO₄ and concentrated to dryness. The crude product thus obtained was chromatographed over silica gel using hexane/acetone mixtures of increasing polarity as eluent, to afford 25 mg of the title compound (37% yield).

LC-MS (Method 2): t_R = 1.47 min; m/z = 336.

EXAMPLE 11

S-Cyano-S-IΘ(methyl(piperidin-4-yl)amino)pyridin-2-yl]pyrazolo[i,5-a]pyridine
a) 5-cyano-3-[6-((1-ethoxycarbonyl)piperidin-4-ylamino)pyridin-2-yl]pyrazolo[1,5-a]pyridine

Following a similar procedure to that described in example 1, but using reference example 3 and 4-amino-1-ethoxycarbonylpiperidine, the desired compound was obtained (48 % yield).

b) 5-cyano-3-[6-(N-methyl(1-ethoxycarbonyl)piperidin-4-ylamino)pyridin-2-yl]pyrazolo[1,5-a]pyridine

To a solution of the compound obtained in the previous section (100 mg, 0.25 mmol) in THF (2 ml), tBuOK (116 mg, 0.384 mmol) and MeI (2.27 ml, 0.64 mmol) were added. The reaction mixture was stirred at room temperature for 18 h and concentrated. The crude residue was chromatographed over silica gel using acetone/hexanes mixtures of increasing polarity as eluent to afford 0.022 g of the desired compound (16 % yield).

c) Title compound

To a solution of the compound obtained in the previous section (22 mg, 0.054 mmol) in AcN (2 ml), TMSI (40 µl, 0.272 mmol) was added. The reaction mixture was stirred at 50 °C for 18 h and concentrated. The crude residue was chromatographed over SCX silica gel to afford 5.8 mg of the title compound (32 % yield).

LC-MS (Method 2): \( t_R = 1.60 \) min; \( m/z = 332 \).

EXAMPLE 12

5-Cyano-3-[6-((1-acetyl)piperidin-3-ylamino)pyridin-2-yl]pyrazolo[1,5-a]pyridine

a) 5-cyano-3-[6-(piperidin-3-ylamino)pyridin-2-yl]pyrazolo[1,5-a]pyridine

Following a similar procedure to that described in example 11 section c, but using example 2d as starting material and 4 M HCl solution in dioxane, the desired compound was obtained (65 % yield).

b) Title compound
To a solution of the compound obtained in the previous section (20 mg, 0.063 mmol) in DMF (1 ml), acetic anhydride (12 µl, 0.126 mmol) and TEA (28 µl, 0.189 mmol) were added. The reaction mixture was stirred at room temperature for 18 h and the solvent was concentrated off. It was quenched with a NaHCO₃ saturated aqueous solution and extracted thrice with EtOAc. The combined organic phases were dried over anhydrous MgSO₄, filtered and concentrated. The crude residue was chromatographed over silica gel using acetone/hexanes mixtures of increasing polarity as eluent to afford 20 mg of the title compound (85% yield). LC-MS (Method 2): tᵣ = 2.52 min; m/z = 361.

**EXAMPLE 13**

5-Cyano-3-[6-(1-(2-cyanoacetyl)piperidin-3-yl)amino]pyridin-2-yl]pyrazolo[1,5-a]pyridine

Following a similar procedure to that described in example 12 section b, but using 2,5-dioxopyrrolidin-1-yl-2-cyanoacetate, the title compound was obtained (55% yield). LC-MS (Method 2): tᵣ = 2.63 min; m/z = 386.

**EXAMPLE 14**

(fi)-5-Cyano-3-[6-(1-(2-cyanoacetyl)piperidin-3-yl)amino]pyridin-2-yl]pyrazolo[1,5-a]pyridine

Following a similar procedure to that described in example 13, but using 3-(F)-amino-1-ethoxycarbonylpiperidine as starting material, the title compound was obtained (62% yield). LC-MS (Method 2): tᵣ = 2.63 min; m/z = 386.

Following a similar procedure to that described in example 14, but using the corresponding starting material, the following compound was obtained:
EXAMPLE 15

(H)-5-Cyano-3-[6-(/V-methyl-1-(2-cyanoacetyl)piperidin-3-ylamino)pyridin-2-yl]pyrazolo[1,5-a]pyridine

a) (fl)-5-Cyano-3-[6-(/A^methyl-1-(ethoxycarbonyl)piperidin-3-ylamino)pyridin-2-yl]pyrazolo[1,5-a]pyridine

Following a similar procedure to that described in example 2 and in example 11 section b, but using 3-(F?)-amino-1-ethoxycarbonylpipedine and (fl)-5-cyano-3-[6-(1-(ethoxycarbonyl)pipedin-3-ylamino)pyridin-2-yl]pyrazolo[1,5-a]pyridine respectevely as starting material, the desired compound was obtained (99 % yield).

b) (fl)-5-Cyano-3-[6-(piperidin-3-yl(/N-methyl)amino)pyridin-2-yl]pyrazolo[1,5-a]pyridine

Following a similar procedure to that described in example 11 section c, but using the compound obtained in previous section, the desired compound was obtained.

c) Title compound

Following a similar procedure to that described in example 13, but using the compound obtained in previous section, the title compound was obtained (27 % yield).

LC-MS (Method 2): t_R = 2.92 min; m/z = 400.

EXAMPLE 16

(S)-5-Cyano-3-[6-(piperidin-3-ylamino)pyridin-2-yl]pyrazolo[1,5-a]pyridine

Following a similar procedure to that described in example 11 section c, but using
example 2r as starting material, the title compound was obtained (74 % yield).

LC-MS (Method 2): \( t_R = 2.20 \text{ min}; \ m/z = 319 \).

**EXAMPLE 17**

**Inhibition of JAK3 activity**

The inhibition of JAK3 kinase activity was determined in 384-well assay microplates using the Z'-Lyte® Kinase Assay kit-Tyr 6 Peptide, supplied by Invitrogen (Ref: PV4122), following manufacturer instructions.

In a final volume of 10 \( \mu L \) per well, 2.5 \( \mu L \) of the product to be tested were incubated dissolved in 4% DMSO (final concentration of the product to be tested, 0.1 - 10000 nM), with 0.3 \( \mu g/mL \) of the catalytic domain of human JAK3 (amino acid sequence 281 - 1124), 2 \( \mu M \) of the substrate peptide Z'-Lyte® Tyr 6 and 4 \( \mu M \) of ATP; all components were dissolved in 50 mm Hepes pH 7.5 buffer, 10 mm of Magnesium chloride (II), 1 mm of EGTA and 0.01 % of Brij® 35. The reaction was started by adding 4 \( \mu M \) of ATP; after a 1 hour incubation period at 25°C, 5 \( \mu L \) of development reagent were added to Z'-Lyte® Tyr 6 and it was incubated for 1 hour at 25°C. Phosphorylation was then quantified in each well using a Safire2® fluorescence meter by Tecan.

The compounds of all examples showed more than 50% inhibition of JAK3 activity at 10 \( \mu M \) in this trial. The compounds 1c, 1f, 1m, 1o, 1u, 1v, 2p, 9b, 13, 14 and 15 showed more than 50% inhibition of JAK3 activity at 0.1 \( \mu M \) in this assay.

**EXAMPLE 18**

**Inhibition of JAK2 activity**

The inhibition of JAK2 kinase activity was determined in 384-well assay microplates using the Z'-Lyte® Kinase Assay kit-Tyr 6 Peptide kit, supplied by Invitrogen (Ref: PV4122), following the manufacturer’s instructions.

In a final volume of 10 \( \mu L \) per well, 2.5 \( \mu L \) of the product to be tested dissolved in 4% DMSO (final concentration of the product to be tested, 0.1 - 10000 nM) was incubated with 0.5 \( \mu g/well \) of the catalytic domain of human JAK2, 2 \( \mu M \) of the substrate peptide Z'-Lyte® Tyr 6 and 16 \( \mu M \) of ATP; all components were dissolved in 50 mm pH 7.5 Hepes buffer, 10 mM Magnesium chloride (II), 1 mM
EGTA and 0.01% Brij® 35. The reaction was started by the addition of said 16 μM ATP; after incubation for 1 hour at 25°C, 5 μl of A Z'-Lyte® Tyr 6 development reagent was added and the mixture was incubated for 1 hour at 25°C. Phosphorylation was then quantified in each well using a Safire2® fluorescence microplate reader from Tecan.

The compounds 1u, 1v, 2p, 9b, 11, 13, 14 and 15 showed more than 50% inhibition of JAK2 activity at 0.5 μM in this assay.
1. A compound of formula I:

or a salt thereof, wherein:

- $R_i$ represents hydrogen, $\text{C}_1\text{t}_4\text{alkyl}$, halo$\text{C}_1\text{t}_4\text{alkyl}$, $\text{hydroxyC}_1\text{t}_4\text{alkyl}$, $\text{R}_7\text{C}_1\text{t}_4\text{alkyl}$, halogen, $-\text{CN}$, $-\text{CONR}_4\text{R}_4$, $-\text{COR}_5$, $-\text{CO}_2\text{R}_5$, $-\text{OR}_4$, $-\text{SO}_2\text{R}_5$, $-\text{SO}_2\text{NR}_4\text{R}_4$, $-\text{NR}_4\text{R}_4$, $-\text{NR}_6\text{COR}_4$, $-\text{NR}_6\text{CONR}_4\text{R}_4$, $-\text{NR}_6\text{CO}_2\text{R}_5$, $-\text{NR}_6\text{SO}_2\text{R}_5$, or $\text{C}_y\text{i}$, wherein $\text{C}_y\text{i}$ is optionally substituted with one or more $\text{R}_8$;

- $R_2$ represents hydrogen, $\text{C}_1\text{t}_4\text{alkyl}$, halo$\text{C}_1\text{t}_4\text{alkyl}$, $\text{hydroxyC}_1\text{t}_4\text{alkyl}$, $\text{R}_7\text{C}_1\text{t}_4\text{alkyl}$ or $\text{C}_y\text{z}$, wherein $\text{C}_y\text{z}$ is optionally substituted with one or more $\text{R}_8$;

- $R_3$ represents $\text{C}_1\text{t}_4\text{alkyl}$, halo$\text{C}_1\text{t}_4\text{alkyl}$, $\text{hydroxyC}_1\text{t}_4\text{alkyl}$, $\text{Rn-C}_1\text{t}_4\text{alkyl}$, $-\text{CONR}_9\text{R}_9$, $-\text{COR}_10$, $-\text{CO}_2\text{R}_10$, $-\text{SO}_2\text{R}_10$, $-\text{SO}_2\text{NR}_9\text{R}_9$ or $\text{C}_y\text{z}$, wherein $\text{C}_y\text{z}$ is optionally substituted with one or more $\text{R}_12$;

or $R_2$ and $R_3$ can be bonded completing, together with the N atom, a $\text{C}_y\text{q}$ group, wherein $\text{C}_y\text{q}$ is optionally substituted with one or more $\text{R}_12$;

- each $\text{R}_4$ independently represents hydrogen or $\text{R}_5$;

- each $\text{R}_5$ independently represents $\text{C}_1\text{t}_4\text{alkyl}$, halo$\text{C}_1\text{t}_4\text{alkyl}$, $\text{C}_1^\text{alkOXyC}_1$;

- $\text{R}_6$ represents hydrogen or $\text{C}_1\text{t}_4\text{alkyl}$;

- $\text{R}_7$ represents $-\text{CN}$, $-\text{CONR}_4\text{R}_4$, $-\text{COR}_5$, $-\text{CO}_2\text{R}_5$, $-\text{OR}_4$, $-\text{SO}_2\text{R}_5$, $-\text{SO}_2\text{NR}_4\text{R}_4$, $-\text{NR}_4\text{R}_4$, $-\text{NR}_6\text{COR}_4$, $-\text{NR}_6\text{CONR}_4\text{R}_4$, $-\text{NR}_6\text{CO}_2\text{R}_5$, $-\text{NR}_6\text{SO}_2\text{R}_5$ or $\text{C}_y\text{z}$, wherein $\text{C}_y\text{z}$ is optionally substituted with one or more $\text{R}_8$;

- each $\text{R}_8$ independently represents $\text{C}_1\text{t}_4\text{alkyl}$, halo$\text{C}_1\text{t}_4\text{alkyl}$, $\text{C}_1^\text{alkOXyC}_1$.
4 alkyl, hydroxyC\textsubscript{1}...4 alkyl, cyanoC\textsubscript{1}...4 alkyl, halogen or hydroxyl;
each R\textsubscript{9} independently represents hydrogen or R\textsubscript{10};
each R\textsubscript{10} independently represents C\textsubscript{1}...alkyl, haloC\textsubscript{1}...4 alkyl, hydroxyC\textsubscript{1}...4 alkyl,
RiR\textsubscript{4}...4 alkyl or Cy\textsubscript{5}, wherein Cy\textsubscript{5} is optionally substituted with one or more Ri\textsubscript{3};
R\textsubscript{11} represents halogen, -CN, -CONRi\textsubscript{4}R\textsubscript{i}4, -CORi\textsubscript{5}, -CO\textsubscript{2}Ri\textsubscript{5}, -ORi\textsubscript{4},
-CONRi\textsubscript{4}R\textsubscript{i}4, SO\textsubscript{2}Ri\textsubscript{5}, -SO\textsubscript{2}NRi\textsubscript{4}R\textsubscript{i}4, -NRi\textsubscript{4}R\textsubscript{i}4, -NRi\textsubscript{6}CORi\textsubscript{4}, -NR\textsubscript{6}CONRi\textsubscript{4}Ri\textsubscript{4},
-NRi\textsubscript{6}CO\textsubscript{2}Ri\textsubscript{5}, -NR\textsubscript{6}SO\textsubscript{2}Ri\textsubscript{5} or Cy\textsubscript{5}, wherein Cy\textsubscript{5} is optionally substituted with one or more Ri\textsubscript{3};
each Ri\textsubscript{2} independently represents C\textsubscript{1}...4 alkyl, haloC\textsubscript{1}...4 alkyl, hydroxyC\textsubscript{1}...4 alkyl,
Rn-Ci\textsubscript{1}...4 alkyl, or Ri\textsubscript{2} represents any of the meanings described for Rn;
each Ri\textsubscript{3} independently represents C\textsubscript{1}...4 alkyl, haloC\textsubscript{1}...4 alkyl, C\textsubscript{1}...4alkoxyC\textsubscript{1}...4 alkyl, hydroxyC\textsubscript{1}...4 alkyl, cyanoC\textsubscript{1}...4 alkyl, halogen, -CN, -CONRi\textsubscript{6}Ri\textsubscript{6}, -CORi\textsubscript{7},
-CO\textsubscript{2}Ri\textsubscript{7}, -OR\textsubscript{16}, -CONRi\textsubscript{6}Ri\textsubscript{6}, -SO\textsubscript{2}Ri\textsubscript{7}, -SO\textsubscript{2}NRi\textsubscript{6}Ri\textsubscript{6}, -NRi\textsubscript{6}Ri\textsubscript{6}, -NRi\textsubscript{6}CORi\textsubscript{6},
-NR\textsubscript{6}CONRi\textsubscript{6}Ri\textsubscript{6}, -NR\textsubscript{6}CO\textsubscript{2}Ri\textsubscript{7} or -NR\textsubscript{6}SO\textsubscript{2}Ri\textsubscript{7};
each Ri\textsubscript{4} independently represents hydrogen or Ri\textsubscript{5};
each Ri\textsubscript{5} independently represents C\textsubscript{1}...4 alkyl, haloC\textsubscript{1}...4 alkyl, C\textsubscript{1}...4alkoxyC\textsubscript{1}...4 alkyl, hydroxyC\textsubscript{1}...4 alkyl, cyanoC\textsubscript{1}...4 alkyl, Cy\textsubscript{5}...C\textsubscript{1}...4 alkyl or Cy\textsubscript{5}, wherein Cy\textsubscript{5} is optionally substituted with one or more Ri\textsubscript{3};
each Ri\textsubscript{6} independently represents hydrogen or Ri\textsubscript{7};
each Ri\textsubscript{7} independently represents C\textsubscript{1}...4 alkyl, haloC\textsubscript{1}...4 alkyl, C\textsubscript{1}...4alkoxyC\textsubscript{1}...4 alkyl, hydroxyC\textsubscript{1}...4 alkyl or cyanoC\textsubscript{1}...4 alkyl;

Cy\textsubscript{1} represents a 3- to 7-membered monocyclic carbocyclic ring that is saturated, partially unsaturated or aromatic, and which optionally contains from 1 to 3 heteroatoms independently selected from N, S and O, wherein said ring is bonded to the rest of the molecule through any available C or N atom, and wherein one or more C or S ring atoms are optionally oxidized forming CO, SO or SO\textsubscript{2} groups;

Cy\textsubscript{2} represents a 3- to 7-membered monocyclic carbocyclic ring that is saturated, partially unsaturated or aromatic, and which optionally contains from 1 to 3 heteroatoms independently selected from N, S and O, wherein said ring is bonded to the rest of the molecule through any available C atom, and wherein one or more C or S ring atoms are optionally oxidized forming CO, SO or SO\textsubscript{2} groups;

Cy\textsubscript{3} represents a 3- to 7-membered monocyclic or 8- to 12-membered
bicyclic carbocyclic ring that is saturated, partially unsaturated or aromatic, and which optionally contains from 1 to 4 heteroatoms independently selected from N, S and O, wherein said ring is bonded to the rest of the molecule through any available C atom, and wherein one or more C or S ring atoms are optionally oxidized forming CO, SO or SO₂ groups;

Cy₄ represents a 3- to 7-membered monocyclic heterocyclic ring that is saturated or partially unsaturated, which is optionally fused to a 5- or 6-membered carbocyclic or heterocyclic ring that is saturated, partially unsaturated or aromatic, wherein Cy₄ optionally contains from 1 to 4 heteroatoms in total independently selected from N, S and O; and wherein one or more C or S atoms of Cy₄ are optionally oxidized forming CO, SO or SO₂ groups; and

Cy₅ represents a 3- to 7-membered monocyclic or 8- to 12-membered bicyclic carbocyclic ring that is saturated, partially unsaturated or aromatic, and which optionally contains from 1 to 4 heteroatoms independently selected from N, S and O, wherein said ring is bonded to the rest of the molecule through any available C or N atom, and wherein one or more C or S ring atoms are optionally oxidized forming CO, SO or SO₂ groups.

2.- A compound according to claim 1 wherein R₁ represents hydrogen or -CN.

3.- A compound according to claim 2 wherein Rᵢ represents -CN.

4.- A compound according to any of claims 1 to 3 wherein R₂ represents hydrogen, Cl₄alkyl, haloCl₄alkyl, hydroxyCl₄alkyl or R₇-Cl₄alkyl.

5.- A compound according to claim 4 wherein R₂ represents hydrogen, Cl₄alkyl, haloCl₄alkyl or hydroxyCl₄alkyl.

6.- A compound according to claim 5 wherein R₂ represents hydrogen or Cl₄alkyl.

7.- A compound according to claim 6 wherein R₂ represents hydrogen, methyl or ethyl.

8.- A compound according to claim 7 wherein R₂ represents hydrogen.

9.- A compound according to claim 7 wherein R₂ represents methyl.

10.- A compound according to claim 7 wherein R₂ represents ethyl.

11.- A compound according to any of claims 1 to 10 wherein R₃ represents Cy₃, wherein Cy₃ is optionally substituted with one or more Ri₂.

12.- A compound according to claim 11 wherein Cy₃ represents a 5- or 6-membered saturated monocyclic carbocyclic ring, which optionally contains 1 or 2
heteroatoms independently selected from N, S and O, wherein said ring is bonded
to the rest of the molecule through any available C atom, and wherein one or more
C or S ring atoms are optionally oxidized forming CO, SO or SO₂ groups, wherein
\( \text{Cy}_3 \) is optionally substituted with one or more \( \text{Ri}_2 \).

13.- A compound according to claim 12 wherein \( \text{Cy}_3 \) represents cyclohexyl, 3-piperidinyl or 4-piperidinyl, wherein \( \text{Cy}_3 \) is optionally substituted with one or more \( \text{Ri}_2 \).

14.- A compound according to claim 12 wherein \( \text{Cy}_3 \) represents cyclohexyl optionally substituted with one or more \( \text{Ri}_2 \).

15.- A compound according to claim 12 wherein \( \text{Cy}_3 \) represents 4-piperidinyl optionally substituted with one or more \( \text{Ri}_2 \).

16.- A compound according to claim 12 wherein \( \text{Cy}_3 \) represents 3-piperidinyl optionally substituted with one or more \( \text{Ri}_2 \).

17.- A compound according to claim 12 wherein \( \text{Cy}_3 \) represents a group of formula \( \text{Cy}_{3a} \) or \( \text{Cy}_{3b} \):

\[
\text{Cy}_{3a} \quad \text{Cy}_{3b}
\]

wherein \( \text{Ri}_{2a} \) represents \(-\text{CORi}_5\); and
wherein additionally \( \text{Cy}_{3a} \) and \( \text{Cy}_{3b} \) are independently optionally substituted with one or more \( \text{Ri}_2 \).

18.- A compound according to claim 12 wherein \( \text{Cy}_3 \) represents a group of formula \( \text{Cy}_{3a} \):

\[
\text{Cy}_{3a}
\]

wherein \( \text{Ri}_{2a} \) represents \(-\text{CORi}_5\); and
wherein additionally \( \text{Cy}_{3a} \) is optionally substituted with one or more \( \text{Ri}_2 \).
19.- A compound according to claim 12 wherein Cy₃ represents a group of formula Cy₃b:

\[
\text{Cy₃b; and}
\]

wherein additionally Cy₃b is optionally substituted with one or more Ri₂.

20.- A compound according to any of claims 17 to 19, wherein each Ri₂ is independently selected from Ci₋₄ alkyl, haloCi₋₄ alkyl, hydroxyCi₋₄ alkyl and R₁₋₁ Ci₋₄ alkyl.

21.- A compound according to claim 12 wherein Cy₃ represents a group of formula Cy₃a:

\[
\text{Cy₃a;}
\]

wherein Ri₂a represents -CORi₅.

22.- A compound according to claim 12 wherein Cy₃ represents a group of formula Cy₃b:

\[
\text{Cy₃b;}
\]

23.- A compound according to any of claims 17, 19 or 22 wherein Ri₄ represents hydrogen.

24.- A compound according to any of claims 17, 18 or 21 wherein Ri₅ represents Ci₋₄ alkyl or cyanoCi₋₄ alkyl.

25.- A compound according to claim 24 wherein Ri₅ represents cyanomethyl.

26.- A compound according to claim 1 selected from:
^ans-5-cyano-3-[6-(4-hydroxycyclohexylamino)pyridin-2-yl]pyrazolo[1,5-a]pyridine,
^ans-5-cyano-3-[6-(4-hydroxycyclohexyl-N-methylamino)pyridin-2-yl]pyrazolo[1,5-a]pyridine,
trans-5-cyano-3-[6-(N-ethyl-N-(4-hydroxycyclohexyl)amino)pyridin-2-yl]pyrazolo[1,5-a]pyridine,
5-cyano-3-[6-(piperidin-4-ylamino)pyridin-2-yl]pyrazolo[1,5-a]pyridine,
5-cyano-3-[6-(methyl(piperidin-4-yl)amino)pyridin-2-yl]pyrazolo[1,5-a]pyridine,
5-cyano-3-[6-[(2-cyanoacetyl)piperidin-3-ylamino]pyridin-2-yl]pyrazolo[1,5-a]pyridine,
(F?)-5-cyano-3-[6-[(2-cyanoacetyl)piperidin-3-ylamino]pyridin-2-yl]pyrazolo[1,5-a]pyridine, and
(F?)-5-cyano-3-[6-(N-methyl-1-(2-cyanoacetyl)piperidin-3-ylamino)pyridin-2-yl]pyrazolo[1,5-a]pyridine,
or a salt thereof.

27.- A compound according to claim 1 selected from:
^ans-5-cyano-3-[6-(4-hydroxycyclohexyl-N-methylamino)pyridin-2-yl]pyrazolo[1,5-a]pyridine,
^ans-5-cyano-3-[6-(N-ethyl-N-(4-hydroxycyclohexyl)amino)pyridin-2-yl]pyrazolo[1,5-a]pyridine,
5-cyano-3-[6-(1-(2-cyanoacetyl)piperidin-3-ylamino)pyridin-2-yl]pyrazolo[1,5-a]pyridine,
(F?)-5-cyano-3-[6-(1-(2-cyanoacetyl)piperidin-3-ylamino)pyridin-2-yl]pyrazolo[1,5-a]pyridine, and
(F?)-5-cyano-3-[6-(N-methyl-1-(2-cyanoacetyl)piperidin-3-ylamino)pyridin-2-yl]pyrazolo[1,5-a]pyridine,
or a salt thereof.

28.- A pharmaceutical composition which comprises a compound of formula I according to any of claims 1 to 27 or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable excipients.

29.- A compound according to any of claims 1 to 27 for use in the treatment or prevention of a disease mediated by JAK3.

30.- A compound according to any of claims 1 to 27 for use in the treatment or prevention of at least one disease selected from transplant rejection, immune,
autoimmune or inflammatory diseases, neurodegenerative diseases, or proliferative disorders.

A compound according to claim 30 for use in the treatment or prevention of a disease selected from transplant rejection, rheumatoid arthritis, psoriatic arthritis, psoriasis, type I diabetes, complications from diabetes, multiple sclerosis, systemic lupus erythematosus, atopic dermatitis, mast cell-mediated allergic reactions, leukemias, lymphomas, and thromboembolic and allergic complications associated with leukemias and lymphomas.

A compound according to any of claims 1 to 27 for use in the treatment or prevention of a disease mediated by JAK2.

A compound according to any of claims 1 to 27 for use in the treatment or prevention of a myeloproliferative disorder.

A compound according to claim 33 for use in the treatment or prevention of a disease selected from polycythemia vera, essential thrombocytosis, idiopathic myelofibrosis, chronic myelogenous leukemia, hypereosinophilic syndrome, chronic neutrophilic leukemia, chronic myelomonocytic leukemia, myelofibrosis with myeloid metaplasia, chronic basophilic leukemia, chronic eosinophilic leukemia, systemic mastocytosis and myelodisplastic syndrome.

A process for the preparation of a compound of formula I according to claim 1, which comprises:

(a) reacting a compound of formula VIII with a compound of formula IX

\[
\begin{align*}
& \text{R}_1 \text{N} \quad \text{IX} \\
& \text{R}_2 \text{R}_3 \text{NH}
\end{align*}
\]

wherein \( R_1 \), \( R_2 \) and \( R_3 \) have the meaning described in claim 1 and \( X \) represents halogen; or

(b) converting, in one or a plurality of steps, a compound of formula XII into a compound of formula I
wherein \( R_i \) has the meaning described in claim 1; or

(c) converting, in one or a plurality of steps, a compound of formula I into another compound of formula I.
## A. CLASSIFICATION OF SUBJECT MATTER

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According to International Patent Classification (IPC) or to both national classification and IPC.

## B. FIELDS SEARCHED

- Minimum documentation searched (classification system followed by classification symbols):
  - C07D
  - A61K
  - A61P

- Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched:

- Electronic data base consulted during the international search (name of data base and, where practical, search terms used):
  - EPO-Internal
  - WPI Data
  - BIOSIS
  - EMBASE
  - CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Further documents are listed in the continuation of Box C.

- Special categories of cited documents:
  - 'A' document defining the general state of the art which is not considered to be of particular relevance.
  - 'E' earlier document but published on or after the international filing date.
  - 'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another document or other special reason (as specified).
  - 'O' document not cited to the art, but other special reason (as specified).
  - 'P' document published prior to the international filing date but later than the priority date claimed.

- 'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention.

- 'X' document of particular relevance, the claimed invention cannot be considered as novel or cannot be considered to involve an inventive step when the document is taken alone.

- 'Y' document of particular relevance, the claimed invention cannot be considered as novel or cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

- 'S' document: member of the same patent family.

Date of the actual completion of the international search: 3 February 2010

Date of mailing of the international search report: 15/02/2010

Name and mailing address of the ISA/Authorized officer:
- European Patent Office, P B 5818 Patentlaan 2 NL - 2280 HV RUISWICK
- Tel (+31-70) 340-2040, Fax (+31-70) 340-3016

Bissmire, Stewart
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<td>ALAM ET AL: &quot;Synthesis and SAR of aminopyrimidines as novel c-Jun N-terminal kinase (JNK) inhibitors&quot; BIOORGANIC &amp; MEDICINAL CHEMISTRY LETTERS, PERGAMON, ELSEVIER SCIENCE, GB, vol. 17, no. 12, 15 June 2007 (2007-06-15), pages 3463-3467, XP022097804 abstract page 3463, left-hand column; figure 1; table 2; compounds 6,13</td>
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<td>WO 03/051886 A (SMITHKLINE BEECHAM CORP [US]; HARRIS PHILLIP ANTHONY [US]; JUNG DAVID) 26 June 2003 (2003-06-26) abstract; claims 1-56; examples 1-63</td>
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