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(54) **PURINE DERIVATIVES**

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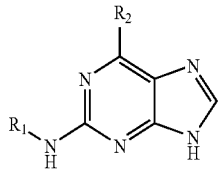
(57) **ABSTRACT**

Purine derivatives of Formula (I), wherein the meanings for the various substituents are as disclosed in the description. These compounds are useful as JAK3 kinase inhibitors.

(I)



PURINE DERIVATIVES

FIELD OF THE INVENTION

[0001] The present invention relates to a new series of purine derivatives, as well as to processes for their preparation, to pharmaceutical compositions comprising them and to their use in therapy.

BACKGROUND OF THE INVENTION

[0002] The Janus kinases (JAKs) are cytoplasmic protein tyrosine kinases that play pivotal roles in pathways that modulate cellular functions in the lympho-hematopoietic 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 intervention.

[0003] 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.

[0004] 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.

[0005] 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.

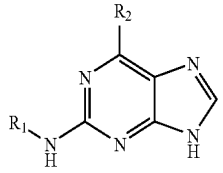
[0006] In conclusion, JAK3 kinase inhibitors have been recognised as a new class of effective immunosuppresive agents useful for transplant rejection prevention and in the prevention or treatment of immune, autoimmune, inflammatory and proliferative diseases such as psoriasis, psoriatic arthritis, rheumatoid arthritis, multiple sclerosis, inflammatory bowel diseases, systemic lupus erythematosus, type I diabetes and complications from diabetes, allergic reactions and leukemia (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(15):1767-84; Cetkovic-Cvrlje M. et al, Arch. Immunol. Ther. Exp. (Warsz), 2004, 52(2):69-82).

[0007] 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 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

[0008] One aspect of the invention relates to a compound of formula I

I



wherein:

[0009] R_1 represents phenyl or a 5- or 6-membered aromatic heterocycle bonded to the NH group through a C atom, each of which can be optionally fused to a 5- or 6-membered saturated, partially unsaturated or aromatic carbocyclic or heterocyclic ring, wherein R_1 can contain from 1 to 4 heteroatoms selected from N, O and S, wherein one or more C or S atoms of the 5- or 6-membered fused ring can be optionally oxidized forming CO, SO or SO_2 groups, and wherein R_1 can be optionally substituted with one or more R_3;

[0010] R_2 represents phenyl or a 5- or 6-membered aromatic heterocycle bonded to the purine ring through a C atom, each of which can be optionally fused to a 5- or 6-membered saturated, partially unsaturated or aromatic carbocyclic or heterocyclic ring, wherein R_2 can contain from 1 to 4 heteroatoms selected from N, O and S, wherein one or more C or S atoms of the 5- or 6-membered fused ring can be optionally oxidized forming CO, SO or SO_2 groups, and wherein R_2 can be optionally substituted with one or more R_4;

[0011] R_3 and R_4 independently represent C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, halogen, —CN, —NO_2, —COR_6, —CO_2R_6, —$CONR_6R_6$, —OR_6, —$OCOR_5$, —$OCONR_5R_5$, —OCO_2R_5, —SR_6, —SO_2R_5, —SOR_5, —$SO_2NR_6R_6$, —$SO_2NR_7COR_5$, —NR_6R_6, —NR_7COR_6, —$NR_7CONR_6R_6$, —$NR_7CO_2R_5$, —$NR_7SO_2R_5$, —C(=N—OH)R_5 or Cy_1, wherein the C_{1-4}alkyl, C_{2-4}alkenyl and C_{2-4}alkynyl groups can be optionally substituted with one or more R_5 and Cy_1 can be optionally substituted with one or more R_9;

[0012] R_5 represents C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl or Cy_2, wherein the C_{1-4}alkyl, C_{2-4}alkenyl and C_{2-4}alkynyl groups can be optionally substituted with one or more R_{10} and Cy_2 can be optionally substituted with one or more R_{11};

[0013] R_6 represents hydrogen or R_5;

[0014] R_7 represents hydrogen or C_{1-4}alkyl;

[0015] R_8 represents halogen, —ON, —NO_2, —COR_{13}, —CO_2R_{13}, —$CONR_{13}R_{13}$, —OR_{13}, —$OCOR_{12}$, —$OCONR_{12}R_{12}$, —OCO_2R_{12}, —SR_{13}, —SO_2R_{12}, —SOR_{12}, —$SO_2NR_{13}R_{13}$, —$SO_2NR_7COR_{12}$, —$NR_{13}R_{13}$, —NR_7COR_{13}, —$NR_7CONR_{13}R_{13}$, —$NR_7CO_2R_{12}$, —$NR_7SO_2R_{12}$, —C(═N—OH)R_{12} or Cy_2, wherein Cy_2 can be optionally substituted with one or more R_{11};

[0016] R_9 represents C_{1-4}alkyl that can be optionally substituted with one or more R_{10}, or R_9 represents any of the meanings described for R_{14};

[0017] R_{10} represents halogen, —ON, —NO_2, —COR_{16}, —CO_2R_{16}, —$CONR_{16}R_{16}$, —OR_{16}, —$OCOR_{15}$, —$OCONR_{15}R_{15}$, —OCO_2R_{15}, —SR_{16}, —SO_2R_{15}, —SOR_{15}, —$SO_2NR_{16}R_{16}$, —$SO_2NR_7COR_{15}$, —$NR_{16}R_{16}$, —NR_7COR_{16}, —$NR_7CONR_{16}R_{16}$, —$NR_7CO_2R_{15}$, —$NR_7SO_2R_{15}$, —C(═N—OH)R_{15} or Cy_2, wherein Cy_2 can be optionally substituted with one or more R_{11};

[0018] R_{11} represents C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl, cyanoC_{1-4}alkyl or any of the meanings described for R_{14};

[0019] R_{12} represents C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl, cyanoC_{1-4}alkyl, Cy_3-C_{1-4}alkyl or Cy_2, wherein Cy_2 can be optionally substituted with one or more R_{11};

[0020] R_{13} represents hydrogen or R_{12};

[0021] R_{14} represents halogen, —ON, —NO_2, —COR_{18}, —CO_2R_{18}, —$CONR_{18}R_{18}$, —OR_{18}, —$OCOR_{17}$, —$OCONR_{17}R_{17}$, —OCO_2R_{17}, —SR_{18}, —SO_2R_{17}, —SOR_{17}, —$SO_2NR_{18}R_{18}$, —$SO_2NR_7COR_{17}$, —$NR_{18}R_{18}$, —NR_7COR_{18}, —$NR_7CONR_{18}R_{18}$, —$NR_7CO_2R_{17}$, —$NR_7SO_2R_{17}$ or —C(═N—OH)R_{17};

[0022] R_{15} represents C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl, cyanoC_{1-4}alkyl or Cy_2, wherein Cy_2 can be optionally substituted with one or more R_{11};

[0023] R_{16} represents hydrogen or R_{15};

[0024] R_{17} represents C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl or cyanoC_{1-4}alkyl;

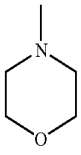
[0025] R_{18} represents hydrogen or R_{17};

[0026] or two R_{17} groups or two R_{18} groups on the same N atom can be bonded completing together with the N atom a saturated 5- or 6-membered ring, which can additionally contain one or two heteroatoms selected from N, S and O and which can be optionally substituted with one or more C_{1-4}alkyl groups;

[0027] Cy_1 and Cy_2 independently represent a 3- to 7-membered monocyclic or 8-to 12-membered bicyclic carbocyclic ring that can be saturated, partially unsaturated or aromatic, and which can optionally contain from 1 to 4 heteroatoms selected from N, S and O, wherein said ring can be bonded to the rest of the molecule through any available C or N atom, and wherein one or more C or S ring atoms can be optionally oxidized forming CO, SO or SO_2 groups;

[0028] Cy_3 represents a ring selected from (a)-(c):

(a)



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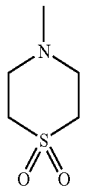
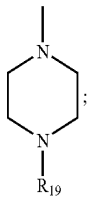
(b)



(c)



and

[0029] R_{19} represents hydrogen or C_{1-4}alkyl.

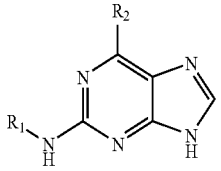
[0030] The present invention also relates to the salts and solvates of the compounds of formula I.

[0031] 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.

[0032] The compounds of formula I are JAK3 kinase inhibitors and therefore can be useful for the treatment or prevention of diseases mediated by this kinase.

[0033] Thus, another aspect of the invention relates to a compound of formula I

I



wherein:

[0034] R_1 represents phenyl or a 5- or 6-membered aromatic heterocycle bonded to the NH group through a C atom, each of which can be optionally fused to a 5- or 6-membered saturated, partially unsaturated or aromatic carbocyclic or heterocyclic ring, wherein R_1 can contain from 1 to 4 heteroatoms selected from N, O and S, wherein one or more C or S atoms of the 5- or 6-membered fused ring can be optionally oxidized forming CO, SO or SO_2 groups, and wherein R_1 can be optionally substituted with one or more R_3;

[0035] R_2 represents phenyl or a 5- or 6-membered aromatic heterocycle bonded to the purine ring through a C atom, each of which can be optionally fused to a 5- or 6-membered saturated, partially unsaturated or aromatic carbocyclic or heterocyclic ring, wherein R_2 can contain from 1 to 4 heteroatoms selected from N, O and S, wherein one or more C or S atoms of the 5- or 6-membered fused ring can be optionally oxidized forming CO, SO or SO_2 groups, and wherein R_2 can be optionally substituted with one or more R_4;

[0036] R_3 and R_4 independently represent C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, halogen, —CN, —NO_2, —COR_E, —CO_2R_6, —$CONR_6R_6$, —OR_6, —$OCOR_5$, —$OCONR_5R_5$,

—OCO_2R_5, —SR_6, —SO_2R_5, —SOR_5, —$SO_2NR_6R_6$, —$SO_2NR_7COR_5$, —NR_6R_6, —NR_7COR_6, —$NR_7CONR_6R_6$, —$NR_7CO_2R_5$, —$NR_7SO_2R_5$, —C(═N—OH)R_5 or Cy_1, wherein the C_{1-4}alkyl, C_{2-4}alkenyl and C_{2-4}alkynyl groups can be optionally substituted with one or more R_8 and Cy_1 can be optionally substituted with one or more R_9;

[0037] R_5 represents C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl or Cy_2, wherein the C_{1-4}alkyl, C_{2-4}alkenyl and C_{2-4}alkynyl groups can be optionally substituted with one or more R_{10} and Cy_2 can be optionally substituted with one or more R_{11};

[0038] R_6 represents hydrogen or R_5;

[0039] R_7 represents hydrogen or C_{1-4}alkyl;

[0040] R_8 represents halogen, —ON, —NO_2, —COR_{13}, —CO_2R_{13}, —$CONR_{13}R_{13}$, —OR_{13}, —$OCOR_{12}$, —$OCONR_{12}R_{12}$, —OCO_2R_{12}, —SR_{13}, —SO_2R_{12}, —SOR_{12}, —$SO_2NR_{13}R_{13}$, —$SO_2NR_7COR_{12}$, —$NR_{13}R_{13}$, —NR_7COR_{13}, —$NR_7CONR_{13}R_{13}$, —$NR_7CO_2R_{12}$, —$NR_7SO_2R_{12}$, —C(═N—OH)R_{12} or Cy_2, wherein Cy_2 can be optionally substituted with one or more R_{11};

[0041] R_9 represents C_{1-4}alkyl that can be optionally substituted with one or more R_{10}, or R_9 represents any of the meanings described for R_{14};

[0042] R_{10} represents halogen, —ON, —NO_2, —COR_{16}, —CO_2R_{16}, —$CONR_{16}R_{16}$, —OR_{16}, —$OCOR_{15}$, —$OCONR_{15}R_{15}$, —OCO_2R_{15}, —SR_{16}, —SO_2R_{15}, —SOR_{15}, —$SO_2NR_{16}R_{16}$, —$SO_2NR_7COR_{15}$, —$NR_{16}R_{16}$, —NR_7COR_{16}, —$NR_7CONR_{16}R_{16}$, —$NR_7CO_2R_{15}$, —$NR_7SO_2R_{15}$, —C(═N—OH)R_{15} or Cy_2, wherein Cy_2 can be optionally substituted with one or more R_{11};

[0043] R_{11} represents C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl, cyanoC_{1-4}alkyl or any of the meanings described for R_{14};

[0044] R_{12} represents C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl, cyanoC_{1-4}alkyl, Cy_3-C_{1-4}alkyl or Cy_2, wherein Cy_2 can be optionally substituted with one or more R_{11};

[0045] R_{13} represents hydrogen or R_{12};

[0046] R_{14} represents halogen, —ON, —NO_2, —COR_{18}, —CO_2R_{18}, —$CONR_{18}R_{18}$, —OR_{18}, —$OCOR_{17}$, —$OCONR_{17}R_{17}$, —OCO_2R_{17}, —SR_{18}, —SO_2R_{17}, —SOR_{17}, —$SO_2NR_{18}R_{18}$, —$SO_2NR_7COR_{17}$, —$NR_{18}R_{18}$, —NR_7COR_{18}, —$NR_7CONR_{18}R_{18}$, —$NR_7CO_2R_{17}$, —$NR_7SO_2R_{17}$ or —C(═N—OH)R_{17};

[0047] R_{15} represents C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl, cyanoC_{1-4}alkyl or Cy_2, wherein Cy_2 can be optionally substituted with one or more R_{11};

[0048] R_{16} represents hydrogen or R_{15};

[0049] R_{17} represents C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl or cyanoC_{1-4}alkyl;

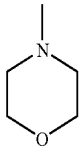
[0050] R_{18} represents hydrogen or R_{17};

[0051] or two R_{17} groups or two R_{18} groups on the same N atom can be bonded completing together with the N atom a saturated 5- or 6-membered ring, which can additionally contain one or two heteroatoms selected from N, S and O and which can be optionally substituted with one or more C_{1-4}alkyl groups;

[0052] Cy_1 and Cy_2 independently represent a 3- to 7-membered monocyclic or 8-to 12-membered bicyclic carbocyclic ring that can be saturated, partially unsaturated or aromatic, and which can optionally contain from 1 to 4 heteroatoms selected from N, S and O, wherein said ring can be bonded to the rest of the molecule through any available C or N atom, and wherein one or more C or S ring atoms can be optionally oxidized forming CO, SO or SO_2 groups;

[0053] Cy_3 represents a ring selected from (a)-(c):

(a)



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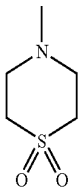

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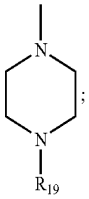


and

[0054] R_{19} represents hydrogen or C_{1-4}alkyl,

for use in therapy.

[0055] Another aspect of this 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.

[0056] 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 diseases mediated by JAKs, particularly JAK3.

[0057] 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; immune, autoimmune or inflammatory diseases; neurodegenerative diseases; and proliferative disorders. In a preferred embodiment, the disease is selected from transplant rejection and immune, autoimmune or inflammatory diseases.

[0058] 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.

[0059] Another aspect of the present invention relates to a compound of formula I or a pharmaceutically acceptable salt thereof for the treatment or prevention of diseases mediated by JAKs, particularly JAK3.

[0060] Another aspect of the present invention relates to a compound of formula I or a pharmaceutically acceptable salt thereof for the treatment or prevention of a disease selected from transplant rejection; immune, autoimmune or inflammatory diseases; neurodegenerative diseases; and proliferative disorders. In a preferred embodiment, the disease is selected from transplant rejection and immune, autoimmune or inflammatory diseases.

[0061] Another aspect of the present invention relates to 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.

[0062] 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 diseases mediated by JAKs, particularly JAK3.

[0063] 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; immune, autoimmune or inflammatory diseases; neurodegenerative diseases; and proliferative disorders. In a preferred embodiment, the disease is selected from transplant rejection and immune, autoimmune or inflammatory diseases.

[0064] 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.

[0065] 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 an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof.

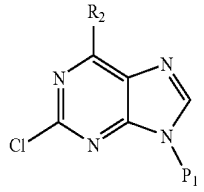
[0066] Another aspect of the present invention relates to a method of treating or preventig a disease selected from transplant rejection, immune, autoimmune or inflammatory diseases, neurodegenerative diseases, and proliferative disorders in a subject in need thereof, especially a human being, which comprises administering to said subject an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof. In a preferred embodiment, the disease is selected from transplant rejection and immune, autoimmune or inflammatory diseases.

[0067] 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 an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof.

[0068] 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 IV with a compound of formula V

IV

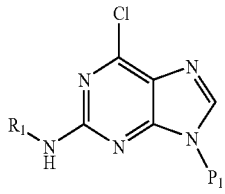


V

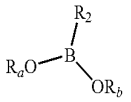
wherein R_1 and R_2 have the previously described meaning and P_1 represents an amine protecting group, followed if required by the removal of the protecting group; or

(b) reacting a compound of formula X with a compound of formula III

X



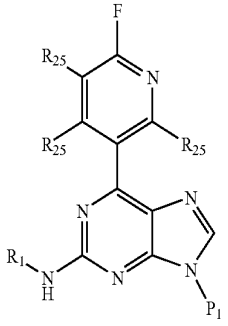
III



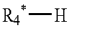
wherein R_1 and R_2 have the previously described meaning, P_1 represents an amine protecting group, and R_a and R_b represent H or C_{1-4}alkyl, or can be bonded forming together with the B and O atoms a 5- or 6-membered ring that can be optionally substituted with one or more methyl groups, followed if required by the removal of the protecting group; or

(c) reacting a compound of formula XV with a compound of formula XII

XV



XII



wherein R_4* represents —NR_6R_6 or Cy_1 bonded through a N atom to the pyridine ring, each R_{25} independently represents hydrogen, halogen, C_{1-4}alkyl, C_{1-4}alkoxy, haloC_{1-4}alkoxy or —SC_{1-4}alky, P_1 represents an amine protecting group and R_1, Cy_1 and R_6 have the meaning previously described, followed if required by the removal of the protecting group; or

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

[0069] In the above definitions, the term 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.

[0070] A C_{2-4}alkenyl group means a straight or branched alkyl chain which contains from 2 to 4 C atoms, and also contains one or two double bonds. Examples include the groups ethenyl, 1-propenyl, 2-propenyl, isopropenyl, 1-butenyl, 2-butenyl, 3-butenyl and 1,3-butadienyl.

[0071] A C_{2-4}alkynyl group means straight or branched alkyl chain which contains from 2 to 4 C atoms, and also contains one or two triple bonds. Examples include the groups ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl and 1,3-butadiynyl.

[0072] A C_{1-4}alkoxy group, as a group or part of a group, means a group —OC_{1-4}alkyl, wherein the 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.

[0073] A halogen group or its abbreviation halo means fluoro, chloro, bromo or iodo.

[0074] A C_{1-4}alkoxyC_{1-4}alkyl group means a group resulting from the replacement of one or more hydrogen atoms from a C_{1-4}alkyl group with one or more C_{1-4}alkoxy groups, 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.

[0075] A haloC_{1-4}alkyl group means a group resulting from the replacement of one or more hydrogen atoms from a C_{1-4}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, pentafluoroethyl, 3-fluoropropyl, 3-chloropropyl, 2,2,3,3-tetrafluoropropyl, 2,2,3,3,3-pentafluoropropyl, heptafluoropropyl, 4-fluorobutyl and nonafluorobutyl.

[0076] A haloC_{1-4}alkoxy group means a group resulting from the replacement of one or more hydrogen atoms from a C_{1-4}alkoxy 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 trifluoromethoxy, fluoromethoxy, 1-chloroethoxy, 2-chloroethoxy, 1-fluoroethoxy, 2-fluoroethoxy, 2-bromoethoxy, 2-iodoethoxy, 2,2,2-trifluoroethoxy, pentafluoroethoxy, 3-fluoropropoxy, 3-chloropropoxy, 2,2,3,3-tetrafluoropropoxy, 2,2,3,3,3-pentafluoropropoxy, heptafluoropropoxy, 4-fluorobutoxy and nonafluorobutoxy.

[0077] A hydroxyC_{1-4}alkyl group means a group resulting from the replacement of one or more hydrogen atoms from a C_{1-4}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.

[0078] A cyanoC_{1-4}alkyl group means a group resulting from the replacement of one or more hydrogen atoms from a C_{1-4}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.

[0079] A Cy_3-C_{1-4}alkyl group means a group resulting from the replacement of one hydrogen atom from a C_{1-4}alkyl group with one Cy_3 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-1-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-dioxotiomorpholin-4-yl)ethyl, 3-(1,1-dioxothiomorpholin-4-yl)propyl and 4-(1,1-dioxothiomorpholin-4-yl)butyl.

[0080] A Cy_2, C_{1-4}alkyl group means a group resulting from the replacement of one hydrogen atom from a C_{1-4}alkyl group with one Cy_2, group as defined below.

[0081] The term Cy_1 or Cy_2 refers to a 3- to 7-membered monocyclic or a 8- to 12-membered bicyclic carbocyclic ring that can be saturated, partially unsaturated or aromatic, and which optionally contains from 1 to 4 heteroatoms selected from N, S and O. When Cy_1 or Cy_2 are saturated or partially unsaturated, one or more C or S ring atoms can be optionally oxidized forming CO, SO or SO_2 groups. Cy_1 and Cy_2 can be optionally substituted as disclosed above in the definition of a compound of formula I; if substituted, the substituents can be the same or different and can be placed on any available position. Cy_1 and Cy_2 can be bonded to the rest of the molecule through any available carbon or nitrogen atom. Examples of Cy_1 and Cy_2 include, among others, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, azetidinyl, aziridinyl, oxyranyl, oxetanyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, oxazolidinyl, pyrazolidinyl, pyrrolidinyl, thiazolidinyl, dioxanyl, morpholinyl, thiomorpholinyl, 1,1-dioxothiomorpholinyl, piperazinyl, homopiperazinyl, piperidinyl, pyranyl, tetrahydropyranyl, azepinyl, oxazinyl, oxazolinyl, pyrrolinyl, thiazolinyl, pyrazolinyl, imidazolinyl, isoxazolinyl, isothiazolinyl, cyclobutanonyl, cyclopentanonyl, cyclohexanonyl, cycloheptanonyl, 2-oxopyrrolidinyl, 2-oxo-piperidinyl, 4-oxo-piperidinyl, 2(1H)-pyridonyl, 2(1H)-pyrazinonyl, 2(1H)-pyrimidinonyl, 3(2H)-pyridazinonyl, azetidinonyl, imidazolidinonyl, oxazolidinonyl, 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, pyridazinyl, benzimidazolyl, benzooxazolyl, benzofuranyl, isobenzofuranyl, indolyl, isoindolyl, benzothiophenyl, benzothiazolyl, quinolinyl, isoquinolinyl, phtalazinyl, quinazolinyl, quinoxalinyl, cinolinyl, naphthyridinyl, indazolyl, imidazopyridinyl, pyrrolopyridinyl, thienopyridinyl, imidazopyrimidinyl, imidazopyrazinyl, imidazopyridazinyl, pyrazolopyrazinyl,

pyrazolopyridinyl, pyrazolopyrimidinyl, benzo[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-isoindolyl, 1,2,3,4-tetrahydroquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, 1-oxo-1,2,3,4-tetrahydroisoquinolinyl, 1-oxo-1,2-dihydroisoquinolinyl and 4-oxo-3,4-dihydroquinazolinyl.

[0082] In a compound of formula I R_1 and R_2 represent a phenyl group or a 5- or 6-membered aromatic heterocycle which is bonded through a C atom to the NH group, in the case of R_1, and to the purine ring, in the case of R_2. Both the phenyl group and the 5- or 6-membered aromatic heterocycle can be optionally fused to a 5- or 6-membered carbocyclic or heterocyclic ring that can be saturated, partially unsaturated or aromatic. The R_1 and R_2 groups can thus be either monocyclic or bicyclic and can contain from 1 to 4 heteroatoms in total selected from N, O and S. When the second ring, that is, the fused 5- or 6-membered carbocyclic or heterocyclic ring, is saturated or partially unsaturated, one or more C or S atoms of said ring can be optionally oxidized forming CO, SO or SO_2 groups. R_1 can be optionally substituted with one or more R_3 and R_2 can be optionally substituted with one or more R_4, as indicated above in the definition of a compound of formula I. Each R_3 and each R_4 is independently selected from the list of possible meanings for said groups indicated in the definition of a compound of formula I. If present, the substituents on R_1 or R_2 can be placed in any available position. Examples of R_1 and R_2 include, among others, 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, pyridazinyl, benzimidazolyl, benzooxazolyl, benzofuranyl, isobenzofuranyl, indolyl, isoindolyl, benzothiophenyl, benzothiazolyl, quinolinyl, isoquinolinyl, phtalazinyl, quinazolinyl, quinoxalinyl, cinolinyl, naphthyridinyl, indazolyl, imidazopyridinyl, pyrrolopyridinyl, thienopyridinyl, imidazopyrimidinyl, imidazopyrazinyl, imidazopyridazinyl, pyrazolopyrazinyl, pyrazolopyridinyl, pyrazolopyrimidinyl, benzo[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-isoindolyl, 1,2,3,4-tetrahydroquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, 1-oxo-1,2,3,4-tetrahydroisoquinolinyl, 1-oxo-1,2-dihydroisoquinolinyl and 4-oxo-3,4-dihydroquinazolinyl.

[0083] In the above definitions of Cy_1, Cy_2, R_1 and R_2, when the examples listed refer to a bicycle in general terms, all possible dispositions of the atoms are included. Thus, for example, the term pyrazolopyridinyl can include groups such as 1H-pyrazolo[3,4-b]pyridinyl, 1H-pyrazolo[1,5-a]pyridinyl, 1H-pyrazolo[3,4-c]pyridinyl, 1H-pyrazolo[4,3-c]pyridinyl and 1H-pyrazolo[4,3-b]pyridinyl; the term imidazopyrazinyl can include groups such as 1H-imidazo[4,5-b]pyrazinyl, imidazo[1,2-a]pyrazinyl and imidazo[1,5-a]pyrazinyl; and the term pyrazolopyrimidinyl can include groups such as 1H-pyrazolo[3,4-d]pyrimidinyl, 1H-pyrazolo[4,3-d]pyrimidinyl, pyrazolo[1,5-a]pyrimidinyl and pyrazolo[1,5-c]pyrimidinyl.

[0084] 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, thienyl or indolyl, all possible positions of attachment are included, unless any limitation is mentioned in the definition of the corresponding group, for example that the ring is bonded through a C atom in R_1 and R_2, in which case such limitation applies. Thus for example, in the definitions for Cy_1 and Cy_2, which do not include any limitation with regard to the position of attachment, the term pyridyl includes 2-pyridyl, 3-pyridyl and 4-pyridyl; thienyl includes 2-thienyl and 3-thienyl; and indolyl includes 1-indolyl, 2-indolyl, 3-indolyl, 4-indolyl, 5-indolyl, 6-indolyl and 7-indolyl.

[0085] 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 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.

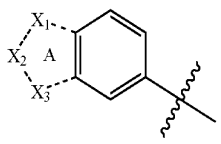
[0086] When in the definition of a substituent two or more groups with the same numbering are indicated (e.g. $—NR_7CONR_6R_6$, $—NR_{16}R_{16}$, $—CONR_{18}R_{18}$, etc.), this does not mean that they must be the same. Each of them is independently selected from the list of possible meanings given for said group, and therefore they can be the same or different.

[0087] The invention thus relates to the compounds of formula I as defined above.

[0088] In another embodiment, the invention relates to the compounds of formula I wherein R_1 represents phenyl or pyridyl, which can be optionally fused to a 5- or 6-membered saturated, partially unsaturated or aromatic carbocyclic or heterocyclic ring, wherein R_1 can contain from 1 to 4 heteroatoms selected from N, O and S, wherein one or more C or S atoms of the 5- or 6-membered fused ring can be optionally oxidized forming CO, SO or SO_2 groups, and wherein R_1 can be optionally substituted with one or more R_3.

[0089] In another embodiment, the invention relates to the compounds of formula I wherein R_1 represents phenyl, pyridyl or a ring of formula R_{1a},

R_{1a}



wherein in ring A X_1, X_2 and X_3 are selected from C, N, O and S and the dashed lines represent single or double bonds, wherein one or two C or S atoms of ring A can be optionally oxidized forming CO, SO or SO_2 groups, and wherein the phenyl, pyridyl and R_{1a} groups can be optionally substituted with one or more R_3.

[0090] In another embodiment, the invention relates to the compounds of formula I wherein R_1 represents phenyl, 3-pyridyl, 4-pyridyl or a ring of formula R_{1a}, each of which can be optionally substituted with one or more R_3.

[0091] In another embodiment, the invention relates to the compounds of formula I wherein R_1 represents phenyl, pyridyl, benzo[1,3]dioxolyl or benzooxazolyl, each of which can be optionally substituted with one or more R_3.

[0092] In another embodiment, the invention relates to the compounds of formula I wherein R_1 represents phenyl, 3-pyridyl, 4-pyridyl, 5-benzo[1,3]dioxolyl or 6-benzooxazolyl,

each of which can be optionally substituted with one or more R_3.

[0093] In another embodiment, the invention relates to the compounds of formula I wherein R_1 represents phenyl optionally substituted with one or more R_3.

[0094] In another embodiment, the invention relates to the compounds of formula I wherein R_1 represents phenyl substituted with one or more R_3.

[0095] In another embodiment, the invention relates to the compounds of formula I wherein R_1 represents phenyl substituted with one, two or three R_3.

[0096] In another embodiment, the invention relates to the compounds of formula I wherein R_1 represents phenyl substituted with one or two R_3.

[0097] In another embodiment, the invention relates to the compounds of formula I wherein R_1 represents phenyl substituted with one or two R_3, which are placed at positions 3, 4 and/or 5 of the phenyl ring.

[0098] In another embodiment, the invention relates to the compounds of formula I wherein each R_3 independently represents C_{1-4}alkyl, halogen, —CN, —COR_6, —CO_2R_6, —$CONR_6R_6$, —OR_6, —SR_6, —SO_2R_5, —$SO_2NR_6R_6$, —$SO_2NR_7COR_5$, —NR_6R_6, —NR_7COR_6, —$NR_7CONR_6R_6$, —$NR_7SO_2R_5$ or Cy_1, wherein the C_{1-4}alkyl group can be optionally substituted with one or more R_8 and Cy_1 can be optionally substituted with one or more R_9.

[0099] In another embodiment, the invention relates to the compounds of formula I wherein each R_3 independently represents C_{1-4}alkyl, halogen, —CN, —OR_6, —SO_2R_5, —$SO_2NR_6R_6$, —$SO_2NR_7COR_5$, —NR_6R_6, —NR_7COR_6, —$NR_7SO_2R_5$ or Cy_1, wherein the C_{1-4}alkyl group can be optionally substituted with one or more R_8 and Cy_1 can be optionally substituted with one or more R_9.

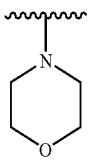
[0100] In another embodiment, the invention relates to the compounds of formula I wherein each R_3 independently represents C_{1-4}alkyl, halogen, haloC_{1-4}alkyl, hydroxyC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, —CN, —OR_6, —SO_2R_5, —$SO_2NR_6R_6$, —$SO_2NR_7COR_5$, —NR_6R_6, —NR_7COR_6, —$NR_7SO_2R_5$ or Cy_1, wherein Cy_1 can be optionally substituted with one or more R_9.

[0101] In another embodiment, the invention relates to the compounds of formula I wherein Cy_1 in R_3 is Cy_{1a} and Cy_{1a} represents a 5- or 6-membered saturated monocyclic heterocycle which contains 1 or 2 heteroatoms selected from N, S and O, wherein said ring can be bonded to the rest of the molecule through any available C or N atom, and wherein one or more C or S ring atoms can be optionally oxidized forming CO, SO or SO_2 groups, wherein said Cy_{1a} can be optionally substituted with one or more R_9.

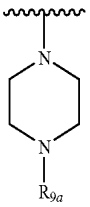
[0102] In another embodiment, the invention relates to the compounds of formula I wherein Cy_1 in R_3 is Cy_{1c} and Cy_{1c} represents a 5- or 6-membered saturated monocyclic heterocycle which contains 1 or 2 heteroatoms selected from N, S and O with the proviso that it contains at least 1 N atom, wherein said ring is bonded to the rest of the molecule through a N atom, wherein one or more C or S ring atoms can be optionally oxidized forming CO, SO or SO_2 groups, and wherein said Cy_{1c} can be optionally substituted with one or more R_9.

[0103] In another embodiment, the invention relates to the compounds of formula I wherein Cy_1 in R_3 represents a ring selected from (i)-(iii):

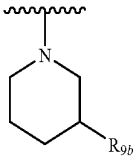
(i)



(ii)



(iii)



wherein R_{9a} represents hydrogen or C_{1-4}alkyl, and R_{9b} represents hydrogen, C_{1-4}alkyl or hydroxy.

[0104] In another embodiment, the invention relates to the compounds of formula I wherein each R_3 independently represents C_{1-4}alkyl, halogen, —OR_6, —$SO_2NR_6R_6$, —$SO_2NR_7COR_5$, —NR_6R_6, —NR_7COR_6 or Cy_{1a}, wherein the C_{1-4}alkyl group can be optionally substituted with one or more R_8 and Cy_{1a} can be optionally substituted with one or more R_9.

[0105] In another embodiment, the invention relates to the compounds of formula I wherein each R_3 independently represents C_{1-4}alkyl, halogen, hydroxyC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, —OR_6, $Cy_{2a}C_{1-4}$alkyl, —$SO_2NR_6R_6$, —$SO_2NR_7COR_5$, —NR_6R_6, —NR_7COR_6 or Cy_{1c}, wherein Cy_{1c} can be optionally substituted with one or more R_9, and wherein Cy_{2a} represents a 5- or 6-membered saturated monocyclic heterocycle which contains 1 or 2 heteroatoms selected from N, S and O and which can be bonded to the rest of the molecule through any available C or N atom, wherein one or more C or S ring atoms can be optionally oxidized forming CO, SO or SO_2 groups, and wherein said Cy_{2a} can be optionally substituted with one or more R_{11}.

[0106] In another embodiment, the invention relates to the compounds of formula I wherein each R_3 independently represents C_{1-4}alkyl, halogen, hydroxyC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, —OR_6, $Cy_{2a}C_{1-4}$alkyl, —$SO_2NR_6R_6$, —$SO_2NR_7COR_5$, —NR_6R_6, —NR_7COR_6 or a ring of formula (i)-(iii), wherein Cy_{2a} can be optionally substituted with one or more R_{11}.

[0107] In another embodiment, the invention relates to the compounds of formula I wherein R_6 in R_3 represents hydrogen or R_5 and R_5 represents C_{1-4}alkyl optionally substituted with one or more R_{10}.

[0108] In another embodiment, the invention relates to the compounds of formula I wherein R_6 in R_3 represents hydrogen or R_5 and R_5 represents C_{1-4}alkyl, hydroxyC_{1-4}alkyl or C_{1-4}alkoxyC_{1-4}alkyl.

[0109] In another embodiment, the invention relates to the compounds of formula I wherein:

[0110] R_1 represents phenyl substituted with one or more R_3;

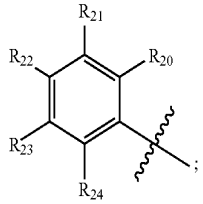
[0111] each R_3 independently represents C_{1-4}alkyl, halogen, haloC_{1-4}alkyl, hydroxyC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, —CN, —OR_6, —SO_2R_5, —$SO_2NR_6R_6$, —$SO_2NR_7COR_5$, —NR_6R_6, —NR_7COR_6, —$NR_7SO_2R_5$ or Cy_{1a}, wherein Cy_{1a} can be optionally substituted with one or more R_9; and

[0112] Cy_{1a} represents a 5- or 6-membered saturated monocyclic heterocycle which contains 1 or 2 heteroatoms selected from N, S and O, wherein said ring can be bonded to the rest of the molecule through any available C or N atom, and wherein one or more C or S ring atoms can be optionally oxidized forming CO, SO or SO_2 groups.

[0113] In another embodiment, the invention relates to the compounds of formula I wherein:

[0114] R_1 represents a ring of formula R_{1b}:

R_{1b}



[0115] one of R_{21}, R_{22} and R_{23} represents hydroxyC_{1-4}alkyl, —CN, —OR_6, —$SO_2NR_6R_6$, —NR_7COR_6, —$NR_7SO_2R_5$ or Cy_{1a}, wherein Cy_{1a} can be optionally substituted with one or more R_9; and

[0116] the remainder of R_{21}, R_{22} and R_{23} as well as R_{20} and R_{24} are independently selected from hydrogen, C_{1-4}alkyl, halogen and C_{1-4}alkoxy.

[0117] In another embodiment, the invention relates to the compounds of formula I wherein:

[0118] R_1 represents phenyl substituted with one or more, preferably one or two R_3; and

[0119] each R_3 independently represents C_{1-4}alkyl, halogen, —OR_6, —$SO_2NR_6R_6$, —$SO_2NR_7COR_5$, —NR_6R_6, —NR_7COR_6 or Cy_{1a}, wherein the C_{1-4}alkyl group can be optionally substituted with one or more R_8 and Cy_{1a} can be optionally substituted with one or more R_9.

[0120] In another embodiment, the invention relates to the compounds of formula I wherein:

[0121] R_1 represents phenyl substituted with one or more, preferably one or two

[0122] R_3; and

[0123] each R_3 independently represents C_{1-4}alkyl, halogen, hydroxyC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, —OR_6, $Cy_{2a}C_{1-4}$alkyl, —$SO_2NR_6R_6$, —$SO_2NR_7COR_5$, —NR_6R_6, —NR_7COR_6 or Cy_{1c}, wherein Cy_{1c} can be optionally substituted with one or more R_9, and wherein Cy_{2a} can be optionally substituted with one or more R_{11}.

[0124] In another embodiment, the invention relates to the compounds of formula I wherein:

[0125] R_1 represents phenyl substituted with one or two R_3, which are placed at positions 3, 4 and/or 5 of the phenyl ring; and

[0126] each R_3 independently represents C_{1-4}alkyl, halogen, hydroxyC_{1-4}alkyl,

[0127] C_{1-4}alkoxyC_{1-4}alkyl, —OR_6, $Cy_{2a}C_{1-4}$alkyl, —$SO_2NR_6R_6$, —$SO_2NR_7COR_5$, —NR_6R_6, —NR_7COR_6 or Cy_{1c}, wherein Cy_{1c} can be optionally substituted with one or more R_9, and wherein Cy_{2a} can be optionally substituted with one or more R_{11}.

[0128] In another embodiment, the invention relates to the compounds of formula I wherein:

[0129] R_1 represents phenyl substituted with one or more, preferably one or two R_3; and

[0130] each R_3 independently represents C_{1-4}alkyl, halogen, hydroxyC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, —OR_6, $Cy_{2a}C_{1-4}$alkyl, —$SO_2NR_6R_6$, —$SO_2NR_7COR_5$, —NR_6R_6, —NR_7COR_6 or a ring of formula (i)-(iii), wherein Cy_{2a} can be optionally substituted with one or more R_{11}.

[0131] In another embodiment, the invention relates to the compounds of formula I wherein:

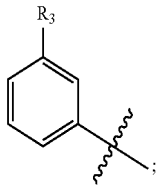
[0132] R_1 represents phenyl substituted with one or two R_3, which are placed at positions 3, 4 and/or 5 of the phenyl ring; and

[0133] each R_3 independently represents C_{1-4}alkyl, halogen, hydroxyC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, —OR_6, $Cy_{2a}C_{1-4}$alkyl, —$SO_2NR_6R_6$, —$SO_2NR_7COR_5$, —NR_6R_6, —NR_7COR_6 or a ring of formula (i)-(iii), wherein Cy_{2a} can be optionally substituted with one or more R_{11}.

[0134] In another embodiment, the invention relates to the compounds of formula I wherein:

[0135] R_1 represents a ring of formula R_{1c}:

R_{1c}



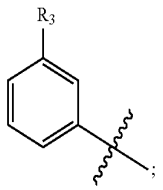
[0136] and

[0137] R_3 represents C_{1-4}alkyl, —NR_6R_6, —$SO_2NR_6R_6$, —$SO_2NR_7COR_5$, —NR_7COR_6 or Cy_{1c}, wherein the C_{1-4}alkyl group can be optionally substituted with one or more R_8 and Cy_{1c} can be optionally substituted with one or more R_9.

[0138] In another embodiment, the invention relates to the compounds of formula I wherein:

[0139] R_1 represents a ring of formula R_{1c}:

R_{1c}

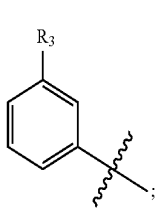


and

[0140] R_3 represents hydroxyC_{1-4}alkyl, $Cy_{2a}C_{1-4}$alkyl, —NR_6R_6, —$SO_2NR_6R_6$, —$SO_2NR_7COR_6$, —NR_7COR_6 or Cy_{1c}, wherein Cy_{1c} can be optionally substituted with one or more R_9 and Cy_{2a} can be optionally substituted with one or more R_{11}.

[0141] In another embodiment, the invention relates to the compounds of formula I wherein:

[0142] R_1 represents a ring of formula R_{1c}:



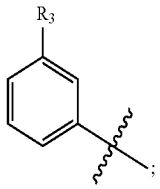
[0143] R_3 represents hydroxyC_{1-4}alkyl, $Cy_{2a}C_{1-4}$alkyl, $—NR_6R_6$, $—SO_2NR_6R_6$, $—SO_2NR_7COR_6$, $—NR_7COR_6$ or Cy_{1c}, wherein Cy_{1c} can be optionally substituted with one or more R_9 and Cy_{2a} can be optionally substituted with one or more R_{11};

[0144] R_5 represents C_{1-4}alkyl, hydroxyC_{1-4}alkyl or C_{1-4}alkoxyC_{1-4}alkyl; and

[0145] R_6 represents hydrogen or R_5.

[0146] In another embodiment, the invention relates to the compounds of formula I wherein:

[0147] R_1 represents a ring of formula R_{1c}:

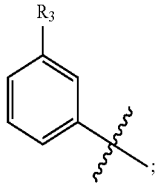


and

[0148] R_3 represents $—SO_2NR_6R_6$, $—NR_7COR_6$ or $Cy_{2a}C_{1-4}$alkyl, wherein Cy_{2a} can be optionally substituted with one or more R_{11}.

[0149] In another embodiment, the invention relates to the compounds of formula I wherein:

[0150] R_1 represents a ring of formula R_{1c}:

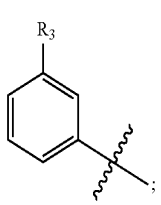


[0151] R_3 represents $—SO_2NR_6R_6$, $—NR_7COR_6$ or $Cy_{2a}C_{1-4}$alkyl, wherein Cy_{2a} can be optionally substituted with one or more R_{11}; and

[0152] R_6 represents hydrogen or C_{1-4}alkyl optionally substituted with one or more R_{10}.

[0153] In another embodiment, the invention relates to the compounds of formula I wherein:

[0154] R_1 represents a ring of formula R_{1c}:

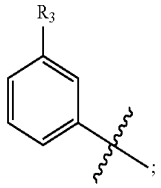


[0155] R_3 represents $—SO_2NR_6R_6$, $—NR_7COR_6$ or $Cy_{2a}C_{1-4}$alkyl, wherein Cy_{2a} can be optionally substituted with one or more R_{11}; and

[0156] R_6 represents hydrogen, C_{1-4}alkyl, hydroxyC_{1-4}alkyl or C_{1-4}alkoxyC_{1-4}alkyl.

[0157] In another embodiment, the invention relates to the compounds of formula I wherein:

[0158] R_1 represents a ring of formula R_{1c}:

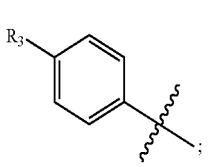


[0159] R_3 represents $—SO_2NR_6R_6$, $—NR_7COR_6$ or $Cy_{2a}C_{1-4}$alkyl, wherein Cy_{2a} can be optionally substituted with one or more R_{11}; and

[0160] R_6 represents hydrogen or C_{1-4}alkyl.

[0161] In another embodiment, the invention relates to the compounds of formula I wherein:

[0162] R_1 represents a ring of formula R_{1d}:

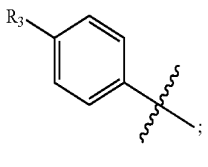


and

[0163] R_3 represents C_{1-4}alkyl, $—NR_6R_6$, $—SO_2NR_6R_6$ or Cy_{1c}, wherein the C_{1-4}alkyl group can be optionally substituted with one or more R_8 and Cy_{1c} can be optionally substituted with one or more R_9.

[0164] In another embodiment, the invention relates to the compounds of formula I wherein:

[0165] R_1 represents a ring of formula R_{1d}:



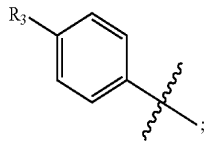
and

[0166] R_3 represents hydroxyC_{1-4}alkyl, $Cy_{2a}C_{1-4}$alkyl, $—NR_6R_6$, $—SO_2NR_6R_6$ or Cy_{1c}, wherein Cy_{1c} can be optionally substituted with one or more R_9 and wherein Cy_{2a} can be optionally substituted with one or more R_{11}.

[0167] In another embodiment, the invention relates to the compounds of formula I wherein:

[0168] R_1 represents a ring of formula R_{1d}:

R_{1d}



[0169] R_3 represents hydroxyC_{1-4}alkyl, $Cy_{2a}C_{1-4}$alkyl, $—NR_6R_6$, $—SO_2NR_6R_6$ or Cy_{1c},

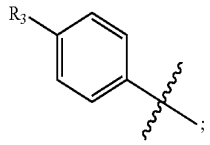
[0170] wherein Cy_{1c} can be optionally substituted with one or more R_9 and wherein Cy_{2a} can be optionally substituted with one or more R_{11}; and

[0171] R_6 represents hydrogen or C_{1-4}alkyl optionally substituted with one or more R_{10}.

[0172] In another embodiment, the invention relates to the compounds of formula I wherein:

[0173] R_1 represents a ring of formula R_{1d}:

R_{1d}



[0174] R_3 represents hydroxyC_{1-4}alkyl, $Cy_{2a}C_{1-4}$alkyl, $—NR_6R_6$, $—SO_2NR_6R_6$ or Cy_{1c},

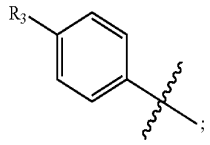
[0175] wherein Cy_{1c} can be optionally substituted with one or more R_9 and wherein Cy_{2a} can be optionally substituted with one or more R_{11}; and

[0176] R_6 represents hydrogen, C_{1-4}alkyl, hydroxyC_{1-4}alkyl or C_{1-4}alkoxyC_{1-4}alkyl.

[0177] In another embodiment, the invention relates to the compounds of formula I wherein:

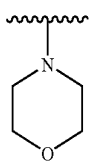
[0178] R_1 represents a ring of formula R_{1d}:

R_{1d}



[0179] R_3 represents hydroxyC_{1-4}alkyl, $Cy_{2a}C_{1-4}$alkyl, $—NR_6R_6$, $—SO_2NR_6R_6$ or a ring of formula (i)-(iii), wherein Cy_{2a} can be optionally substituted with one or more R_{11};

(i)



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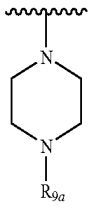
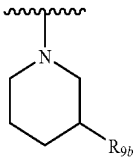
(ii)



(iii)



[0180] R_6 represents hydrogen, C_{1-4}alkyl, hydroxyC_{1-4}alkyl or C_{1-4}alkoxyC_{1-4}alkyl;

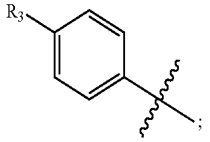
[0181] R_{9a} represents hydrogen or C_{1-4}alkyl; and

[0182] R_{9b} represents hydrogen, C_{1-4}alkyl or hydroxy.

[0183] In another embodiment, the invention relates to the compounds of formula I wherein:

[0184] R_1 represents a ring of formula R_{1d}:

R_{1d}



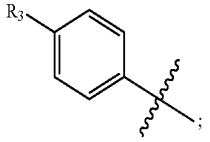
and

[0185] R_3 represents $—SO_2NR_6R_6$ or Cy_{1c} optionally substituted with one or more R_9.

[0186] In another embodiment, the invention relates to the compounds of formula I wherein:

[0187] R_1 represents a ring of formula R_{1d}:

R_{1d}



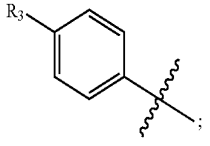
[0188] R_3 represents $—SO_2NR_6R_6$ or Cy_{1c} optionally substituted with one or more R_9; and

[0189] R_6 represents hydrogen or C_{1-4}alkyl optionally substituted with one or more R_{10}.

[0190] In another embodiment, the invention relates to the compounds of formula I wherein:

[0191] R_1 represents a ring of formula R_{1d}:

R_{1d}



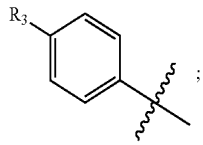
and

[0192] R_3 represents Cy_{1c} optionally substituted with one or more R_9.

[0193] In another embodiment, the invention relates to the compounds of formula I wherein:

[0194] R_1 represents a ring of formula R_{1d}:

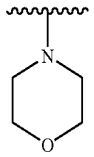
R_{1d}



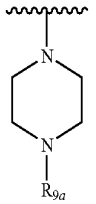
;

[0195] R_3 represents a ring of formula (i)-(iii)

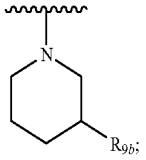
(i)



(ii)



(iii)



;

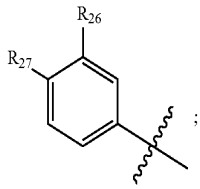
[0196] R_{9a} represents hydrogen or C_{1-4}alkyl; and

[0197] R_{9b} represents hydrogen, C_{1-4}alkyl or hydroxy.

[0198] In another embodiment, the invention relates to the compounds of formula I wherein:

[0199] R_1 represents a ring of formula R_{1e}:

R_{1e}



;

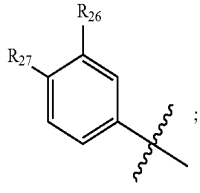
[0200] R_{26} represents halogen or $—SO_2NR_6R_6$; and

[0201] R_{27} represents C_{1-4}alkyl, C_{1-4}alkoxyalkyl or $—OR_6$.

[0202] In another embodiment, the invention relates to the compounds of formula I wherein:

[0203] R_1 represents a ring of formula R_{1e}:

R_{1e}



;

[0204] R_{26} represents halogen or $—SO_2NR_6R_6$;

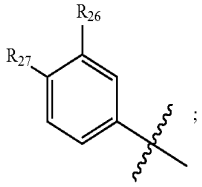
[0205] R_{27} represents C_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl or $—OR_6$; and

[0206] R_6 represents hydrogen, C_{1-4}alkyl, hydroxyC_{1-4}alkyl or C_{1-4}alkoxyC_{1-4}alkyl.

[0207] In another embodiment, the invention relates to the compounds of formula I wherein:

[0208] R_1 represents a ring of formula R_{1e}:

R_{1e}



;

[0209] R_{26} represents halogen or $—SO_2NR_6R_6$;

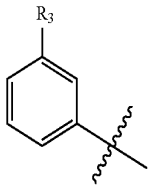
[0210] R_{27} represents C_{1-4}alkyl C_{1-4}alkoxyC_{1-4}alkyl or $—OR_6$; and

[0211] R_6 represents hydrogen or C_{1-4}alkyl.

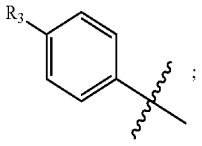
[0212] In another embodiment, the invention relates to the compounds of formula I wherein:

[0213] R_1 represents a group selected from R_{1c} and R_{1d}:

R_{1c}



R_{1d}



;

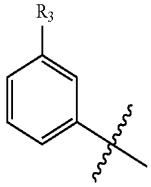
[0214] R_3 in R_{1c} represents $—SO_2NR_6R_6$, $—NR_7COR_6$ or $Cy_{2a}C_{1-4}$alkyl, wherein Cy_{2a} can be optionally substituted with one or more R_{11}; and

[0215] R_3 in R_{1d} represents $—SO_2NR_6R_6$ or Cy_{1c} optionally substituted with one or more R_9.

[0216] In another embodiment, the invention relates to the compounds of formula I wherein:

[0217] R_1 represents a group selected from R_{1c} and R_{1d}:

R_{1c}



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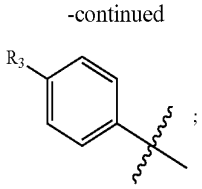


R_{1d}

[0218] R_3 in R_{1c} represents $—SO_2NR_6R_6$, $—NR_7COR_6$ or $Cy_{2a}C_{1-4}$alkyl, wherein Cy_{2a} can be optionally substituted with one or more R_{11};

[0219] R_3 in R_{1d} represents $—SO_2NR_6R_6$ or Cy_{1c} optionally substituted with one or more R_9; and

[0220] R_6 represents hydrogen or C_{1-4}alkyl optionally substituted with one or more R_{10}.

[0221] In another embodiment, the invention relates to the compounds of formula I wherein R_2 represents phenyl or a 5- or 6-membered aromatic heterocycle bonded to the purine ring through a C atom, which can be optionally fused to a 5- or 6-membered saturated, partially unsaturated or aromatic carbocyclic or heterocyclic ring, wherein R_2 can contain from 1 to 4 heteroatoms selected from N, O and S, wherein the adjacent atoms to the C atom at the position of attachment to the purine ring are C atoms, wherein one or more C or S atoms of the 5- or 6-membered fused ring can be optionally oxidized forming CO, SO or SO_2 groups, and wherein R_2 can be optionally substituted with one or more R_4.

[0222] In another embodiment, the invention relates to the compounds of formula I wherein R_2 represents phenyl, pyridyl, indolyl or thienyl, which can all be optionally substituted with one or more R_4.

[0223] In another embodiment, the invention relates to the compounds of formula I wherein R_2 represents phenyl, 3-pyridyl, 5-indolyl or 3-thienyl which can all be optionally substituted with one or more R_4.

[0224] In another embodiment, the invention relates to the compounds of formula I wherein R_2 represents phenyl optionally substituted with one or more R_4.

[0225] In another embodiment, the invention relates to the compounds of formula I wherein R_2 represents phenyl substituted with one or more R_4.

[0226] In another embodiment, the invention relates to the compounds of formula I wherein R_2 represents a 5- or 6-membered aromatic heterocycle bonded to the purine ring through a C atom, which can be optionally fused to a 5- or 6-membered saturated, partially unsaturated or aromatic carbocyclic or heterocyclic ring, wherein R_2 contains from 1 to 4 heteroatoms selected from N, O and S, wherein one or more C or S atoms of the 5- or 6-membered fused ring can be optionally oxidized forming CO, SO or SO_2 groups, and wherein R_2 can be optionally substituted with one or more R_4.

[0227] In another embodiment, the invention relates to the compounds of formula I wherein R_2 represents a 5- or 6-membered aromatic heterocycle bonded to the purine ring through a C atom, which can be optionally fused to a 5- or 6-membered saturated, partially unsaturated or aromatic carbocyclic or heterocyclic ring, wherein R_2 contains from 1 to 4 heteroatoms selected from N, O and S, wherein the adjacent atoms to the C atom at the position of attachment to the purine ring are C atoms, wherein one or more C or S atoms of the 5- or 6-membered fused ring can be optionally oxidized forming CO, SO or SO_2 groups, and wherein R_2 can be optionally substituted with one or more R_4.

[0228] In another embodiment, the invention relates to the compounds of formula I wherein R_2 represents a 5- or 6-membered aromatic heterocycle bonded to the purine ring through a C atom, which can be optionally fused to a 5- or 6-membered aromatic carbocyclic or heterocyclic ring, wherein R_2 contains from 1 to 4 heteroatoms selected from N, O and S, wherein the adjacent atoms to the C atom at the position of attachment to the purine ring are C atoms, and wherein R_2 can be optionally substituted with one or more R_4.

[0229] In another embodiment, the invention relates to the compounds of formula I wherein R_2 represents a 5- or 6-membered aromatic heterocycle bonded to the purine ring through a C atom, wherein R_2 contains 1 or 2 heteroatoms selected from N, O and S, and wherein R_2 can be optionally substituted with one or more R_4.

[0230] In another embodiment, the invention relates to the compounds of formula I wherein R_2 represents a 5- or 6-membered aromatic heterocycle bonded to the purine ring through a C atom, wherein R_2 contains 1 or 2 heteroatoms selected from N, O and S, wherein the adjacent atoms to the C atom at the position of attachment to the purine ring are C atoms, and wherein R_2 can be optionally substituted with one or more R_4.

[0231] In another embodiment, the invention relates to the compounds of formula I wherein R_2 represents 3-pyridyl, 5-indolyl, 3-pyrrolyl, 3-thienyl or 4-pyrazolyl, which can be optionally substituted with one or more R_4.

[0232] In another embodiment, the invention relates to the compounds of formula wherein R_2 represents 3-pyridyl optionally substituted with one or more R_4.

[0233] In another embodiment, the invention relates to the compounds of formula wherein R_2 represents 4-pyrazolyl optionally substituted with one or more R_4.

[0234] In another embodiment, the invention relates to the compounds of formula wherein R_2 represents 3-thienyl optionally substituted with one or more R_4.

[0235] In another embodiment, the invention relates to the compounds of formula wherein R_2 represents 5-indolyl optionally substituted with one or more R_4.

[0236] In another embodiment, the invention relates to the compounds of formula wherein R_2 represents 3-pyrrolyl optionally substituted with one or more R_4.

[0237] In another embodiment, the invention relates to the compounds of formula wherein R_2 is optionally substituted with one or two R_4.

[0238] In another embodiment, the invention relates to the compounds of formula wherein R_2 represents 3-pyridyl substituted with one or two R_4.

[0239] In another embodiment, the invention relates to the compounds of formula wherein R_2 represents 4-pyrazolyl substituted with one or two R_4.

[0240] In another embodiment, the invention relates to the compounds of formula wherein R_2 represents 3-thienyl substituted with one or two R_4.

[0241] In another embodiment, the invention relates to the compounds of formula wherein R_2 represents 5-indolyl substituted with one or two R_4.

[0242] In another embodiment, the invention relates to the compounds of formula wherein R_2 represents 3-pyrrolyl substituted with one or two R_4.

[0243] In another embodiment, the invention relates to the compounds of formula wherein each R_4 independently represents C_{1-4}alkyl, halogen, —CN, $—COR_6$, $—CO_2R_6$, $—CONR_6R_6$, $—OR_6$, $—SR_6$, $—SO_2R_5$, $—SO_2NR_6R_6$,

—$SO_2NR_7COR_5$, —NR_6R_6, —NR_7COR_6, —$NR_7CONR_6R_6$, —$NR_7SO_2R_5$ or Cy_1, wherein the C_{1-4}alkyl group can be optionally substituted with one or more R_8 and Cy_1 can be optionally substituted with one or more R_9.

[0244] In another embodiment, the invention relates to the compounds of formula I wherein each R_4 independently represents C_{1-4}alkyl, halogen, —CN, —$CONR_6R_6$, —OR_6, —SR_6, —SO_2R_6, —$SO_2NR_6R_6$, —NR_6R_6, —NR_7COR_6 or Cy_1, wherein Cy_1 can be optionally substituted with one or more R_9.

[0245] In another embodiment, the invention relates to the compounds of formula I wherein Cy_1 in R_4 is Cy_{1b} and Cy_{1b} represents a 3- to 7-membered saturated monocyclic heterocycle which contains 1 or 2 heteroatoms selected from N, S and O, wherein said ring can be bonded to the rest of the molecule through any available C or N atom, and wherein one or more C or S ring atoms can be optionally oxidized forming CO, SO or SO_2 groups, wherein said Cy_{1b} can be optionally substituted with one or more R_9.

[0246] In another embodiment, the invention relates to the compounds of formula I wherein Cy_1 in R_4 is Cy_{1d} and Cy_{1d} represents a 3- to 7-membered saturated monocyclic heterocycle which contains 1 or 2 heteroatoms selected from N, S and O with the proviso that at least it contains 1 N atom, wherein said ring is bonded to the rest of the molecule through a N atom, and wherein one or more C or S ring atoms can be optionally oxidized forming CO, SO or SO_2 groups, wherein said Cy_{1d} can be optionally substituted with one or more R_9.

[0247] In another embodiment, the invention relates to the compounds of formula I wherein Cy_1 in R_4 is Cy_{1c} and Cy_{1c} represents a 5- or 6-membered saturated monocyclic heterocycle which contains 1 or 2 heteroatoms selected from N, S and O with the proviso that it contains at least 1 N atom, wherein said ring is bonded to the rest of the molecule through a N atom, wherein one or more C or S ring atoms can be optionally oxidized forming CO, SO or SO_2 groups, and wherein said Cy_{1c} can be optionally substituted with one or more R_9.

[0248] In another embodiment, the invention relates to the compounds of formula I wherein:

[0249] each R_4 independently represents C_{1-4}alkyl, halogen, —CN, —$CONR_6R_6$, —OR_6, —SR_6, —SO_2R_6, —$SO_2NR_6R_6$, —NR_6R_6, —NR_7COR_6 or Cy_{1b}, wherein Cy_{1b} can be optionally substituted with one or more R_9.

[0250] In another embodiment, the invention relates to the compounds of formula I wherein each R_4 independently represents C_{1-4}alkyl, halogen, —$CONR_6R_6$, —SR_6, —SOR_6, —SO_2R_6, —NR_6R_6, —$NR_7SO_2R_5$, —$NR_7CONR_6R_6$ or Cy_{1d}, wherein the C_{1-4}alkyl group can be optionally substituted with one or more R_8 and Cy_{1d} can be optionally substituted with one or more R_9.

[0251] In another embodiment, the invention relates to the compounds of formula I wherein each R_4 independently represents C_{1-4}alkyl, halogen, hydroxyC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, —$CONR_6R_6$, —SR_6, —SOR_5, —SO_2R_5, —NR_6R_6, —$NR_7SO_2R_5$, —$NR_7CONR_6R_6$ or Cy_{1c}, wherein Cy_{1c} can be optionally substituted with one or more R_9.

[0252] In another embodiment, the invention relates to the compounds of formula I wherein R_6 in R_4 represents hydrogen or R_5 and R_5 represents C_{1-4}alkyl optionally substituted with one or more R_{10}.

[0253] In another embodiment, the invention relates to the compounds of formula I wherein R_6 in R_4 represents hydrogen or R_5 and R_5 represents C_{1-4}alkyl, hydroxyC_{1-4}alkyl or C_{1-4}alkoxyC_{1-4}alkyl.

[0254] In another embodiment, the invention relates to the compounds of formula I wherein:

[0255] R_2 represents phenyl, pyridyl, indolyl or thienyl which can be optionally substituted with one or more R_4; and

[0256] R_4 represents C_{1-4}alkyl, halogen, —CN, —$CONR_6R_6$, —OR_6, —SR_6, —SO_2R_5, —$SO_2NR_6R_6$, —NR_6R_6, —NR_7COR_6 or Cy_{1b}, wherein Cy_{1b} can be optionally substituted with one or more R_9.

[0257] In another embodiment, the invention relates to the compounds of formula I wherein:

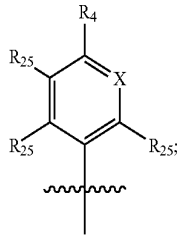
[0258] R_2 represents phenyl, pyridyl, indolyl or thienyl which can be optionally substituted with one or more R_4; and

[0259] R_4 represents C_{1-4}alkyl, halogen, —CN, —$CONR_6R_6$, —OR_6, —SR_6, —SO_2R_5, —$SO_2NR_6R_6$, —NR_6R_6 or —NR_7COR_6.

[0260] In another embodiment, the invention relates to the compounds of formula I wherein:

[0261] R_2 represents a group of formula R_{2a}:

R_{2a}



[0262] R_4 represents —OR_6, —NR_6R_6 or Cy_{1b}, wherein Cy_{1b} can be optionally substituted with one or more R_9;

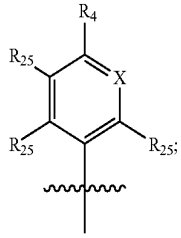
[0263] X represents CR_{25} or N; and

[0264] each R_{25} independently represents hydrogen, halogen, C_{1-4}alkyl, C_{1-4}alkoxy, haloC_{1-4}alkoxy or —SC_{1-4}alkyl.

[0265] In another embodiment, the invention relates to the compounds of formula I wherein:

[0266] R_2 represents a group of formula R_{2a}:

R_{2a}



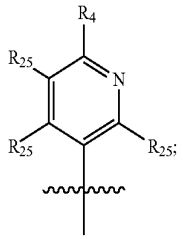
[0267] R_4 represents —OR_6, —NR_6R_6 or Cy_{1b}, wherein Cy_{1b} can be optionally substituted with one or more R_9;

[0268] X represents N; and

[0269] each R_{25} independently represents hydrogen, halogen, C_{1-4}alkyl, C_{1-4}alkoxy, haloC_{1-4}alkoxy or —SC_{1-4}alkyl.

[0270] In another embodiment, the invention relates to the compounds of formula I wherein:

[0271] R_2 represents a group of formula:

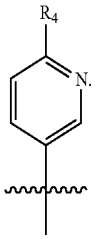


and

[0272] each R_{25} independently represents hydrogen, halogen or C_{1-4}alkyl.

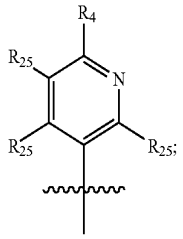
[0273] In another embodiment, the invention relates to the compounds of formula I wherein:

[0274] R_2 represents a group of formula:



[0275] In another embodiment, the invention relates to the compounds of formula I wherein:

[0276] R_2 represents a group of formula:

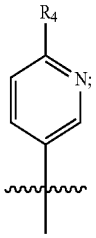


[0277] R_4 represents —NR_6R_6 or Cy_{1d}, wherein Cy_{1d} can be optionally substituted with one or more R_9; and

[0278] each R_{25} independently represents hydrogen, halogen or C_{1-4}alkyl.

[0279] In another embodiment, the invention relates to the compounds of formula I wherein:

[0280] R_2 represents a group of formula:

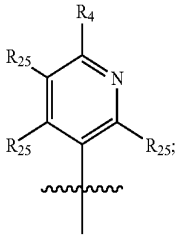


and

[0281] R_4 represents —NR_6R_6 or Cy_{1d}, wherein Cy_{1d} can be optionally substituted with one or more R_9.

[0282] In another embodiment, the invention relates to the compounds of formula I wherein:

[0283] R_2 represents a group of formula:

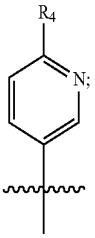


[0284] R_4 represents —NR_6R_6 or Cy_{1c}, wherein Cy_{1c} can be optionally substituted with one or more R_9; and

[0285] each R_{25} independently represents hydrogen, halogen or C_{1-4}alkyl.

[0286] In another embodiment, the invention relates to the compounds of formula I wherein:

[0287] R_2 represents a group of formula:

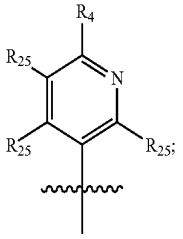


and

[0288] R_4 represents —NR_6R_6 or Cy_{1c}, wherein Cy_{1c} can be optionally substituted with one or more R_9.

[0289] In another embodiment, the invention relates to the compounds of formula I wherein:

[0290] R_2 represents a group of formula:



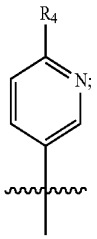
[0291] R_4 represents —NR_6R_6 or Cy_{1c}, wherein Cy_{1c} can be optionally substituted with one or more R_9;

[0292] R_6 represents C_{1-4}alkyl optionally substituted with one or more R_{10}; and

[0293] each R_{25} independently represents hydrogen, halogen or C_{1-4}alkyl.

[0294] In another embodiment, the invention relates to the compounds of formula I wherein:

[0295] R_2 represents a group of formula:

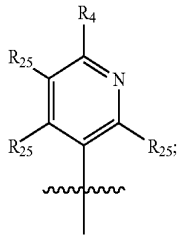


[0296] R_4 represents —NR_6R_6 or Cy_{1c}, wherein Cy_{1c} can be optionally substituted with one or more R_9; and

[0297] R_6 represents C_{1-4}alkyl optionally substituted with one or more R_{10}.

[0298] In another embodiment, the invention relates to the compounds of formula I wherein:

[0299] R_2 represents a group of formula:



[0300] R_4 represents —NR_6R_6 or Cy_{1c}, wherein Cy_{1c} can be optionally substituted with one or more R_9;

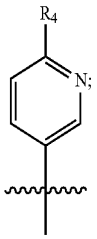
[0301] R_6 represents C_{1-4}alkyl, hydroxyC_{1-4}alkyl or C_{1-4}alkoxyC_{1-4}alkyl;

[0302] R_9 represents C_{1-4}alkyl, —OR_{18}, —$CONR_{18}R_{18}$ or —COR_{18}; and

[0303] each R_{25} independently represents hydrogen, halogen or C_{1-4}alkyl.

[0304] In another embodiment, the invention relates to the compounds of formula I wherein:

[0305] R_2 represents a group of formula:



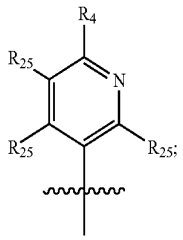
[0306] R_4 represents —NR_6R_6 or Cy_{1c}, wherein Cy_{1c} can be optionally substituted with one or more R_9;

[0307] R_6 represents C_{1-4}alkyl, hydroxyC_{1-4}alkyl or C_{1-4}alkoxyC_{1-4}alkyl; and

[0308] R_9 represents C_{1-4}alkyl, —OR_{18}, —$CONR_{18}R_{18}$ or —COR_{18}.

[0309] In another embodiment, the invention relates to the compounds of formula I wherein:

[0310] R_2 represents a group of formula:



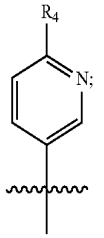
[0311] R_4 represents —NR_6R_6;

[0312] R_6 represents C_{1-4}alkyl optionally substituted with one or more R_{10}; and

[0313] each R_{25} independently represents hydrogen, halogen or C_{1-4}alkyl.

[0314] In another embodiment, the invention relates to the compounds of formula I wherein:

[0315] R_2 represents a group of formula:

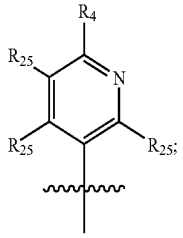


[0316] R_4 represents —NR_6R_6; and

[0317] R_6 represents C_{1-4}alkyl optionally substituted with one or more R_{10}.

[0318] In another embodiment, the invention relates to the compounds of formula I wherein:

[0319] R_2 represents a group of formula:



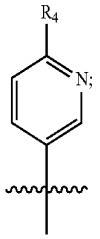
[0320] R_4 represents —NR_6R_6;

[0321] R_6 represents C_{1-4}alkyl, hydroxyC_{1-4}alkyl or C_{1-4}alkoxyC_{1-4}alkyl; and

[0322] each R_{25} independently represents hydrogen, halogen or C_{1-4}alkyl.

[0323] In another embodiment, the invention relates to the compounds of formula I wherein:

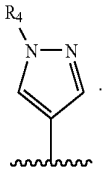
[0324] R_2 represents a group of formula:



[0325] R_4 represents —NR_6R_6; and

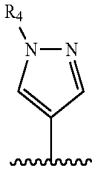
[0326] R_6 represents C_{1-4}alkyl, hydroxyC_{1-4}alkyl or C_{1-4}alkoxyC_{1-4}alkyl.

[0327] In another embodiment, the invention relates to the compounds of formula I wherein R_2 represents a group of formula:



[0328] In another embodiment, the invention relates to the compounds of formula I wherein:

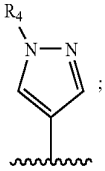
[0329] R_2 represents a group of formula:



[0330] R_4 represents C_{1-4}alkyl optionally substituted with one or more R_8.

[0331] In another embodiment, the invention relates to the compounds of formula I wherein:

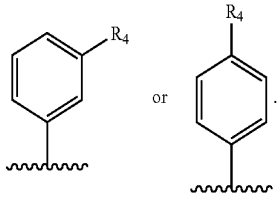
[0332] R_2 represents a group of formula:



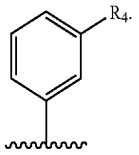
and

[0333] R_4 represents C_{1-4}alkyl, hydroxyC_{1-4}alkyl or C_{1-4}alkoxyC_{1-4}alkyl.

[0334] In another embodiment, the invention relates to the compounds of formula I wherein R_2 represents

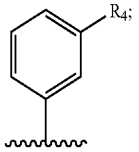


[0335] In another embodiment, the invention relates to the compounds of formula I wherein R_2 represents a group of formula:



[0336] In another embodiment, the invention relates to the compounds of formula I wherein:

[0337] R_2 represents a group of formula:

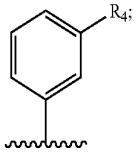


and

[0338] R_4 represents —$CONR_6R_6$, —SR_6, —SOR_5, or —SO_2R_5.

[0339] In another embodiment, the invention relates to the compounds of formula I wherein:

[0340] R_2 represents a group of formula:



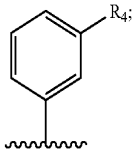
[0341] R_4 represents —$CONR_6R_6$, —SR_6, —SOR_5, or —SO_2R_5;

[0342] R_5 represents C_{1-4}alkyl optionally substituted with one or more R_{10}; and

[0343] R_6 represents hydrogen or R_5.

[0344] In another embodiment, the invention relates to the compounds of formula I wherein:

[0345] R_2 represents a group of formula:

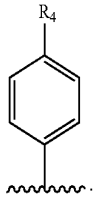


[0346] R_4 represents —$CONR_6R_6$, —SR_6, —SOR_5, or —SO_2R_5;

[0347] R_5 represents C_{1-4}alkyl, haloC_{1-4}alkyl, hydroxyC_{1-4}alkyl or C_{1-4}alkoxyC_{1-4}alkyl; and

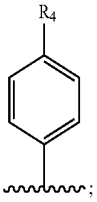
[0348] R_6 represents hydrogen or R_5.

[0349] In another embodiment, the invention relates to the compounds of formula I wherein R_2 represents a group of formula:



[0350] In another embodiment, the invention relates to the compounds of formula I wherein:

[0351] R_2 represents a group of formula:

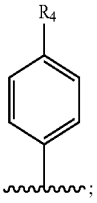


and

[0352] R_4 represents $—NR_6R_6$, $—NR_7SO_2R_5$, or $—NR_7CONR_6R_6$.

[0353] In another embodiment, the invention relates to the compounds of formula I wherein:

[0354] R_2 represents a group of formula:



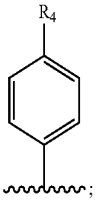
[0355] R_4 represents $—NR_6R_6$, $—NR_7SO_2R_5$, or $—NR_7CONR_6R_6$;

[0356] R_5 represents C_{1-4}alkyl optionally substituted with one or more R_{10}; and

[0357] R_6 represents hydrogen or R_5.

[0358] In another embodiment, the invention relates to the compounds of formula I wherein:

[0359] R_2 represents a group of formula:



[0360] R_4 represents $—NR_6R_6$, $—NR_7SO_2R_5$, or $—NR_7CONR_6R_6$;

[0361] R_5 represents C_{1-4}alkyl, hydroxyC_{1-4}alkyl or C_{1-4}alkoxyC_{1-4}alkyl; and

[0362] R_6 represents hydrogen or R_5.

[0363] Furthermore, the present invention covers all possible combinations of the particular and preferred embodiments described above.

[0364] In another embodiment, the invention relates to a compound of formula I which provides more than 50% inhibition of JAK3 activity at 10 μM, more preferably at 1 μM and still more preferably at 0.1 μM, in a JAK3 assay such as the one described in example 27.

[0365] In another embodiment, the invention relates to a compound of formula I selected from the list of compounds described in examples 1 to 26a.

[0366] 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, trifluoromethanesulfonic 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, N-methylglucamine, procaine and the like.

[0367] There is no limitation on the type of salt that can be used, provided that these are pharmaceutically acceptable when used for therapeutic purposes. The term pharmaceutically acceptable salt refers to 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.

[0368] 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 a 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.

[0369] 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.

[0370] 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.

[0371] 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.

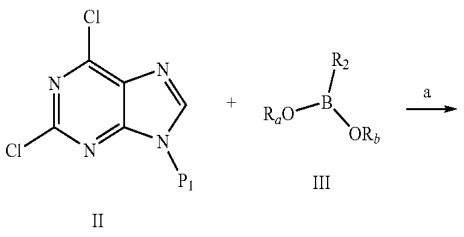
[0372] Some of the compounds of the present invention may exist as several diastereoisomers and/or several optical isomers. Diastereoisomers can be separated by conventional techniques such as chromatography or fractional crystallization. Optical isomers can be resolved by conventional techniques of 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.

[0373] 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 by conventional protecting groups. Both the nature of these protecting groups and the procedures for their introduction or removal are well known in the art (see for example Greene T. W. and Wuts P. G. M, "Protective Groups in Organic Synthesis", John Wiley & Sons, 3rd edition, 1999). As an example, as protecting groups of an amino function the tetrahydropyranyl (THP) 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.

[0374] 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.

[0375] In general, compounds of formula I can be obtained in three steps by the method described in Scheme 1:

Scheme 1



II III

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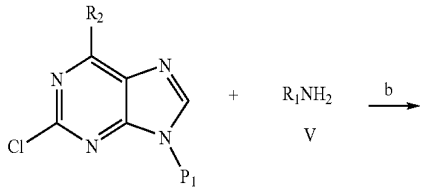
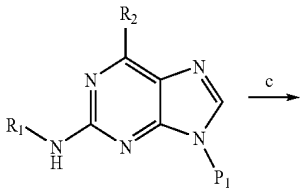
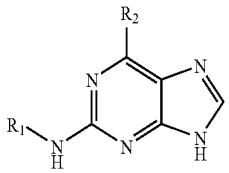


IV V



VI



I

wherein R_1 and R_2 have the meaning previously described in relation with a compound of formula I; P_1 represents an amine protecting group, such as for example tetrahydropyranyl (THP); and R_a and R_b represent H or C_{1-4}alkyl, or can be bonded forming together with the B and O atoms a 5- or 6-membered ring that can be optionally substituted with one or more methyl groups.

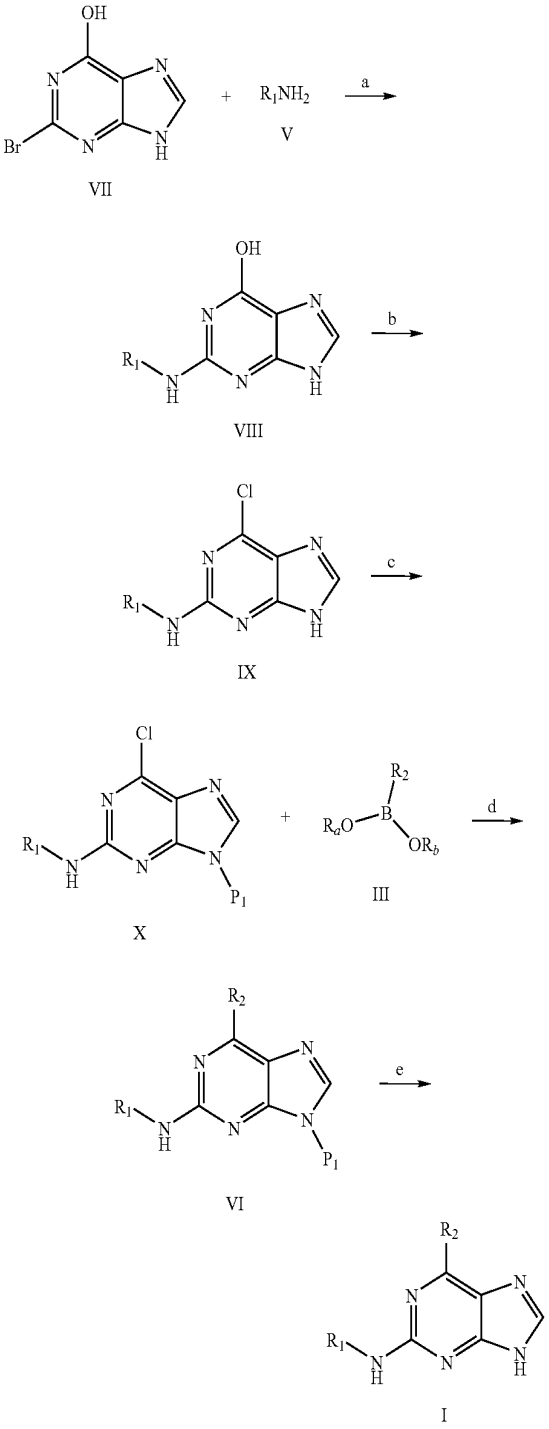
[0376] In a first step (step a), a compound of formula II is reacted with a compound of formula III under the conditions reported in the literature for Suzuki couplings to give a compound of formula IV. For example, the reaction can be carried out in the presence of a base, such as Na_2CO_3, NaOH, Cs_2CO_3, CsF or $Ba(OH)_2$, and a palladium catalyst, such as $Pd(PPh_3)_4$, $Pd_2(dba)_3$ or $Pd(OAc)_2$, in a solvent, such as dimethoxyethane, toluene, N,N-dimethylformamide, tetrahydrofuran or dioxane, optionally in the presence of water, and heating, preferably at around 90° C.

[0377] In step b a compound of formula IV is reacted with an amine of formula V in the presence of a base, such as potassium tert-butoxide, Cs_2CO_3, LiHMDS, K_2CO_3 or K_2PO_3, in the presence of a phosphine, such as BINAP or 4,5-bis(diphenylphosphine)-9,9-dimethyl-9H-xanthene (Xantphos), and of a palladium catalyst, such as $Pd_2(dba)_3$ or $Pd(OAc)_2$, in a solvent such as toluene, dioxane or tetrahydrofuran, and heating, preferably at around 100° C., to give a compound of formula VI.

[0378] Finally, the protecting group of a compound of formula VI is cleavaged under the standard conditions described in the literature to give a compound I. For example, in case THP is used as P_1, the cleavage is performed by treating compound VI with a 4M dioxane/$HCl_{(g)}$ mixture at room temperature.

[0379] Alternatively, the compounds of formula I can also be obtained using the method described in Scheme 2:

Scheme 2



wherein R_1, R_2, P_1, R_a and R_b have the meaning previously described.

[0380] Step a is carried out by reacting VII with an amine of formula V in a solvent, such as 2-methoxyethanol or n-butanol, heating, preferably at around 120° C., to give a compound of formula VIII.

[0381] Thereafter a compound of formula VIII is converted into a compound of formula IX in the presence of a chlorinating agent, such as $POCl_3$ or dichlorophenylphosphoric acid, and a base such as N,N-dimethylaniline, and heating, preferably at reflux.

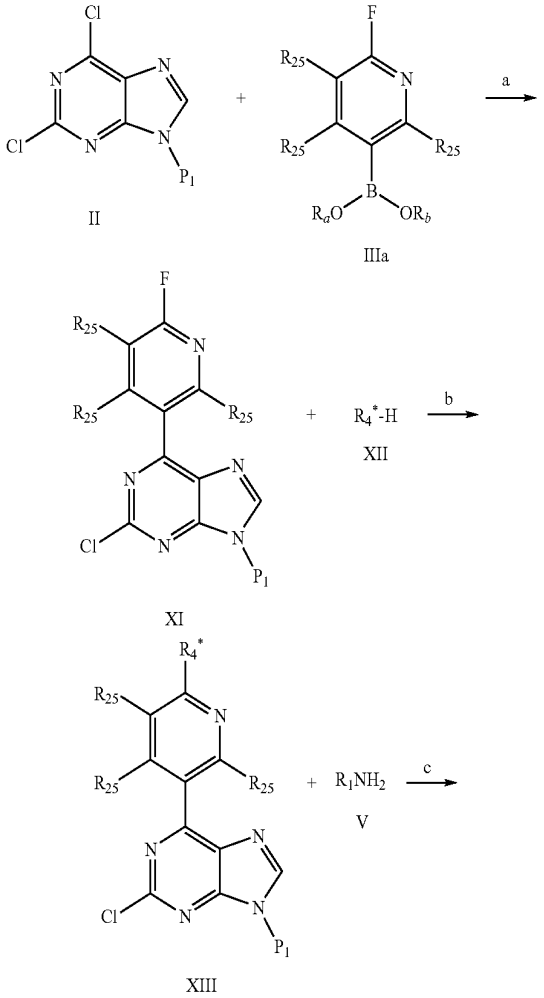
[0382] In a third step, the amino group of a compound of formula IX is protected with an amine protecting group P_1, such as THP, under standard conditions, to give a compound of formula X. If P_1 is THP, the reaction is carried out in the presence of an acid, such as p-toluensulfonic acid, pyridinium p-toluensulfonate, Amberlyst® or HCl, in a solvent, such as ethyl acetate, and heating, preferably at around 50° C.

[0383] The conversion of X into a compound of formula VI by reaction with a compound III is carried out in the same conditions described in step a of Scheme 1.

[0384] Finally, a compound of formula VI is deprotected following the method described in step c of Scheme 1, to give a compound of formula I.

[0385] Alternatively, a compound of formula I wherein R_2=6-R_4*-pyridin-3-yl and R_4*=—NR_6R_6 or Cy_1 bonded through a N atom to the pyridine ring (compounds Ia) can be also obtained by the method described in Scheme 3:

Scheme 3



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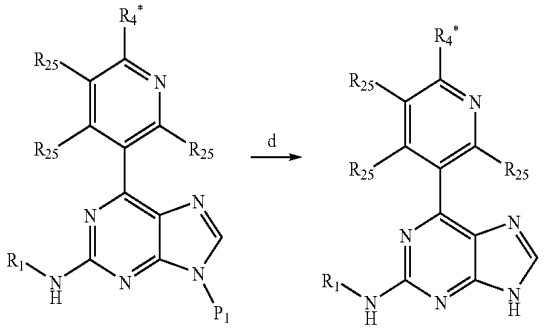


XIV

Ia

wherein R_4* represents —NR_6R_6 or Cy_1 bonded through a N atom to the pyridine ring, each R_{25} independently represents hydrogen, halogen, C_{1-4}alkyl, C_{1-4}alkoxy, haloC_{1-4}alkoxy or —SC_{1-4}alky, and P_1, R_1, Cy_1, R_a, and R_b have the meaning previously described.

[0386] In a first step, the compound of formula II is allowed to react with a compound of formula IIIa following a similar procedure to that described for step a of Scheme 1 to give a compound of formula XI.

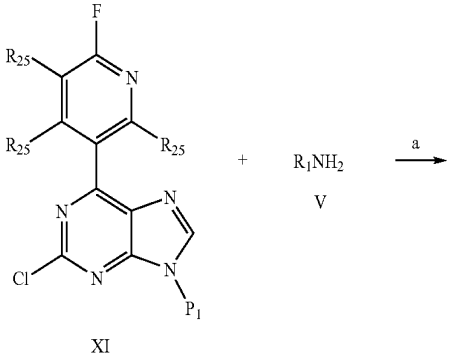
[0387] The compound of formula XI thus obtained is allowed to react with an amine of formula XII, in a solvent such as n-butanol, in the presence of a base such as diisopropylethylamine, and heating, preferably at around 120° C., to give a compound of formula XIII.

[0388] The compound of formula XIII thus obtained is then allowed to react with an amine of formula V following the procedure described in step b of Scheme 1 to give a compound of formula XIV.

[0389] Finally a compound of formula XIV is deprotected to give a compound of formula Ia following the procedure described in step c of Scheme 1.

[0390] Alternatively, a compound of formula Ia can be obtained from a compound of formula XI in three steps, as shown in Scheme 4:

Scheme 4



XI

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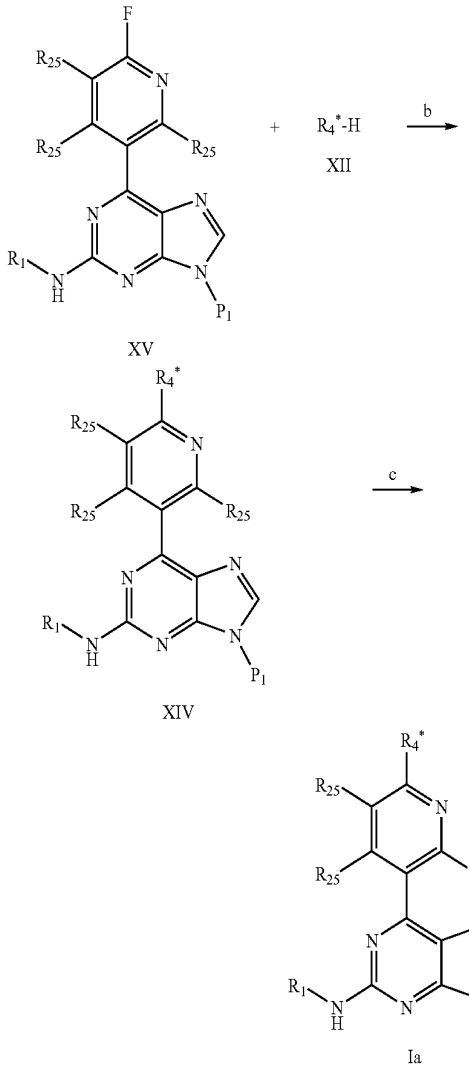


XV

XIV

Ia

wherein P_1, R_1, R_4* and R_{25} have the meaning previously described.

[0391] In a first step, a compound of formula XI is allowed to react with an amine of formula V following the procedure described in step b of Scheme 1 to yield a compound of formula XV.

[0392] Next, a compound of formula XV is allowed to react with an amine of formula XII following a similar procedure to that described in step b of Scheme 3, to give a compound of formula XIV.

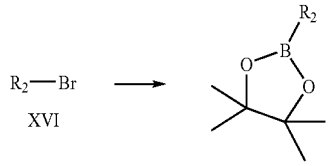
[0393] And, finally, the amino protecting group of a compound of formula XIV is cleavaged using the method described in step c of Scheme 1, to give a compound of formula Ia.

[0394] The compounds of formula II can be prepared from 2,6-dichloropurine following any of the methods described in the literature for protecting amino groups.

[0395] The compounds of formula III and IIIa are commercially available or can be prepared by well-known methods described in the literature.

[0396] The compounds of formula III with a cyclic structure (IIIb) can be prepared from a compound of formula XVI following the procedure shown in Scheme 5:

Scheme 5



wherein R_2 has the meaning previously described.

[0397] The reaction is carried out by reacting a compound of formula XVI with bis(pinacolato)diboron and [1,1'-bis (diphenylphosphine)ferrocene]-dichloropalladium in the presence of a base, such as potassium acetate, in a solvent, such as N,N-dimethylformamide or dioxane, and heating, preferably at around 90° C., to give a compound of formula IIIb.

[0398] The compounds of formula V, VII, XII and XVI are commercially available or can be prepared by well-known methods described in the literature, and can be protected with suitable protecting groups.

[0399] 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.

[0400] Said transformations can be carried out upon R_1 or R_2 groups and include, for example:

[0401] 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 $NiCl_2$, or $SnCl_2$;

[0402] 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 triacetoxyborohydride;

[0403] 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 triethylamine or pyridine;

[0404] the conversion of an amine into an amide, carbamate or urea under standard conditions;

[0405] the alkylation of an amide by treatment with an alkylating agent under basic conditions;

[0406] the conversion of an alcohol into an ether, ester or carbamate under standard conditions;

[0407] the alkylation of a thiol to give a thioeter under standard conditions;

[0408] the partial or total oxidation of an alcohol to give ketones, aldehydes or carboxylic acids under standard oxidizing conditions;

[0409] the reduction of an aldehyde or ketone by treatment with a reducing agent such as sodium borohydride;

[0410] 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 $LiAlH_4$;

[0411] the oxidation of a thioeter to a sulfoxide or sulfone under standard conditions;

[0412] the conversion of an alcohol into a halogen by reaction with $SOCl_2$, PBr_3, tetrabutylammonium bromide in the presence of P_2O_5, or PI_3;

[0413] the conversion of halogen into an amine by reaction with an amine, optionally in the presence of a suitable solvent, and preferably heating; and

[0414] the conversion of a primary amide into a —CN group under standard conditions.

[0415] 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.

[0416] Some of these interconversion reactions are explained in greater detail in the examples.

[0417] 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.

[0418] 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 or 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(15):1767-84; Cetkovic-Cvrlje M. et al, Arch. Immunol. Ther. Exp. (Warsz), 2004, 52(2):69-82).

[0419] Acute or chronic transplant rejection reactions that can be prevented or treated 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(12):1014-21; Borie D C. et al, Transplantation 2005, 79(7):791-801; Paniagua R. et al, Transplantation 2005, 80(9):1283-92; Higuchi T. et al, J. Heart Lung Transplant. 2005, 24(10):1557-64; Saemann M D. et al, Transpl Int. 2004, 17(9):481-89; Silva Jr H T. et al, Drugs 2006, 66(13): 1665-1684).

[0420] Immune, autoimmune or 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 hematological disorders (e.g. hemolytic anemia, aplastic anemia, idiopathic thrombocytopenia, and neutropenia), autoimmune gastritis and inflammatory bowel diseases (e.g. ulcerative colitis and Crohn's disease), scleroderma, type I diabetes and complications from diabetes, type B hepatitis, type C hepatitis, primary biliary cirrhosis, myasthenia gravis, multiple sclerosis, systemic lupus erythematosus, psoriasis, atopic dermatitis, contact dermatitis, eczema, skin sunburns, suppression of HIV replication, infertility of autoimmune origin, autoimmune thyroid disease (Grave's disease), interstitial cystitis, and mast cell-mediated allergic reactions such as asthma, angiodema, anaphylaxis, bronchitis, rhinitis and sinusitis (see e.g. Sorbera L A. et al, Drugs of the Future 2007,

32(8):674-680; 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(15):1767-84; Muller-Ladner U. et al, J. Immunol. 2000, 164(7): 3894-3901; Walker J G. et al, Ann. Rheum. Dis. 2006, 65(2):149-56; Milici A J. et al, Arthritis Rheum 0.2006, 54 (9, Suppl): abstr 789; Kremer J M. et al, Arthritis Rheum. 2006, 54, 4116, presentation no. L40; Cetkovic-Cvrlje M. et al, Arch Immunol. Ther. Exp. (Warsz), 2004, 52(2): 69-82; Malaviya R. et al, J. Pharmacol. Exp. Ther. 2000, 295(3):912-26; Malaviya R. et al, J. Biol. Chem. 1999, 274 (38):27028-38; Wilkinson B et al, Ann. Rheum. Dis. 2007, 66(Suppl 2): Abst. THU0099; Matsumoto M. et al, J. Immunol. 1999, 162(2):1056-63).

[0421] 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 V N. et al, Biochem. Biophys. Res. Commun. 2000, 267(1):22-5).

[0422] Proliferative disorders that can be treated or prevented with the compounds of the present invention include, among others, leukemias, lymphomas, glioblastoma multiforme, colon carcinoma, as well as thromboembolic and allergic complications associated with these diseases (see e.g. Sudbeck E A. et al, Clin. Cancer Res. 1999, 5(6):1569-82; Narla R K. et al, Clin. Cancer Res. 1998, 4(10):2463-71; Lin Q. et al, Am J. Pathol. 2005, 167(4):969-80; Tibbles H E. et al, J. Biol. Chem. 2001, 276(21):17815-22).

[0423] Biological assays that can be used to determine the ability of a compound to inhibit JAKs, particularly JAK3, are well known in the art. For example, a compound to be tested can be incubated in the presence of JAK3 to determine whether inhibition of JAK3 enzymatic activity occurs, as described in the assay of example 27. 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 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 González-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 or prevention of transplant rejection, incorporated herein by reference).

[0424] For selecting active compounds, testing at 10 μM must result in an activity of more than 50% inhibition of JAK3 activity in the test provided in example 27. 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.

[0425] 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.

[0426] 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.

[0427] 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.

[0428] 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, flavouring and colouring agents.

[0429] 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, suspending, sweetening, flavouring agents, preservatives and buffers.

[0430] 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.

[0431] 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 glycerides, or on a hydrophilic base such as polyethylene glycols (macrogol).

[0432] The compounds of the invention can also be formulated for their topical application for the treatment 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.

[0433] For the nasal administration or for inhalation, the compound can be formulated as an aerosol and it can be conveniently released using suitable propellants.

[0434] 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 single or divided doses.

[0435] The following examples illustrate the scope of the invention.

EXAMPLES

[0436] The following abbreviations have been used in the examples:
AcN: acetonitrile
AcOH: acetic acid
BINAP: 2,2'-bis(diphenylphosphine)-1,1'-binaphthyl
n-BuOH: 1-butanol
CDI: 1,1'-carbonyldiimidazole
d. doublet
dd: double doublet

DIEA: N,N-diisopropylethylamine

[0437] DMAP: 4-(dimethylamino)pyridine
DME: 1,2-dimethoxyethane

DMF: N,N-dimethylformamide

[0438] EDC: N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide
EtOAc: ethyl acetate
EtOH: ethanol
HBTU: O-Benzotriazol-1-yl-N,N,N',N',-tetramethyluronium hexafluorophosphate
HOBT: 1-hydroxybenzotriazole
HPLC: high performance liquid chromatography
LC-MS: liquid chromatography-mass spectroscopy
m: multiplet
MeOH: methanol

NMM: N-methylmorpholine

[0439] NMR: nuclear magnetic resonance
$Pd(PPh_3)_4$: tetrakis(triphenylphosphine) palladium (0)
$Pd_2(dba)_3$: tris(dibenzylidenacetone)dipalladium(0)
s: singlet
TEA: triethylamine
THF: tetrahydrofurane
TMS: tetramethylsylane
t_R: retention time
X-Phos: 2-dicyclohexylphosphino-2',4',6'-triisopropyl-biphenyl

[0440] LC-MS spectra have been performed using the following chromatographic methods:
Method 1: Column X-Terra, MS C18 5 μm (100 mm×2.1 mm), temperature: 30° C., flow: 0.35 mL/min, eluent: A=AcN, B=NH_4HCO_3 10 mM, gradient: 0 min A 10%; 10 min A 90%; 15 min A 90%; 15.01 min A 10%.
Method 2: Column X-bridge, MS C18 2.5 μm (50 mm×2.1 mm), temperature: 50° C., flow: 0.50 mL/min, eluent: A=NH_4HCO_3 10 mM, B=AcN, C=H_2O, gradient: 0 min A 10%, B 10%; 4 min A 10%, B 85%; 4.75 min A 10%, B 85%; 4.76 min A 10%, B 10%.
Method 3: Column Tracer Excel 120, ODSB 5 μm (10 mm×0.21 mm), temperature: 30° C., flow: 0.35 mL/min, eluent: A=AcN, B=0.1% HCOOH, gradient: 0 min 10% A-10 min 90% A.
Method 4: Column YMC, 3 μm (50 mm×4.6), temperature: 30° C., flow: 2.6 mL/min, eluent: A=H_2O (0.1% HCOOH) B=AcN (0.1% HCOOH), gradient: 0 min 5% B; 4.8 min 95% B; 6 min 95% B.
Method 5: Column Acquity HPLC BEH C18 1.7 μm (2.1×50 mm), temperature: 40° C., flow: 0.50 mL/min, eluent: A=AcN, B=NH_4HCO_3 10 mM, gradient: 0 min A 10%; 0.25 min A 10%; 3.00 min A 90%; 3.75 min A 90%.

Reference Example 1

2,6-Dichloro-9-(tetrahydropyran-2-yl)-9H-purine

[0441] To a suspension of 2,6-dichloropurine (2.00 g, 10.58 mmol) in EtOAc (36 mL) under Ar-atmosphere, 3,4-dihydro-2H-pyrane (2.40 mL, 26.40 mmol) and p-toluensulfonic acid (0.30 g, 1.59 mmol) were added. The resulting mixture was stirred at 57° C. for 4 h. It was allowed to reach room temperature. EtOAc was evaporated. The crude product obtained was chromatographed over silica gel using Hexane/EtOAc mixtures of increasing polarity as eluent, to afford 2.30 g of the title compound (80% yield).

[0442] LC-MS (method 1): t_R=6.79 min; m/z=271 (MH^-).

Reference Example 2

2-Chloro-6-(6-fluoropyridin-3-yl)-9-(tetrahydropyran-2-yl)-9H-purine

[0443] To a solution of reference example 1 (0.40 g, 1.46 mmol) in DME (14 mL) under Ar-atmosphere, 2-fluoro-5-pyridylboronic acid (0.20 g, 1.46 mmol), $Pd(PPh_3)_4$ (0.17 g, 0.14 mmol) and a solution of Na_2CO_3 (0.31 g, 2.92 mmol) in H_2O (1.46 mL) were added. The mixture was heated at 90° C. overnight. After cooling, it was diluted with EtOAc and washed thrice with H_2O. The organic phase was dried over Na_2SO_4 and concentrated to dryness. The crude product obtained was chromatographed over silica gel using Hexane/EtOAc mixtures of increasing polarity as eluent, to afford 0.16 g of the title compound (33% yield).

[0444] LC-MS (method 1): t_R=8.32 min; m/z=334 (MH^+).

Reference Example 3

2-[4-(tert-Butoxycarbonylamino)piperidin-1-yl]-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)pyridine

a) 5-Bromo-2-[4-(tert-butoxycarbonylamino)piperidin-1-yl]pyridine

[0445] To a suspension of 2,5-dibromopyridine (3.43 g, 14.50 mmol) and DIEA (3.78 mL, 21.70 mmol) in n-BuOH (35 mL), 4-(tert-butoxycarbonylamino)piperidine (3.19 g, 0.06 mmol) was added. The mixture was heated for 48 h at 120° C., 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 2.83 g of the desired compound (55% yield).

[0446] ^{1}H NMR (300 MHZ, $CDCl_3$) 8 (TMS): 8.17 (d, J=3.0 Hz, 1H), 7.50 (dd, J=8.8 J=3.0 Hz, 1H), 6.55 (d, J=8.8 Hz, 1H, 1H), 4.45 (broad s, 1H), 4.14 (m, 2H), 3.75 (m, 1H), 2.96 (m, 2H), 2.00 (m, 2H), 1.44 (s, 9H), 1.42 (m, 2H).

b) Title Compound

[0447] To a solution of the compound obtained in the previous section (2.83 g, 7.97 mmol) in DMF (91 mL), bis (pinacolato)diboron (4.05 g, 15.90 mmol), potassium acetate (3.90 g, 39.80 mmol) and [1,1'-bis(diphenylphosphine)ferrocene]dichloropalladium (II) (0.09 g, 0.11 mmol) were added. The reaction mixture was heated at 90° C. overnight. It was cooled until room temperature. DMF was evaporated, the residue was taken up in EtOAc and washed twice with H_2O. The organic phase was dried over Na_2SO_4 and concentrated to dryness. The crude product obtained was chromatographed over silica gel using Hexane/EtOAc mixtures of increasing polarity as eluent, to afford the desired compound in a quantitative yield.

[0448] LC-MS (method 2) t_R=3.18 min; m/z=404.5 (MH^-).

Reference Example 4

2-[4-(4-Acetyl-[1,4]diazepan-1-yl)phenyl]-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane

a) 1-Acetyl-4-(4-bromophenyl)-[1,4]diazepan

[0449] To a solution of 1,4-dibromobenzene (3.30 g, 14 mmol) in toluene (44 mL) under Ar-atmosphere, sodium tert-butoxide (1.88 g, 19.60 mol), BINAP (0.17 g, 0.28 mmol), $Pd_2(dba)_3$ (0.13 g, 0.14 mmol) and 1-acetylhomopiperazine (2 g, 14 mmol) were added at room temperature. The reaction mixture was heated at 80° C. overnight. The resulting mixture was cooled, diluted with MeOH and filtered over Celite®. The filtrate was concentrated to dryness. The crude product obtained was chromatographed over silica gel using Hexane/EtOAc mixtures of increasing polarity as eluent, to afford 3.42 g of the desired compound (82% yield).

[0450] LC-MS (method 1): t_R=7.08 min; m/z=299 (MH^+).

b) Title Compound

[0451] Following a similar procedure to that described in reference example 3 section b, but using the compound obtained in the previous section instead of 5-bromo-2-[4-(tert-butoxycarbonylamino)piperidin-1-yl]pyridine, the desired compound was obtained (56% yield).

[0452] LC-MS (method 1): t_R=7.59 min; m/z=345 (MH^+).

Following a similar procedure to that described in reference example 4, but using in each case the corresponding starting materials, the following compound was obtained:

Reference example	Compound name	Starting material	HPLC method	t_R (min)	m/z
4a	2-{4-[3-(hydroxymethyl)piperidin-1-yl]phenyl}-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane	3-hydroxymethylpiperidine hydrochloride	1	8.46	318

Reference Example 5

2-[4-(4-tert-Butoxycarbonyl-[1,4]diazepan-1-yl) phenyl]-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane

[0453] Following a similar procedure to that described in reference example 4, but using 1-tert-butoxycarbonylhomopiperazine instead of 1-acetylhomopiperazine, the desired compound was obtained (16% yield).

[0454] LC-MS (method 1): t_R=10.97 min; m/z=403 (MH^+).

Reference Example 6

2-{4-[(4-tert-Butoxycarbonyl)piperazin-1-yl)sulfonyl]phenyl}-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane

a) 4-Bromo-1-[(4-tert-butoxycarbonyl)piperazin-1-yl)sulfonyl]benzene

[0455] To a solution of 4-bromobenzenesulfonyl chloride (10 g, 39.13 mmol) in pyridine (120 mL), DMAP (1 mg) and 1-tert-butoxycarbonylpiperazine (7.20 g, 39.13 mmol) were added. The mixture was stirred at 60° C. for 18 h. It was cooled until room temperature and evaporated. The residue was washed with a saturated aqueous solution of $NaHCO_3$ and extracted thrice with EtOAc. The organic phase was dried over Na_2SO_4 and concentrated to dryness. The crude product obtained was chromatographed over silica gel using Hexane/EtOAc mixtures of increasing polarity as eluent, to afford 8.50 g of the desired compound (53% yield).

b) Title Compound

[0456] Following a similar procedure to that described in reference example 3 section b, but using the compound obtained in the previous section instead of 5-bromo-2-[4-(tert-butoxycarbonylamino)piperidin-1-yl]pyridine, the desired compound was obtained (63% yield).

[0457] LC-MS (method 1): t_R=6.64 min; m/z=369 (MH^-).

Reference Example 7

3-Amino-N-(2-hydroxyethyl)benzenesulfonamide

a) N-(2-hydroxyethyl)-3-nitrobenzenesulfonamide

[0458] To a solution of 3-nitrobenzenesulfonyl chloride (0.50 g, 2.25 mmol) in THF (5 mL), 2-aminoethanol (1.83 mL, 30.38 mmol) was added. The mixture was stirred at room temperature for 18 h. It was diluted with EtOAc and washed thrice with 0.5 N HCl. The organic phase was dried over Na_2SO_4 and concentrated to dryness. The crude product thus obtained was directly used in the next step.

b) Title Compound

[0459] To a solution of the compound obtained in the previous section (0.64 g, 2.60 mmol) in MeOH (15 mL) under Ar-atmosphere, 10% Pd/C (64 mg) was added at room temperature. The resulting mixture was stirred under H_2 overnight, filtered and the filtrate was concentrated to dryness. The crude product thus obtained was chromatographed over silica gel using Hexane/EtOAc mixtures of increasing polarity as eluent, to afford 0.39 g of the desired compound (69% yield).

[0460] LC-MS (method 1): t_R=2.21 min; m/z=217 (MH^+).

Reference Example 8

[4-(3-Hydroxypiperidin-1-yl)phenyl]amine

a) 4-(3-Hydroxypiperidin-1-yl)nitrobenzene

[0461] To a solution of 4-fluoronitrobenzene (1 g, 7.09 mmol) in AcN (16 mL), 3-hydroxypiperidine hydrochloride (1.04 g, 7.57 mmol) and DIEA (1.32 mL, 7.57 mmol) were added. The mixture was stirred and refluxed for 18 h. The resulting mixture was cooled until room temperature and evaporated. The crude product thus obtained was chromatographed over silica gel using Hexane/EtOAc mixtures of increasing polarity as eluent, to afford 1.15 g of the desired compound (51% yield).

b) Title Compound

[0462] Following a similar procedure to that described in reference example 7 section b, but using the compound obtained in the previous section, the desired compound was obtained in quantitative yield.

[0463] LC-MS (method 1): t_R=3.06 min; m/z=193 (MH^+).

Following a similar procedure to that described in reference example 8, but using in each case the corresponding starting materials, the following compounds were obtained:

Reference Example	Compound name	Starting material	HPLC method	t_R (min)	m/z
8a	[4-(3-tert-butoxycarbonylaminopyrrolidin-1-yl)phenyl]amine	3-tert-butoxycarbonylaminopyrrolidine	1	5.41	308
8b	[4-(3-hydroxypyrrolidin-1-yl)phenyl]amine	3-hydroxypyrrolidine	1	2.53	179
8c	[4-(3-tert-butoxycarbonylaminopiperidin-1-yl)phenyl]amine	3-tert-butoxycarbonylaminopiperidine	1	6.67	292
8d	[4-(3-(S)-hydroxypiperidin-1-yl)phenyl]amine	3-(S)-hydroxypiperidine hydrochloride (1)	1	5.94	223
8e	[4-(3-(R)-Hydroxypiperidin-1-yl)phenyl]amine	3-(R)-hydroxypiperidine hydrochloride (1)	1	5.94	223
8f	[4-(cis-3,5-dimethylpiperazin-1-yl)phenyl]amine	cis-2,6-dimethylpiperazine	5	0.56	206

(1) Step b was performed as described below in reference example 10 section b.

Reference Example 9

2-{4-[(S)-3-hydroxypiperidin-1-yl]phenyl}-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane

a) 4-Bromo-1-(3-(S)-hydroxypiperidin-1-yl)benzene

[0464] To a solution of reference example 8d (0.37 g, 1.92 mmol) in 8.2 mL HBr 48%, a solution of $NaNO_2$ (0.133 g, 1.92 mmol) in 1.4 mL of H_2O was slowly added at 0° C. The mixture was stirred for 15 minutes and added to a solution of CuBr (0.151 g, 1.06 mmol) in 2.7 mL HBr 48%. The resulting mixture was stirred and refluxed for 2 h. The suspension thus obtained was partitioned between 2N NaOH and ethyl acetate. The organic layer was washed with aqueous NaCl, dried over Na_2SO_4 and concentrated to dryness. The desired compound was obtained (0.387 g, 84%).

b) Title Compound

[0465] Following a similar procedure to that described in reference example 3 section b, but using the compound obtained in the previous section instead of 5-bromo-2-[4-(tert-butoxycarbonylamino)piperidin-1-yl]pyridine, the desired compound was obtained (71% yield).

[0466] LC-MS (method 1): t_R=8.02 min; m/z=304 (MH^+).

Reference Example 10

3-(4-Aminophenyl)-1-[(2-(trimethylsilyl)ethoxy) methyl]-1H-pyrazole

a) 3-(4-Nitrophenyl)-1-[(2-(trimethylsilyl)ethoxy) methyl]-1H-pyrazole

[0467] To a solution of 3-(4-nitrophenyl)pyrazole (200 mg, 1.06 mmol) in $CHCl_3$ (3 mL) and DIEA (0.55 mL, 3.18 mmol) under Ar-atmosphere, 2-(trimethylsilyl)-ethoxymethyl chloride (282 μL, 1.59 mmol) was added at 0° C. The resulting mixture was stirred at room temperature overnight. Water was added and the phases were separated. The aqueous layer was extracted twice with $CHCl_3$. The combined organic phases were dried over Na_2SO_4 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 the desired compound in quantitative yield.

[0468] LC-MS: (method 1): t_R=10.51 min; m/z=320 (MH^+)

b) Title Compound

[0469] To a solution of the compound obtained in the previous section (350 mg, 1.08 mmol) and $NiCl_2.6H_2O$ (104 mg, 044 mmol) in MeOH/THF (27 mL/14 mL), $NaBH_4$ (175 mg, 4.62 mmol) was added. The resulting mixture was stirred for 1 h at room temperature. The mixture was partitioned between 1N NaOH and ethyl acetate, and the organic layer was washed with aqueous NaCl and dried over Na_2SO_4. The crude product thus obtained was chromatographed over silica gel using hexane/EtOAc mixtures of increasing polarity as eluent, to afford the desired compound in quantitative yield.

[0470] LC-MS (method 1): t_R=8.54 min; m/z=290 (MH^+).

Reference Example 11

2-[2-Methoxycarbonyl-1-(4-toluoyl)sulfonylpyrrole-4-yl]-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane

a) 4-Iodo-2-methyloxycarbonyl-1-(4-toluoyl)sulfonylpyrrole

[0471] To a solution of 4-iodo-2-methoxycarbonylpyrrole (4.576 g, 18.3 mmol) in 50 mL dichloromethane was added triethylamine (5.7 mL, 40.10 mmol), N,N-dimethylaminopyridine (0.245 g, 2.00 mmol), and p-toluoylsulfonyl chloride (3.823 g, 20.05 mmol). The mixture was stirred at room temperature overnight. The solution was consecutively washed with 1N HCl, $NaHCO_3$ saturated aqueous solution, and NaCl saturated solution. The organic layer was dried over Na_2SO_4 and concentrated to dryness. The resulting crude product was recrystallized in tert-buthylmethylether to obtain 4.562 g (62% yield) of the title compound as a yellow solid.

b) Title Compound

[0472] To a solution of the compound obtained in the previous section (1.00 g, 2.47 mmol) in DMF (30 mL), bis(pinacolato)diboron (1.25 g, 4.92 mmol), potassium acetate (1.21 g, 12.34 mmol) and [1,1'-bis(diphenylphosphine)ferrocene]dichloropalladium (II) (0.20 g, 0.245 mmol) were added. The reaction mixture was heated at 95° C. overnight under an Ar-atmosphere. The mixture was cooled to room temperature, the solvent was evaporated, and the residue was triturated with 200 mL diethyl ether. The resulting suspension was filtered and evaporated to dryness. The crude product thus obtained was chromatographed over silica gel using hexane/EtOAc mixtures of increasing polarity as eluent, to afford 0.86 g of the desired compound (86% yield).

[0473] LC-MS (method 5) t_R=2.95 min; m/z=405 (MH^+).

Reference Example 12

4-(2-Hydroxy-2-methylpropyl)phenylamine

a) Ethyl 4-benzyloxycarbonylaminophenylacetate

[0474] To a solution of ethyl 4-aminophenylacetate (1.00 g, 5.5 mmol) and Na_2CO_3 (0.77 g, 7.2 mmol) in H_2O:THF (10 mL:3 mL), benzyl chloroformiate (0.8 mL, 5.5 mmol) was added. The mixture was stirred at room temperature overnight. The resulting mixture was diluted with dichloromethane (50 mL) and partitioned between H_2O and dichloromethane. The organic phase was dried over Na_2SO_4 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 1.1 g of the desired compound.

b) Benzyl 4-(2-hydroxy-2-methylpropyl)phenylcarbamate

[0475] To a solution of the compound obtained in the previous section (1.1 g, 3.537 mmol) in THF (30 mL) at 0° C., a solution of methylmagnesium bromide (12.2 mL, 3M in diethyl ether) was added. The resulting mixture was stirred for 1 h at room temperature and the resulting suspension was evaporated to dryness. The crude product thus obtained was chromatographed over silica gel using hexane/EtOAc mixtures of increasing polarity as eluent, to afford 0.87 g of the desired compound (82% yield).

c) Title Compound

[0476] Following a similar procedure to that described in reference example 7 section b, but using the compound obtained in the previous section, the desired compound was obtained in quantitative yield.

[0477] LC-MS (method 5): t_R=1.19 min; m/z=166 (MH^+).

Reference Example 13

N-(3-Aminophenyl)-N-methylacetamide

a) N-(3-Nitrophenyl)-N-methylacetamide

[0478] To a solution of 3-nitro-N-methylaniline (650 mg, 4.27 mmol) in CH_2Cl_2 (10 mL) under Ar-atmosphere, acetyl chloride (0.33 mL, 4.7 mmol), a catalytic amount of DMAP and DIEA (1.49 mL, 8.5 mmol) were added. The resulting mixture was stirred at room temperature overnight. The resulting residue was diluted with H_2O, the phases were separated and the aqueous phase extracted with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and concentrated to dryness. The crude product thus obtained was directly used in the next step.

[0479] LC-MS (method 5): t_R=1.43 min; m/z=195 (MH^+).

b) Title Compound

[0480] Following a similar procedure to that described in reference example 7 section b, but using the compound obtained in the previous section, the desired compound was obtained (65% yield).

[0481] LC-MS (method 5): t_R=1.02 min; m/z=165 (MH^+).

Following a similar procedure to that described in reference example 13, but using in each case the corresponding starting materials, the following compounds were obtained:

Reference example	Compound name	reagent for step a)	HPLC method	t_R (min)	m/z
13a	N-(3-aminophenyl)-N-isopropylacetamide	Isobutyryl chloride	5	1.89	193
13b	N-(3-aminophenyl)-N-cyclopropylacetamide	Cyclopropane carbonyl chloride	5	1.38	191

Reference Example 14

2-[1-(Methanesulfonyl)-1H-indol-5-yl]-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane

a) 5-Bromo-1-(methanesulfonyl)-1H-indole

[0482] To a solution of 5-bromoindole (1 g, 5.1 mmol) in THF (10 mL) under Ar-atmosphere, methanesulfonyl chloride (0.88 mL, 12.75 mmol), and TEA (2.23 mL, 15.3 mmol) were added. The mixture was stirred at room temperature overnight. The resulting mixture was evaporated and the crude product thus obtained was directly used in the next step.

[0483] LC-MS (method 4): t_R=3.30 min; m/z=276 (MH^+).

b) Title Compound

[0484] Following a similar procedure to that described in reference example 3 section b, but using the compound obtained in the previous section instead of 5-bromo-2-[4-(tent-butoxycarbonylamino)piperidin-1-yl]pyridine, the desired compound was obtained (56% yield).

[0485] LC-MS (method 4): t_R=3.68 min; m/z=322 (MH^+).

Example 1

6-[6-(4-Aminopiperidin-1-yl)pyridin-3-yl]-2-[4-(4-morpholino)phenyl]amino-9H-purine

a) 6-[6-[4-(tert-Butoxycarbonyl)aminopiperidin-1-yl] pyridin-3-yl]-2-chloro-9-(tetrahydropyran-2-yl)-9H-purine

[0486] Following a similar procedure to that described in reference example 2, but using the compound obtained in reference example 3 instead of 2-fluoro-5-pyridylboronic acid, the desired compound was obtained (93% yield).

[0487] LC-MS (method 1): t_R=9.72 min; m/z=514 (MH^+).

b) 6-{6-[4-(tert-Butoxycarbonyl)aminopiperidin-1-yl]pyridin-3-yl}-2-[4-(4-morpholino)phenyl]amino-9-(tetrahydropyran-2-yl)-9H-purine

[0488] To a solution of the compound obtained in the previous section (70 mg, 0.136 mmol) in toluene (1.75 mL) under Ar-atmosphere, sodium tert-butoxide (18 mg, 0.190 mmol), BINAP (7 mg, 0.010 mmol), $Pd_2(dba)_3$ (16 mg, 0.005 mmol) and [4-(4-morpholino)phenyl]amine (36 mg, 0.200 mmol) were added at room temperature. The reaction mixture was heated at 100° C. overnight. It was diluted with EtOAc and washed thrice with H_2O. The organic phase was dried over Na_2SO_4 and concentrated to dryness. The crude product obtained was chromatographed over silica gel using Hexane/EtOAc mixtures of increasing polarity as eluent, to afford 63 mg of the desired compound (71% yield).

[0489] LC-MS (method 1): t_R=9.52 min; m/z=656 (MH^+)

c) Title Compound

[0490] In a flask were mixed, under Ar-atmosphere, the compound obtained in the previous section (63 mg, 0.09 mmol) and a mixture of 4M dioxane/$HCl_{(g)}$ (3 mL). It was stirred at room temperature overnight and concentrated to dryness. The resulting residue was washed with a 1N NaOH and extracted with $CHCl_3$. The organic phase was dried over Na_2SO_4 and concentrated to dryness. The crude product obtained was chromatographed over silica gel using $CHCl_3$/MeOH/NH_3 mixtures of increasing polarity as eluent, to afford 26 mg of the desired compound (58% yield).

[0491] LC-MS (method 1): t_R=4.95 min; m/z=472 (MH^+).

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

Example	Compound name	Reagent for step a)	Reagent for step b)	HPLC method	t_R (min)	m/z
1a	6-[6-(4-aminopiperidin-1-yl)pyridin-3-yl]-2-(4-methanesulfonylphenyl)amino-9H-purine	Reference Example 3	(4-methanesulfonylphenyl)amine	1	4.72	465
1b	2-(4-acetamidophenyl)amino-6-[6-(4-aminopiperidin-1-yl)pyridin-3-yl]-9H-purine	Reference Example 3	N-(4-aminophenyl)acetamide	1	4.41	444
1c	2-(4-acetylphenyl)amino-6-[6-(4-aminopiperidin-1-yl)pyridin-3-yl]-9H-purine	Reference Example 3	4'-aminoacetophenone	1	5.23	429
1d	6-[6-(4-aminopiperidin-1-yl)pyridin-3-yl]-2-(4-methylsulfanylphenyl)amino-9H-purine	Reference Example 3	(4-methylsulfanylphenyl)amine	1	6.21	433
1e	6-[4-(4-acetyl-[1,4]diazepan-1-yl)phenyl]-2-(2-thiazolyl)amino-9H-purine	Reference Example 4	2-aminothiazole	1	5.56	435
1f	6-[6-(4-aminopiperidin-1-yl)pyridin-3-yl]-2-(4-methoxymethylphenyl)amino-9H-purine	Reference Example 3	4-aminobenzylic alcohol	1	5.42	431
1g	6-[6-(4-aminopiperidin-1-yl)pyridin-3-yl]-2-(4-hydroxyphenyl)amino-9H-purine	Reference Example 3	4-aminophenol	1	4.49	403
1h	6-[6-(4-aminopiperidin-1-yl)pyridin-3-yl]-2-(4-trifluoromethanesulfonylphenyl)amino-9H-purine	Reference Example 3	(4-trifluoromethanesulfonylphenyl)amine	1	7.00	519
1i	6-[6-(4-aminopiperidin-1-yl)pyridin-3-yl]-2-(4-cyanophenyl)amino-9H-purine	Reference Example 3	4-aminobenzonitrile	1	5.55	412

-continued

Example	Compound name	Reagent for step a)	Reagent for step b)	HPLC method	t_R (min)	m/z
1j	6-[6-(4-aminopiperidin-1-yl)pyridin-3-yl]-2-[3-(1-piperidinyl)phenyl]amino-9H-purine	Reference Example 3	[3-(1-piperidinyl)phenyl]amine	1	6.63	470
1k	6-[6-(4-aminopiperidin-1-yl)pyridin-3-yl]-2-[4-(1-piperidinyl)phenyl]amino-9H-purine	Reference Example 3	[4-(1-piperidinyl)phenyl]amine	3	3.41	470
1l	6-[6-(4-aminopiperidin-1-yl)pyridin-3-yl]-2-(4-benzoylphenyl)amino-9H-purine	Reference Example 3	4-aminobenzophenone	1	6.59	491
1m	6-[6-(4-aminopiperidin-1-yl)pyridin-3-yl]-2-[4-(2-hydroxyethyl)phenyl]amino-9H-purine	Reference Example 3	2-(4-aminophenyl)ethanol	1	4.71	431
1n	6-[6-(4-aminopiperidin-1-yl)pyridin-3-yl]-2-[4-(4-methylpiperazin-1-yl)phenyl]amino-9H-purine	Reference Example 3	[4-(4-methylpiperazin-1-yl)phenyl]amine	3	2.80	485
1o	6-[6-(4-aminopiperidin-1-yl)pyridin-3-yl]-2-(3-methanesulfonylphenyl)amino-9H-purine	Reference Example 3	(3-methanesulfonylphenyl)amine	1	4.34	465
1p	6-[6-(4-aminopiperidin-1-yl)pyridin-3-yl]-2-[3-(4-pyridyl)phenyl]amino-9H-purine	Reference Example 3	[3-(4-pyridyl)phenyl]amine	1	5.79	464
1q	2-(3-acetamidophenyl)amino-6-[6-(4-aminopiperidin-1-yl)pyridin-3-yl]-9H-purine	Reference Example 3	N-(3-aminophenyl)acetamide	1	4.67	444
1r	6-[6-(4-aminopiperidin-1-yl)pyridin-3-yl]-2-(3-methylsulfonamidophenyl)amino-9H-purine	Reference Example 3	N-(3-aminophenyl)methylsulfonamide	1	4.81	480
1s	6-[6-(4-aminopiperidin-1-yl)pyridin-3-yl]-2-(3-aminosulfonylphenyl)amino-9H-purine	Reference Example 3	3-amino-N-tert-butylbenzenesulfonamide	1	4.50	466
1t	6-[6-(4-aminopiperidin-1-yl)pyridin-3-yl]-2-(4-aminosulfonylphenyl)amino-9H-purine	Reference Example 3	4-amino-N-tert-butylbenzenesulfonamide	1	4.39	466
1u	6-[6-(4-aminopiperidin-1-yl)pyridin-3-yl]-2-(3-methylsulfanylphenyl)amino-9H-purine	Reference Example 3	(3-methylsulfanylphenyl)amine	1	6.23	433
1v	6-[6-(4-aminopiperidin-1-yl)pyridin-3-yl]-2-(3-benzoylphenyl)amino-9H-purine	Reference Example 3	3-aminobenzophenone	1	6.66	491
1w	6-[6-(4-aminopiperidin-1-yl)pyridin-3-yl]-2-(3-benzyloxyphenyl)amino-9H-purine	Reference Example 3	(3-benzyloxyphenyl)amine	1	7.36	493
1x	6-[6-(4-aminopiperidin-1-yl)pyridin-3-yl]-2-(3-phenylaminophenyl)amino-9H-purine	Reference Example 3	(3-phenylaminophenyl)amine	1	6.76	478
1y	6-[6-(4-aminopiperidin-1-yl)pyridin-3-yl]-2-[4-(1-piperazinyl)phenyl]amino-9H-purine	Reference Example 3	[4-(1-piperazinyl)phenyl]amine	3	2.50	471
1z	6-[6-(4-aminopiperidin-1-yl)pyridin-3-yl]-2-[3-(1-piperazinyl)phenyl]amino-9H-purine	Reference Example 3	[3-(1-piperazinyl)phenyl]amine	1	5.86	471
1aa	6-[6-(4-aminopiperidin-1-yl)pyridin-3-yl]-2-(3,4,5-trimethoxyphenyl)amino-9H-purine	Reference Example 3	(3,4,5-trimethoxyphenyl)amine	1	5.30	477

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Example	Compound name	Reagent for step a)	Reagent for step b)	HPLC method	t_R (min)	m/z
1ab	6-[6-(4-aminopiperidin-1-yl)pyridin-3-yl]-2-(3,4-dimethoxyphenyl)amino-9H-purine	Reference Example 3	(3,4-dimethoxyphenyl)amine	1	5.08	447
1ac	6-[6-(4-aminopiperidin-1-yl)pyridin-3-yl]-2-[3-(N,N-dimethylaminosulfonyl)phenyl]amino-9H-purine	Reference Example 3	4-amino-N,N-dimethylaminobenzenesulfonamide	1	5.54	494
1ad	6-[6-(4-aminopiperidin-1-yl)pyridin-3-yl]-2-{3-[N-(2-hydroxyethyl)aminosulfonyl]phenyl}-amino-9H-purine	Reference Example 3	Reference Example 7	1	4.58	510
1ae	6-[6-(4-aminopiperidin-1-yl)pyridin-3-yl]-2-[3-(N-methylaminosulfonyl)phenyl]amino-9H-purine	Reference Example 3	3-amino-N-methylbenzene sulfonamide	1	4.98	480
1af	6-[6-(4-aminopiperidin-1-yl)pyridin-3-yl]-2-[4-(N-methylaminosulfonyl)phenyl]amino-9H-purine	Reference Example 3	4-amino-N-methylbenzene sulfonamide	1	4.91	480
1ag	6-[6-(4-aminopiperidin-1-yl)pyridin-3-yl]-2-(3,5-dimethoxyphenyl)amino-9H-purine	Reference Example 3	(3,5-dimethoxyphenyl)amine	1	5.81	447
1ah	6-[6-(4-aminopiperidin-1-yl)pyridin-3-yl]-2-[4-(1,1-dioxothiomorpholin-4-yl)phenyl]amino-9H-purine	Reference Example 3	[4-(1,1-dioxothiomorpholin-4-yl)phenyl]amine	1	4.83	520
1ai	6-[6-(4-aminopiperidin-1-yl)pyridin-3-yl]-2-[4-(N,N-diethylamino)phenyl]amino-9H-purine	Reference Example 3	[4-(N,N-diethylamino)phenyl]amine	1	6.62	458
1aj	6-[6-(4-aminopiperidin-1-yl)pyridin-3-yl]-2-{4-[N-(2-hydroxyethyl)aminosulfonyl]phenyl}-amino-9H-purine	Reference Example 3	4-amino-N-(2-hydroxyethyl)benzenesulfonamide	1	4.49	510
1ak	6-[6-(4-aminopiperidin-1-yl)pyridin-3-yl]-2-(3-cyanophenyl)amino-9H-purine	Reference Example 3	3-aminobenzonitrile	1	5.85	412
1al	2-(4-aminosulfonylphenyl)amino-6-(1H-indol-5-yl)-9H-purine	5-indolylboronic acid	3-amino-N-tert-butylbenzenesulfonamide	4	2.13	406
1am	6-[6-(4-aminopiperidin-1-yl)pyridin-3-yl]-2-(3-bencylphenyl)amino-9H-purine	Reference Example 3	(3-benzylphenyl)amine	1	7.34	477
1an	6-[6-(4-aminopiperidin-1-yl)pyridin-3-yl]-2-[4-(3-hydroxypiperidin-1-yl)phenyl]amino-9H-purine	Reference Example 3	Reference Example 8	1	4.88	486
1ao	2-(3-acetylphenyl)amino-6-[6-(4-aminopiperidin-1-yl)pyridin-3-yl]-9H-purine	Reference Example 3	3'-aminoacetophenone	1	5.37	429
1ap	6-[4-(4-acetyl-[1,4]diazepan-1-yl)phenyl]-2-(3,4-methylendioxyphenyl)amino-9H-purine	Reference Example 4	(3,4-methylendioxyphenyl)amine	1	6.69	472
1aq	6-[4-(4-acetyl-[1,4]diazepan-1-yl)phenyl]-2-[4-(piperidin-3-yl)phenyl]amino-9H-purine	Reference Example 4	N-tert-butoxycarbonyl-3-(4-aminophenyl)piperidine	1	5.41	511
1ar	6-[4-(4-acetyl-[1,4]diazepan-1-yl)phenyl]-2-[4-(3-aminopyrrolidin-1-yl)phenyl]amino-9H-purine	Reference Example 4	Reference Example 8a	1	5.26	512
1as	6-[4-([1,4]diazpan-1-yl)phenyl]-2-[4-(4-morpholino)phenyl]amino-9H-purine	Reference Example 5	[4-(4-morpholino)phenyl]amine	1	5.67	471

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Example	Compound name	Reagent for step a)	Reagent for step b)	HPLC method	t_R (min)	m/z
1at	6-[4-(4-acetyl-[1,4]diazepan-1-yl)phenyl]-2-[4-(4-morpholino)phenyl]amino-9H-purine	Reference Example 4	[4-(4-morpholino)phenyl]amine	1	5.91	513
1au	6-[4-(4-acetyl-[1,4]diazepan-1-yl)phenyl]-2-[4-(3-hydroxypiperidin-1-yl)phenyl]amino-9H-purine	Reference Example 4	Reference Example 8	1	5.62	527
1av	2-(3-acetylphenyl)amino-6-(3-methoxyphenyl)-9H-purine	3-methoxyphenylboronic acid	3'-aminoacetophenone	4	2.90	360
1aw	6-[4-(4-acetyl-[1,4]diazepan-1-yl)phenyl]-2-(3-pyridyl)amino-9H-purine	Reference Example 4	3-aminopyridine	1	5.21	429
1ax	6-[4-(4-acetyl-[1,4]diazepan-1-yl)phenyl]-2-(4-pyridyl)amino-9H-purine	Reference Example 4	4-aminopyridine	1	5.10	429
1ay	2-(4-aminosulfonylphenyl)amino-6-(3-trifluoromethylphenyl)-9H-purine	3-trifluoromethylphenyl boronic acid	4-amino-N-tert-butylbenzenesulfonamide	4	3.85	435
1az	2-(4-aminosulfonylphenyl)amino-6-(3-methoxyphenyl)-9H-purine	3-methoxyphenylboronic acid	4-amino-N-tert-butylbenzenesulfonamide	4	2.33	397
1ba	2-(4-aminosulfonylphenyl)amino-6-(3-chlorophenyl)-9H-purine	3-chlorophenylboronic acid	4-amino-N-tert-butylbenzenesulfonamide	4	2.68	401
1bb	6-[6-(4-aminopiperidin-1-yl)pyridin-3-yl]-2-(2-methylbenzooxazol-6-yl]amino-9H-purine	Reference Example 3	6-amino-2-methylbenzooxazol	1	4.93	442
1bc	6-[4-(N-acetyl)aminophenyl]-2-(3-aminosulfonylphenyl)amino-9H-purine	6-[4-(N-acetyl)aminophenyl]boronic acid	3-amino-N-tert-butylbenzenesulfonamide	4	1.92	424
1bd	2-[4-(3-hydroxypyrrolidin-1-yl)phenyl]amino-6-(3-methoxyphenyl)-9H-purine	3-methoxyphenylboronic acid	Reference Example 8b	4	2.12	403
1be	2-(3-phenylaminophenyl)amino-6-(3-methoxyphenyl)-9H-purine	3-methoxyphenylboronic acid	(3-phenylaminophenyl)amine	4	3.42	409
1bf	2-[4-(3-aminopyrrolidin-1-yl)phenyl]amino-6-(3-methoxyphenyl)-9H-purine	3-methoxyphenylboronic acid	Reference Example 8a	4	1.72	402
1bg	2-[4-(3-hydroxypiperidin-1-yl)phenyl]amino-6-(3-methoxyphenyl)-9H-purine	3-methoxyphenylboronic acid	Reference Example 8	4	1.73	417
1bh	2-(3-phenylaminophenyl)amino-6-(3-trifluoromethylphenyl)-9H-purine	3-trifluoromethylphenyl boronic acid	(3-phenylaminophenyl)amine	4	3.88	447
1bi	2-(3-phenylaminophenyl)amino-6-(thien-3-yl)-9H-purine	3-thiophenboronic acid	(3-phenylaminophenyl)amine	4	3.37	385
1bj	2-(3-aminosulfonylphenyl)amino-6-(3-methoxyphenyl)-9H-purine	3-methoxyphenylboronic acid	3-amino-N-tert-butylbenzenesulfonamide	4	2.38	397
1bk	2-(3-aminosulfonylphenyl)amino-6-(3-trifluoromethylphenyl)-9H-purine	3-trifluoromethylphenyl boronic acid	3-amino-N-tert-butylbenzenesulfonamide	4	2.87	435
1bl	6-(1H-indol-5-yl)-2-(3-phenylaminophenyl)amino-9H-purine	5-indolylboronic acid	(3-phenylaminophenyl)amine	4	3.05	418

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Example	Compound name	Reagent for step a)	Reagent for step b)	HPLC method	t_R (min)	m/z
1bm	2-(3-aminosulfonylphenyl)amino-6-(thien-3-yl)-9H-purine	3-thiophenboronic acid	3-amino-N-tert-butylbenzenesulfonamide	4	2.25	373
1bn	6-(2,5-difluorophenyl)-2-(3-phenylaminophenyl)amino-9H-purine	2,5-difluorophenyl boronic acid	(3-phenylaminophenyl)amine	4	3.22	415
1bo	6-(3-methanesulfonylphenyl)-2-(3-phenylaminophenyl)amino-9H-purine	3-methanesulfonylphenylboronic acid	(3-phenylaminophenyl)amine	4	3.15	457
1bp	6-[4-(N-acetyl)aminophenyl]-2-(3-phenylaminophenyl)amino-9H-purine	6-[4-(N-acetyl)aminophenyl]boronic acid	(3-phenylaminophenyl)amine	4	2.85	436
1bq	2-(3-aminosulfonylphenyl)amino-6-(3-methanesulfonylphenyl)-9H-purine	3-methanesulfonylphenylboronic acid	3-amino-N-tert-butylbenzenesulfonamide	4	2.12	445
1br	2-(3-Aminosufonylphenyl)amino-6-{4-[(S)-3-hydroxypiperidin-1-yl]phenyl}-9H-purine	Reference example 9	3-amino-N-tert-butylbenzenesulfonamide	1	5.44	466
1bs	2-[3-(aminosulfonyl)phenyl]amino-6-(4-(methylaminocarbonyl)phenyl)-9H-purine	4-(methylaminocarbonyl)phenyl boronic acid	3-aminobenzenesulfonamide (1)	5	1.29	424
1bt	2-[3-(acetylamino)phenyl]amino-6-(4-(cyclopropylaminocarbonyl)phenyl)-9H-purine	4-(cyclopropylaminocarbonyl)phenyl boronic acid	N-(3-aminophenyl)acetamide (1)	5	1.48	428
1bu	2-[3-(acetylamino)phenyl]amino-6-(3-carbamoyl)phenyl-9H-purine	3-carbamoylphenylboronic acid	N-(3-aminophenyl)acetamide (1)	5	1.31	388
1bv	2-[3-(aminosulfonyl)phenyl]amino-6-(3-carbamoyl)phenyl-9H-purine	3-carbamoylphenylboronic acid	3-aminobenzenesulfonamide (1)	5	1.26	410
1bw	6-(3-carbamoyl)phenyl-2-[4-(4-morpholino)phenyl]amino-9H-purine	3-carbamoylphenylboronic acid	[4-(4-morpholino)phenyl]amine (1)	5	1.47	416
1bx	6-(3-carbamoyl)phenyl-2-[4-(2-hydroxyethyl)phenyl]amino-9H-purine	3-carbamoylphenylboronic acid	4-(2-hydroxyethyl)phenylamine (1)	5	1.33	375
1by	6-(3-carbamoyl)phenyl-2-[4-(2-hydroxyethyl)sulfonylphenyl]amino-9H-purine	3-carbamoylphenylboronic acid	Reference Example 7 (1)	5	1.23	454
1bz	2-[4-(2-hydroxyethyl)sulfonylphenyl]amino-6-(thien-3-yl)-9H-purine	3-thiopheneboronic acid	Reference Example 7 (1)	5	1.61	417
1ca	6-(3-carbamoyl)phenyl-2-[4-(4-methylpiperazin-1-yl)phenyl]amino-9H-purine	3-carbamoylphenylboronic acid	[4-(4-methylpiperazin-1-yl)phenyl]amine (1)	5	1.37	429
1cb	6-(4-acetylamino)phenyl-2-(4-methyl-3-aminosulfonylphenyl)amino-9H-purine	4-(acetylamino)phenyl boronic acid	2-methyl-5-aminobenzenesulfonamide	4	2.05	438
1cc	6-(4-acetylamino)phenyl-2-(4-methoxy-3-aminosulfonylphenyl)amino-9H-purine	4-(acetylamino)phenyl boronic acid	5-amino-2-methoxybenzene sulfonamide	4	1.87	454

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Example	Compound name	Reagent for step a)	Reagent for step b)	HPLC method	t_R (min)	m/z
1cd	6-(4-acetylamino)phenyl-2-(3-methylaminosulfonylphenyl)amino-9H-purine	4-(acetylamino)phenyl boronic acid	3-amino-N-methylbenzene sulfonamide	4	2.15	438
1ce	6-(3-carbamoyl)phenyl-2-[3-(pyrrolidin-1-ylmethyl)phenyl]amino-9H-purine	3-carbamoylphenylboronic acid	3-(pyrrolidin-1-ylmethyl)aniline (1)	5	1.35	451
1cf	6-(3-methanesulfonyl)phenyl-2-(4-methoxy-3-aminosulfonylbenzene)amino-9H-purine	3-(methanesulfonyl)phenylboronic acid	5-amino-2-methoxybenzenesulfonamide (1)	4	2.12	475
1cg	2-(3-Aminosufonylphenyl)amino-6-(4-dimethylaminophenyl)-9H-purine	4-N-(dimethylamino)phenyl boronic acid	3-aminobenzenesulfonamide (1)	5	1.74	410
1ch	2-[3-(acetylamino)phenyl]amino 6-(3-methylsulfanylphenyl)-9H-purine	3-(methylsulfanyl)phenylboronic acid	N-(3-aminophenyl)acetamide	5	1.90	391
1ci	2-[4-(3-(R)-hydroxypiperidin-1-yl)phenyl]amino-6-(3-methylsulfanylphenyl)-9H-purine	3-(methylsulfanyl)phenylboronic acid	Reference Example 8e (1)	1	7.16	433
1cj	2-(3-aminosulfonyl)phenylamino-6-(4-methylsulfanylphenyl)-9H-purine	4-(methylsulfanyl)phenylboronic acid	3-aminobenzenesulfonamide (1)	1	6.72	413
1ck	2-[3-(acetylamino)phenyl]amino 6-(4-methanesulfonyl)phenyl-9H-purine	3-(Methanesulfonyl)phenylboronic acid	N-(3-aminophenyl)acetamide (1)	5	1.45	423
1cl	2-[(4-piperidin-3-yl)phenyl]amino-6-(thien-3-yl)-9H-purine	3-thiopheneboronic acid	4-(N-tert-butoxycarbonylpiperidin-3-yl)phenylamine	4	1.72	377
1cm	2-(4-hydroxyethylphenyl)amino-6-(thien-3-yl)-9H-purine	3-thiopheneboronic acid	2-(4-aminophenyl)ethanol	4	2.37	338
1cn	6-[4-(N-acetyl)aminophenyl]-2-(3,4-dimethoxyphenyl)amino-9H-purine	4-(N-acetyl)aminophenylboronic acid	3,4-dimethoxyphenylamine	4	2.15	405
1co	2-[3-(acetylamino)phenyl]amino-(3-methanesulfonyl)phenyl-9H-purine	3-(methanesulfonyl)phenylboronic acid	N-(3-aminophenyl)acetamide	4	2.23	423
1cp	2-(3-hydroxyphenyl)amino-6-(3-methanesulfonyl)phenyl-9H-purine	3-(methanesulfonyl)phenylboronic acid	3-hydroxyaniline	4	2.27	382
1cq	2-[4-(1,1-dioxothiomorpholin-4-yl)phenyl]amino-6-(3-methanesulfonyl)phenyl-9H-purine	3-(methanesulfonyl)phenylboronic acid	[4-(1,1-dioxothiomorpholin-4-yl)phenyl]amine	4	2.33	499
1cr	2-(3,4-dimethoxyphenyl)amino-6-(3-methanesulfonyl)phenyl-9H-purine	3-(methanesulfonyl)phenylboronic acid	3,4-dimethoxyphenylamine	4	2.48	426

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Example	Compound name	Reagent for step a)	Reagent for step b)	HPLC method	t_R (min)	m/z
1cs	6-[4-(N-acetyl)amino]phenyl-2-[4-(1,1-dioxothiomorpholin-4-yl) phenyl]amino-9H-purine	4-(N-acetyl)aminophenylboronic acid	[4-(1,1-dioxothiomorpholin-4-yl)phenyl]amine	4	2.07	478
1ct	2-[(4-hydroxyethyl)phenyl)]amino-6-(3-methanesulfonyl)phenyl-9H-purine	3-(methanesulfonyl)phenylboronic acid	2-(4-aminophenyl)ethanol	2	2.22	410
1cu	6-(3-methanesulfonyl)phenyl-2-(3-nitrophenyl)amino-9H-purine	3-(methanesulfonyl)phenylboronic acid	3-nitrophenylamine	4	2.93	411
1cv	6-[4-(dimethylamino)]phenyl-2-[4-(4-morpholino)phenyl]amino-9H-purine	4-(dimethylamino)phenylboronic acid	[4-(4-morpholino)phenyl]amine	5	2.00	416
1cw	2-[(3-ethoxycarbonyl)phenyl]amino-6-(3-methanesulfonyl)phenyl-9H-purine	3-(methanesulfonyl)phenylboronic acid	Ethyl-3-aminobenzoate	4	3.02	438
1cx	6-(4-N-methylamio)phenyl-2-[4-(4-morpholino)phenyl]amino-9H-purine	N-tert-butoxycarbonyl-N-methylamine-4-(4,4,5,5-tetramethyl-1,3,2-dioxoborolan-2-yl)aniline	[4-(4-morpholino)phenyl]amine	4	1.90	402
1cy	2-(3-aminosufonylphenyl)amino-6-(4-carbamoylphenyl) 9H-purine	4-carbamoylphenylboronic acid	3-aminobenzenesulfonamide (1)	5	1.13	410
1cz	2-[(3-fluoro-4-methoxy)phenyl]amino-6-(3-methanesulfonyl)phenyl-9H-purine	3-(methanesulfonyl)phenylboronic acid	3-fluoro-4-methoxyaniline (1)	4	2.77	414
1da	6-(3-methanesulfonyl)phenyl-2-[(4-piperazin-1-yl)phenyl]amino-9H-purine	3-(methanesulfonyl)phenylboronic acid	4-[4-tert-butoxycarbonylpiperazin-1-yl]phenylamine	4	1.63	449
1db	6-[4-(N-acetyl)amino]phenyl-2-[(3-pyrrolidin-1-ylmethyl)phenyl]amino-9H-purine	4-(N-acetyl)aminophenylboronic acid	3-(pyrrolidin-1-ylmethyl)aniline (1)	4	1.53	428
1dc	6-(3-methanesulfonyl)phenyl-2-[(3-pyrrolidin-1-ylmethyl)phenyl]amino-9H-purine	3-(methanesulfonyl)phenylboronic acid	3-(pyrrolidin-1-ylmethyl)aniline (1)	4	1.63	449
1dd	6-(3-methanesulfonyl)phenyl-2-[3-(2-pyrrolidinyl)phenyl]amino-9H-purine	3-(methanesulfonyl)phenylboronic acid	N-tert-butoxycarbonyl-2-(3-aminophenyl)pyrrolidine (1)	4	1.42	435
1de	2-(3-aminosufonylphenyl)amino-6-[1-(methanesulfonyl)-1H-indol-5-yl]-9H-purine	Reference Example 14	3-aminobenzenesulfonamide (1)	4	2.55	484

(1) In section b, wo equivalents of K_2CO_3 were used instead of NaOtBu, 0.1 equivalents of X-Phos were used instead of BINAP, and tert-butanol was used instead of toluene.

Example 2

6-[6-(4-Acetyl[1,4]diazepan-1-yl)pyridin-3-yl]-2-[4-(4-morpholino)phenyl]amino-9H-purine

a) 6-[6-(4-Acetyl[1,4]diazepan-1-yl)pyridin-3-yl]-2-chloro-9-(tetrahydropyran-2-yl)-9H-purine

[0492] To a solution of reference example 2 (0.30 g, 0.89 mmol) and DIEA (0.47 mL, 2.69 mmol) in n-BuOH (25 mL), N-acetylhomopiperazine (0.51 g, 3.59 mmol) was added. The mixture was heated for 18 h at 120° C., it was allowed to cool, and was concentrated to dryness. The crude product obtained was chromatographed over silica gel using hexane/EtOAc mixtures of increasing polarity as eluent, to afford 0.26 g of the desired compound (63% yield).

[0493] LC-MS (method 1): t_R=7.24 min; m/z=456 (MH^+).

b) 6-[6-(4-Acetyl[1,4]diazepan-1-yl)pyridin-3-yl]-2-[4-(4-morpholino)phenyl]amino-9-(tetrahydropyran-2-yl)-9H-purine

[0494] Following a similar procedure to that described in example 1 section b, but using the compound obtained in the previous section, the desired compound was obtained (76% yield).

[0495] LC-MS (method 2): t_R=2.55 min; m/z=598 (MH^+).

c) Title Compound

[0496] Following a similar procedure to that described in example 1 section c, but using the compound obtained in the previous section, the title compound of the example was obtained (53% yield).

[0497] LC-MS (method 1): t_R=4.34 min; m/z=514 (MH^+).

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

Example	Compound name	reagent for step a)	reagent for step b)	HPLC method	t_R (min)	m/z
2a	6-[6-(3-hydroxypiperidin-1-yl)pyridin-3-yl]-2-(3-phenylaminophenyl)amino-9H-purine	3-hydroxypiperidine hydrochloride	(3-phenylaminophenyl)amine	1	7.45	479
2b	6-[6-(4-acetyl[1,4]diazepan-1-yl)pyridin-3-yl]-2-(3-phenylaminophenyl)amino-9H-purine	N-acetylhomopiperazine	(3-phenylaminophenyl)amine	1	7.07	520
2c	6-[6-(4-acetyl[1,4]diazepan-1-yl)pyridin-3-yl]-2-[4-(3-hydroxypiperidin-1-yl)phenyl]amino-9H-purine	N-acetylhomopiperazine	Reference Example 8	1	5.35	528
2d	6-[6-(4-acetyl[1,4]diazepan-1-yl)pyridin-3-yl]-2-(3-ethoxyphenyl)amino-9H-purine	N-acetylhomopiperazine	(3-ethoxyphenyl)amine	1	6.69	473
2e	2-[4-(3-hydroxypiperidin-1-yl)phenyl]amino-6-[6-(3-hydroxypiperidin-1-yl)pyridin-3-yl]-9H-purine	3-hydroxypiperidine hydrochloride	Reference Example 8	3	3.58	487
2f	6-[6-(3-hydroxypiperidin-1-yl)pyridin-3-yl]-2-[4-(4-morpholino)phenyl]amino-9H-purine	3-hydroxypiperidine hydrochloride	[4-(4-morpholino)phenyl]amine	3	4.20	473
2g	6-[6-(3-aminopiperidin-1-yl)pyridin-3-yl]-2-[4-(4-morpholino)phenyl]amino-9H-purine	3-N-tert-butoxycarbonylaminopiperidine	[4-(4-morpholino)phenyl]amine	3	3.90	472
2h	6-[6-(3-aminopiperidin-1-yl)pyridin-3-yl]-2-(3-ethoxyphenyl)amino-9H-purine	3-N-tert-butoxycarbonylaminopiperidine	(3-ethoxyphenyl)amine	1	6.52	431
2i	6-[6-(3-aminopiperidin-1-yl)pyridin-3-yl]-2-(3-phenylaminophenyl)amino-9H-purine	3-N-tert-butoxycarbonylaminopiperidine	(3-phenylaminophenyl)amine	1	7.13	478
2j	6-[6-(3-aminopiperidin-1-yl)pyridin-3-yl]-2-[4-(3-hydroxypiperidin-1-yl)phenyl]amino-9H-purine	3-N-tert-butoxycarbonylaminopiperidine	Reference Example 8	1	5.16	486

-continued

Example	Compound name	reagent for step a)	reagent for step b)	HPLC method	t_R (min)	m/z
2k	6-[6-(4-acetyl[1,4]diazepan-1-yl)pyridin-3-yl]-2-(3-aminosulfonylphenyl)amino-9H-purine	N-acetylhomopiperazine	3-amino-N-tert-butylbenzenesulfonamide	1	4.93	508
2l	2-(3-ethoxyphenyl)amino-6-[6-(piperazin-1-yl)pyridin-3-yl]-9H-purine	N-tert-butoxycarbonylpiperazine	(3-ethoxyphenyl)amine	1	6.18	417
2m	2-(3-aminosulfonylphenyl)amino-6-[6-(piperazin-1-yl)pyridin-3-yl]-9H-purine	N-tert-butoxycarbonylpiperazine	3-amino-N-tert-butylbenzenesulfonamide	1	4.27	452
2n	2-(3-phenylaminophenyl)amino-6-[6-(piperazin-1-yl)pyridin-3-yl]-9H-purine	N-tert-butoxycarbonylpiperazine	(3-phenylaminophenyl)amine	1	6.81	464
2o	6-[6-(4-methylpiperazin-1-yl)pyridin-3-yl]-2-[4-(4-morpholino)phenyl]amino-9H-purine	N-methylpiperazine	[4-(4-morpholino)phenyl]amine	4	1.37	472
2p	6-(6-cyclohexylaminopyridin-3-yl)-2-[4-(4-morpholino)phenyl]amino-9H-purine	cyclohexylamine	[4-(4-morpholino)phenyl]amine	4	1.90	471
2q	2-[4-(4-morpholino)phenyl]amino-6-[6-(piperazin-1-yl)pyridin-3-yl]-9H-purine	N-tert-butoxycarbonylpiperazine	[4-(4-morpholino)phenyl]amine	4	1.35	458
2r	2-(3-aminosufonylphenyl)amino-6-[6-(N-methylpropylamino)pyridin-3-yl]-9H-purine	N-methylpropylamine	3-aminobenzenesulfonamide (1)	5	1.90	439
2s	2-(3-acetylaminophenyl)amino-6-[6-(N-methylpropylamino)pyridin-3-yl]-9H-purine	N-methylpropylamine	N-(3-aminophenyl)acetamide	5	1.89	417
2t	2-(3-acetylaminophenyl)amino-6-[6-(4-hydroxypiperidin-1-yl)pyridin-3-yl]-9H-purine	4-hydroxypiperidine (2)	N-(3-aminophenyl)acetamide	4	1.5	445
2u	2-(3-acetylphenyl)amino-6-[6-(4-hydroxypiperidin-1-yl)pyridin-3-yl]-9H-purine	4-hydroxypiperidine (2)	3'-aminoacetophenone (1)	4	1.75	430
2v	2-(3-aminosufonylphenyl)amino-6-[6-(4-hydroxypiperidin-1-yl)pyridin-3-yl]-9H-purine	4-hydroxypiperidine (2)	3-aminobenzenesulfonamide (1)	4	1.47	467
2w	6-[6-(3-hydroxypiperidin-1-yl)pyridin-3-yl]-2-[4-(pyrazol-3-yl)phenyl]amino-9H-purine	3-hydroxypiperidine hydrochloride	Reference Example 10 (3)	4	167	454

(1) Two equivalents of K_2CO_3 were used instead of NaOtBu, 0.1 equivalents of X-Phos were used instead of BINAP, and tert-buthanol was used instead of toluene.

(2) Using ethanol, instead of n-butanol.

(3) An additional deprotection step was necessary: over a solution of the product obtained in section c (1 eq) in THF (10 mL) 4.8 eq. of a 1M solution of TBAF were added. The reaction was refluxed for 5 h and the mixture thus obtained was partitioned between H_2O and dichloromethane. The organic phase was dried over Na_2SO_4 and concentrated to dryness. The crude product thus obtained was chromatographed over silica gelusing $CHCl_3$:MeOH:NH_3 mixtures of increasing polarity as eluent, to afford the desired compound.

Example 3

6-[6-(4-Acetylpiperazin-1-yl)pyridin-3-yl]-2-(3-phenylaminophenyl)amino-9H-purine

[0498] To a solution of example 2n (24.90 mg, 0.05 mmol) in CH_2Cl_2 (0.50 mL) and TEA (11.22 μL, 0.08 mmol) under Ar-atmosphere, acetic anhydride (5.58 μL, 0.06 mmol) was added at 0° C. The resulting mixture was stirred at room temperature for 1 h. Water was added and the phases were separated. The aqueous layer was extracted twice with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and concentrated to dryness. The crude product obtained was chromatographed over silica gel using 10% EtOAc/MeOH as eluent, to afford 16.4 mg of the title compound of the example (60% yield).

[0499] LC-MS (method 1): t_R=6.82 min; m/z=506 (MH^+). Following a similar procedure to that described in example 3, but using in each case the corresponding starting materials, these compounds were obtained:

Example	Compound name	Starting material	HPLC method	t_R (min)	m/z
3a	6-[6-(4-acetylpiperazin-1-yl)pyridin-3-yl]-2-(3-ethoxyphenyl)amino-9H-purine	Example 2l	1	6.40	459
3b	6-[6-(4-acetylpiperazin-1-yl)pyridin-3-yl]-2-(3-aminosulfonylphenyl)amino-9H-purine	Example 2m	1	4.75	494

Example 4

6-[6-(4-Aminopiperidin-1-yl)pyridin-3-yl]-2-[3-(4-morpholino)phenyl]amino-9H-purine

a) 6-Hydroxy-2-[3-(4-morpholino)phenyl]amino-9H-purine

[0500] To a solution of 2-bromohypoxanthine (0.50 g, 2.32 mmol) in 2-methoxyethanol (6 mL) and H_2O (5 mL), [3-(4-morpholino)phenyl]amine (0.86 g, 4.87 mmol) was added. The mixture was heated for 18 h at 120° C. It was cooled and H_2O (20 mL) was added. A white solid precipitated which was separated by filtration and dried under vacuum. 0.71 g of the desired compound was obtained (99% yield).

[0501] LC-MS (method 1): t_R=3.62 min; m/z=313 (MH^+).

b)
6-Chloro-2-[3-(4-morpholino)phenyl]amino-9H-purine

[0502] In a flask were mixed, under Ar-atmosphere, the compound obtained in the previous section (0.71 g, 2.30 mmol), $POCl_3$ (5.5 mL) and N,N-dimethylaniline (0.70 mL). The mixture was refluxed for 1 h. It was cooled and, at 0° C., the mixture was poured over H_2O. Sodium acetate was added until pH=4. A white solid precipitated which was separated by filtration and dried in a vacuum heater. 0.46 g of the desired compound was obtained (61% yield).

[0503] LC-MS (method 2): t_R=2.13 min; m/z=331 (MH^+).

c) 6-Chloro-2-[3-(4-morpholino)phenyl]amino-9-(tetrahydropyran-2-yl)-9H-purine

[0504] Following a similar procedure to that described in reference example 1, but using the compound obtained in the previous section, 0.41 g of the desired compound was obtained (71% yield).

[0505] LC-MS (method 1): t_R=7.34 min; m/z=415 (MH^+).

d) 6-[6-[4-(tert-Butoxycarbonyl)aminopiperidin-1-yl]pyridin-3-yl]-2-[3-(4-morpholino)phenyl]amino-9-(tetrahydropyran-2-yl)-9H-purine

[0506] Following a similar procedure to that described in example 1 section a, but using the compound obtained in the previous section, the desired compound was obtained (50% yield).

[0507] LC-MS (method 1): t_R=7.67 min; m/z=656 (MH^+).

e) Title Compound

[0508] Following a similar procedure to that described in example 1 section c, but using the compound obtained in the previous section, the title compound of the example was obtained (8% yield).

[0509] LC-MS (method 1): t_R=5.52 min; m/z=472 (MH^+).

Following a similar procedure to that described in example 4, but using in each case the corresponding starting materials, these compounds were obtained:

Example	Compound name	reagent for step a)	reagent for step b)	HPLC method	t_R (min)	m/z
4a	2-(3-ethoxyphenyl)amino-6-(3-pyridyl)-9H-purine	(3-methoxyphenyl)amine	3-pyridylboronic acid	1	6.48	333
4b	6-[6-(4-aminopiperidin-1-yl)pyridin-3-yl]-2-phenylamino-9H-purine	aniline	Reference Example 3	1	5.51	387
4c	2-(3-methoxyphenyl)amino-6-(4-trifluoromethylphenyl)-9H-purine	(3-methoxyphenyl)amine	4-trifluoromethylphenylboronic acid	4	3.60	386
4d	6-(3-methoxyphenyl)-2-(3-methoxyphenyl)amino-9H-purine	(3-methoxyphenyl)amine	3-methoxyphenylboronic acid	4	3.05	348
4e	6-[4-(piperazin-1-sulfonyl)phenyl]-2-phenylamino-9H-purine	aniline	Reference Example 6	1	6.43	436
4f	6-(3-methoxyphenyl)-2-[4-(4-morpholino)phenyl]amino-9H-purine	[4-(4-morpholino)phenyl]amine	3-methoxyphenylboronic acid	4	2.32	403
4g	6-(5-bromo-2-fluorophenyl)-2-[4-(4-morpholino)phenyl]amino-9H-purine	[4-(4-morpholino)phenyl]amine	5-bromo-2-fluorophenylboronic acid	1	7.15	471

-continued

Example	Compound name	reagent for step a)	reagent for step b)	HPLC method	t_R (min)	m/z
4h	6-(1H-indol-5-yl)-2-[4-(4-morpholino)phenyl]amino-9H-purine	[4-(4-morpholino)phenyl]amine	5-indolylboronic acid	4	2.00	412
4i	6-(3-chlorophenyl)-2-[4-(4-morpholino)phenyl]amino-9H-purine	[4-(4-morpholino)phenyl]amine	3-chlorophenylboronic acid	4	2.78	407
4j	6-(3-acetylphenyl)-2-[4-(4-morpholino)phenyl]amino-9H-purine	[4-(4-morpholino)phenyl]amine	3-acetylphenylboronic acid	4	2.25	415
4k	6-(3-cyanophenyl)-2-[4-(4-morpholino)phenyl]amino-9H-purine	[4-(4-morpholino)phenyl]amine	3-cyanophenylboronic acid	4	2.38	398
4l	2-[4-(4-morpholino)phenyl]amino-6-(thien-3-yl)-9H-purine	[4-(4-morpholino)phenyl]amine	3-thiophenboronic acid	4	2.18	379
4m	6-[4-(N-acetyl)aminophenyl]-2-[4-(4-morpholino)phenyl]amino-9H-purine	[4-(4-morpholino)phenyl]amine	6-[4-(N-acetyl)aminophenyl]boronic acid	4	1.82	430
4n	6-(3-chloro-4-fluorophenyl)-2-[4-(4-morpholino)phenyl]amino-9H-purine	[4-(4-morpholino)phenyl]amine	3-chloro-4-fluorophenylboronic acid	4	2.93	425
4o	6-(5-fluoro-2-methoxyphenyl)-2-[4-(4-morpholino)phenyl]amino-9H-purine	[4-(4-morpholino)phenyl]amine	5-fluoro-2-methoxyphenylboronic acid	4	2.02	421
4p	6-(2,5-difluorophenyl)-2-[4-(4-morpholino)phenyl]amino-9H-purine	[4-(4-morpholino)phenyl]amine	2,5-difluorophenylboronic acid	4	2.10	409
4q	6-(3-fluoro-4-methoxyphenyl)-2-[4-(4-morpholino)phenyl]amino-9H-purine	[4-(4-morpholino)phenyl]amine	3-fluoro-4-methoxyphenylboronic acid	4	2.47	421
4r	6-[6-(4-aminopiperidin-1-yl)pyridin-3-yl]-2-(3-ethoxyphenyl)amino-9H-purine	(3-ethoxyphenyl)amine	Reference Example 3	1	5.99	431
4s	6-(3-methanesulfonylphenyl)-2-[4-(4-morpholino)phenyl]amino-9H-purine	[4-(4-morpholino)phenyl]amine	3-methanesulfonylphenylboronic acid	4	2.02	451
4t	6-(2-chloro-5-methylphenyl)-2-[4-(4-morpholino)phenyl]amino-9H-purine	[4-(4-morpholino)phenyl]amine	2-chloro-5-methylphenylboronic acid	4	2.27	421
4u	6-[4-(N-isobutyryl)aminophenyl]-2-[4-(4-morpholino)phenyl]amino-9H-purine	[4-(4-morpholino)phenyl]amine	4-(N-isobutyryl)aminophenylboronic acid	4	2.17	458
4v	6-[4-(N-benzoyl)aminophenyl]-2-[4-(4-morpholino)phenyl]amino-9H-purine	[4-(4-morpholino)phenyl]amine	4-(N-benzoyl)aminophenyl boronic acid	4	2.47	492
4w	6-(3-bromophenyl)-2-[4-(4-morpholino)phenyl]amino-9H-purine	[4-(4-morpholino)phenyl]amine	3-bromophenylboronic acid	1	8.05	451

Example 5

2-(4-Aminosulfonylphenyl)amino-6-[6-(piperidin-4-yl)aminopyridin-3-yl]-9H-purine

a) 2-(4-tert-Butylaminosulfonylphenyl)amino-6-(6-fluoropyridin-3-yl)-9-(tetrahydropyran-2-yl)-9H-purine

[0510] Following a similar procedure to that described in example 1 section b, but using reference example 2 and 4-tert-butylaminosulfonylaniline, the desired compound was obtained (90% yield).

[0511] LC-MS (method 1): t_R=8.86 min; m/z=526 (MH^+).

b) 2-(4-tert-Butylaminosulfonylphenyl)amino-6-[6-[1-(tert-butoxycarbonyl)piperidin-4-yl]aminopyridin-3-yl]-9-(tetrahydropyran-2-yl)-9H-purine

[0512] Following a similar procedure to that described in example 2 section a, but using the compound obtained in the previous section and 4-amino-1-tert-butoxycarbonylpiperidine, the desired compound was obtained (86% yield).

[0513] LC-MS (method 1): t_R=9.81 min; m/z=706 (MH^+).

c) Title Compound

[0514] Following a similar procedure to that described in example 1 section c, but using the compound obtained in the previous section, the title compound of the example was obtained (31% yield).

[0515] LC-MS (method 1): t_R=4.28 min; m/z=466 (MH^+).

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

Example	Compound name	reagent for step a)	reagent for step b)	HPLC method	t_R (min)	m/z
5a	2-[4-(4-morpholino)phenyl]amino-6-[6-(morpholin-4-yl)pyridin-3-yl]-9H-purine	[4-(4-morpholino)phenyl]amine	morpholine	4	1.72	459
5b	2-[4-(1,1-dioxothiomorpholin-4-yl)phenyl]amino-6-[6-(3-hydroxypiperidin-1-yl)pyridin-3-yl]-9H-purine	[4-(1,1-dioxothiomorpholin-4-yl)phenyl]amine	3-hydroxypiperidine hydrochloride	4	1.65	521
5c	2-[4-(4-morpholino)phenyl]amino-6-[6-(piperidin-1-yl)pyridin-3-yl]-9H-purine	[4-(4-morpholino)phenyl]amine	piperidine	4	1.80	457
5d	6-[6-(3-hydroxypyrrolidin-1-yl)pyridin-3-yl]-2-[4-(4-morpholino)phenyl]amino-9H-purine	[4-(4-morpholino)phenyl]amine	3-hydroxypyrrolidine	4	1.40	459
5e	6-[6-(2-hydroxyethyl)aminopyridin-3-yl]-2-[4-(4-morpholino)phenyl]amino-9H-purine	[4-(4-morpholino)phenyl]amine	2-aminoethanol	4	1.32	433
5f	6-[6-(3-hydroxypropyl)aminopyridin-3-yl]-2-[4-(4-morpholino)phenyl]amino-9H-purine	[4-(4-morpholino)phenyl]amine	3-aminopropanol	4	1.36	447
5g	6-[6-(3-dimethylaminopyrrolidin-1-yl)pyridin-3-yl]-2-[4-(4-morpholino)phenyl]amino-9H-purine	[4-(4-morpholino)phenyl]amine	3-dimethylaminopyrrolidine	4	1.25	486
5h	6-[6-(3-hydroxypiperidin-1-yl)pyridin-3-yl]-2-(3-phenoxyphenyl)amino-9H-purine	3-phenoxyaniline	3-hydroxypiperidine hydrochloride	4	2.48	480
5i	2-[4-(3-aminopiperidin-1-yl)phenyl]amino-6-[6-(3-hydroxypiperidin-1-yl)pyridin-3-yl]-9H-purine	Reference Example 8c	3-hydroxypiperidine hydrochloride	4	1.30	486
5j	6-[6-(3-aminopyrrolidin-1-yl)pyridin-3-yl]-2-[4-(4-morpholino)phenyl]amino-9H-purine	[4-(4-morpholino)phenyl]amine	3-tert-butoxycarbonyl aminopyrrolidine	4	1.15	458
5k	6-[6-(2-aminoethyl)aminopyridin-3-yl]-2-[4-(4-morpholino)phenyl]amino-9H-purine	[4-(4-morpholino)phenyl]amine	ethylendiamine	4	1.14	432

-continued

Example	Compound name	reagent for step a)	reagent for step b)	HPLC method	t_R (min)	m/z
5l	6-[6-(4-hydroxipiperidin-1-yl)pyridin-3-yl]-2-[4-(4-morpholino)phenyl]amino-9H-purine	[4-(4-morpholino)phenyl]amine	4-hydroxypiperidine hydrochloride	4	1.47	473
5m	6-[6-(4-aminomethylpiperidin-1-yl)pyridin-3-yl]-2-[4-(4-morpholino)phenyl]amino-9H-purine	[4-(4-morpholino)phenyl]amine	4-aminomethylpiperidine	4	1.25	486
5n	2-[4-(4-morpholino)phenyl]amino-6-[6-(pyrrolidin-3-ylmethyl)aminopyridin-3-yl]-9H-purine	[4-(4-morpholino)phenyl]amine	3-(aminomethyl)-1-tert-butoxycarbonyl pyrrolidine	4	1.19	472
5o	6-[6-(3-hydroxypiperidin-1-yl)pyridin-3-yl]-2-(3-methoxy-5-trifluorophenyl)amino-9H-purine	3-methoxy-5-trifluoromethylaniline	3-hydroxypiperidine hydrochloride	4	2.42	486
5p	6-(6-methoxypyridin-3-yl)-2-[4-(4-morpholino)phenyl]amino-9H-purine	[4-(4-morpholino)phenyl]amine	N-methylpropylamine (1)	5	1.79	404
5q	2-[3-(2-hydroxyethyl)phenyl]amino-6-[6-(N-methylpropylamino)pyridin-3-yl]-9H-purine	3-(2-hydroxyethyl)phenylamine (2)	N-methylpropylamine	5	2.03	404
5r	2-(3-aminosufonylphenyl)amino-6-[6-(3-(S)-hydroxypiperidin-1-yl)pyridin-3-yl]-9H-purine	3-amino-N-tert-butylbenzene sulfonamide	(S)-3-hydroxypiperidine hydrochloride	1	5.15	467
5s	2-(3-aminosulfonylphenyl)amino-6-[6-(3-(R)-hydroxypiperidin-1-yl)pyridin-3-yl]-9H-purine	3-amino-N-tert-butylbenzene sulfonamide	(R)-3-hydroxypiperidine hydrochloride	1	5.14	467
5t	6-[6-(3-acetylpiperidin-1-yl)pyridin-3-yl]-2-(3-aminosulfonylphenyl)amino-9H-purine	3-amino-N-tert-butylbenzene sulfonamide	3-acetylpiperidine hydrochloride	1	6.10	493
5u	6-[(6-N-methylpropylamino)pyridin-3-yl]-2-[4-(4-morpholino)phenyl]amino-9H-purine	[4-(4-morpholino)phenyl]amine (3)	N-methylpropylamine	5	2.16	445
5v	2-[4-(4-methylpiperazin-1-yl)phenyl]amino-6-[(6-N-methylpropylamino)pyridin-3-yl]-9H-purine	[4-(4-methylpiperazin-1-yl)phenyl]amine	N-methylpropylamine	5	2.01	458
5w	2-[4-(3-hydroxypiperidin-1-yl)phenyl]amino-6-[(6-N-methylpropylamino)pyridin-3-yl]-9H-purine	Reference Example 8	N-methylpropylamine	5	2.03	460
5x	6-[(6-N-methylpropylamino)pyridin-3-yl]-2-[4-(piperidin-3-yl)phenyl]amino-9H-purine	N-tert-butoxycarbonyl-3-(4-aminophenyl)piperidine	N-methylpropylamine	5	1.78	443
5y	2-[(4-hydroxyethyl)phenyl]amino-6-[6-(N-methypropylamino)pyridin-3-yl]-9H-purine	4-(2-hydroxyethyl)phenylamine	N-methylpropylamine	5	1.97	404
5z	2-[4-(N-diethylamino)phenyl]amino-6-(6-N-methylpropylamino)pyridin-3-yl]-9H-purine	N,N-diethyl-1,4-phenylenediamine	N-methylpropylamine	5	2.7	431
5aa	6-(6-N-methylpropylamino)pyridin-3-yl]-2-[(3-pyrrolidinyl-1-ylmethyl)phenyl]amino-9H-purine	3-(pyrrolidin-1-ylmethyl)aniline	N-methylpropylamine	5	2.1	443

-continued

Example	Compound name	reagent for step a)	reagent for step b)	HPLC method	t_R (min)	m/z
5ab	2-(3-isobutyroylaminophenyl)amino-6-[(6-N-methylpropylamino)pyridin-3-yl]-9H-purine	N-(3-aminophenyl)isobutyramide	N-methylpropylamine	5	2.21	445
5ac	2-[4-(2-hydroxyethyl)aminosulfonylphenyl]amino-6-[(6-N-methylpropylamino)pyridin-3-yl]-9H-purine	Reference Example 7	N-methylpropylamine	5	1.84	483
5ad	6-[6-(3-(R)-hydroxypiperidin-1-yl)pyridin-3-yl]-2-(4-morpholino)phenyl]amino-9H-purine	[4-(4-morpholino)phenyl]amine	(R)-3-hydroxypiperidine hydrochloride	5	1.65	473
5ae	6-[6-(3-(S)-hydroxypiperidin-1-yl)pyridin-3-yl]-2-(4-morpholino)phenyl]amino-9H-purine	[4-(4-morpholino)phenyl]amine	(S)-3-hydroxypiperidine hydrochloride	5	1.65	473
5af	2-[4-(4-methylpiperazin-1-yl)phenyl]amino-6-[6-(2-(R)-methylpyrrolidin-1-yl)pyridin-3-yl]-9H-purine	[4-(4-methylpiperazin-1-yl)phenyl]amine	(R)-2-methylpyrrolidine	5	1.99	470
5ag	2-[4-(4-methylpiperazin-1-yl)phenyl]amino-6-[6-(2-(S)-methylpyrrolidin-1-yl)pyridin-3-yl]-9H-purine	[4-(4-methylpiperazin-1-yl)phenyl]amine	(S)-2-methylpyrrolidine	5	1.99	470
5ah	2-[4-(4-methylpiperazin-1-yl)phenyl]amino-6-[6-(2-(S)-methylpiperidin-1-yl)pyridin-3-yl]-9H-purine	[4-(4-methylpiperazin-1-yl)phenyl]amine	(S)-2-methylpiperidine	5	2.22	484
5ai	2-[4-(4-methylpiperazin-1-yl)phenyl]amino-6-[6-(2-(R)-methylpiperidin-1-yl)pyridin-3-yl]-9H-purine	[4-(4-methylpiperazin-1-yl)phenyl]amine	(R)-2-methylpiperidine	5	2.22	484
5aj	6-(6-N-dimethylamino)pyridin-3-yl]-2-[4-(4-methylpiperazin-1-yl)phenyl]amino-9H-purine	[4-(4-methylpiperazin-1-yl)phenyl]amine	N,N-dimethylamine	5	1.68	430
5ak	6-[6-(2-methoxyethyl)methylaminopyridin-3-yl]-2-[4-(4-methylpiperazin-1-yl)phenyl]amino-9H-purine	[4-(4-methylpiperazin-1-yl)phenyl]amine	N-(2-methoxyethyl)methylamine	5	1.72	475
5al	2-[(4-hydroxyethyl)phenyl]amino-6-[6-(2-methoxyethyl)methylaminopyridin-3-yl]-9H-purine	4-(2-hydroxyethyl)phenylamine	N-(2-methoxyethyl)methylamine	5	1.68	420
5am	2-[(3-hydroxyethyl)phenyl]amino-6-[6-(2-methoxyethyl)methylaminopyridin-3-yl]-9H-purine	3-(2-hydroxyethyl)phenylamine	N-(2-methoxyethyl)methylamine	5	1.74	421
5an	6-[6-(2-methoxyethyl)methylaminopyridin-3-yl]-2-[4-(pyrrolidin-1-ylmethyl)phenyl]amino-9H-purine	4-(pyrrolidin-1-ylmethyl)aniline	N-(2-methoxyethyl)methylamine	5	1.60	457
5ao	6-[6-(2-methoxyethyl)methylaminopyridin-3-yl]-2-[4-(piperazin-1-yl)phenyl]amino-9H-purine	[4-(piperazin-1-yl)phenyl]amine	N-(2-methoxyethyl)methylamine	5	1.42	460
5ap	2-[4-(2-hydroxy-2-methylpropyl)]phenylamino-6-[(6-N-methylpropylamino)pyridin-3-yl]-9H-purine	Reference Example 12	N-methylpropylamine	5	2.18	433
5aq	2[4-(cis-3,5-dimethylpiperazin-1-yl)phenyl]amino-6-[(6-N-methylpropylamino)pyridin-3-yl]-9H-purine	Reference Example 8f (3)	N-methylpropylamine	5	1.85	472

-continued

Example	Compound name	reagent for step a)	reagent for step b)	HPLC method	t_R (min)	m/z
5ar	2-(N-methyl-3-acetylaminophenyl)amino-6-[(6-N-methylpropylamino)pyridin-3-yl]-9H-purine	Reference Example 13 (3)	N-methylpropylamine	5	2.04	431
5as	2-(N-methyl-3-isobutyroylaminophenyl)amino-6-[(6-N-methylpropylamino)pyridin-3-yl]-9H-purine	Reference Example 13a (3)	N-methylpropylamine	5	2.25	457
5at	2-(N-methyl-3-cyclopropylcarbonylaminophenyl)amino-6-[(6-N-methylpropylamino)pyridin-3-yl]-9H-purine	Reference Example 13b (3)	N-methylpropylamine	5	2.31	459

(1) Methanol was added at deprotection step 5c to improve solubility

(2) Cesium carbonate was used instead of NaOtBu.

(3) Two equivalents of K_2CO_3 were used instead of NaOtBu, 0.1 equivalents of X-Phos were used instead of BINAP, and tert-buthanol was used instead of toluene.

Example 6

2-(4-Aminosulfonylphenyl)amino-6-(6-hydroxypyridin-3-yl)-9H-purine

[0516] In a flask were mixed, under Ar-atmosphere, the compound obtained in example 5 section a (70 mg, 0.13 mmol) and a mixture of 4M dioxane/$HCl_{(g)}$ (5 mL) with dioxane (4 mL). The reaction mixture was stirred at room temperature overnight and concentrated to dryness. The residue was washed with a saturated $NaHCO_3$ aqueous solution and extracted thrice with EtOAc. The phases were separated and the organic phase was dried over Na_2SO_4 and concentrated to dryness. The crude product obtained was purified by HPLC to afford 11 mg of the title compound of the example (21% yield).

[0517] LC-MS (method 1): t_R=3.93 min; m/z=384 (MH^+).

Example 7

2-(4-Aminocarbonylphenyl)amino-6-[6-(4-aminopiperidin-1-yl)pyridin-3-yl]-9H-purine

a) 6-[6-[4-(tert-Butoxycarbonyl)aminopiperidin-1-yl]pyridin-3-yl]-2-(4-ethoxycarbonylphenyl)amino-9-(tetrahydropyran-2-yl)-9H-purine

[0518] Following a similar procedure to that described in example 1 section b, but using ethyl 4-aminobenzoate instead of [4-(4-morpholino)phenyl]amine, the desired compound was obtained (34% yield).

[0519] LC-MS (method 1): t_R=10.54 min; m/z=643 (MH^+).

b) 6-[6-[4-(tert-Butoxycarbonyl)aminopiperidin-1-yl]pyridin-3-yl]-2-(4-carboxyphenyl)amino-9-(tetrahydropyran-2-yl)-9H-purine

[0520] To a solution of the compound obtained in the previous section (93 mg, 0.14 mmol) in EtOH (2 mL), a solution of KOH (54 mg, 0.96 mmol) in H_2O (2 mL) was added. The reaction mixture was stirred at 90° C. for 72 h. It was cooled until room temperature. The residue was washed with H_2O and extracted with EtOAc. The aqueous layer was cooled to 0° C. and adjusted to pH=4 by the addition of 1N HCl and it was extracted thrice with EtOAc. The combined organic phases were dried over anhydrous $MgSO_4$ and concentrated to dryness, to afford 60 mg (67% yield) of the desired compound.

[0521] LC-MS (method 2): t_R=2.27 min; m/z=615 (MH^+).

c) 2-(4-Aminocarbonylphenyl)amino-6-[6-[4-(tert-butoxycarbonyl)aminopiperidin-1-yl]pyridin-3-yl]-9-(tetrahydropyran-2-yl)-9H-purine

[0522] To a solution of the compound obtained in the previous section (60 mg, 0.09 mmol) in DMF (1.5 mL) under Ar-atmosphere, EDC.HCl (23 mg, 0.10 mmol), HOBT (13 mg, 0.09 mmol), NMM (43 μL, 0.36 mmol) and finally a 30% aqueous NH_3 solution (43 μL, 0.97 mmol) were added. The resulting mixture was stirred at room temperature overnight and concentrated to dryness. The resulting residue was diluted in a mixture EtOAc/H_2O (1:1), the phases were separated and the aqueous layer was extracted with EtOAc. The combined organic phases were dried over Na_2SO_4 and concentrated to dryness. The crude product obtained was chromatographed over silica gel using hexane/EtOAc mixtures of increasing polarity as eluent, to afford 46 mg of the desired compound (76% yield).

[0523] LC-MS (method 2): t_R=2.69 min; m/z=614 (MH^+).
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d) Title Compound

[0524] Following a similar procedure to that described in example 1 section c, but using the compound obtained in the previous section, the title compound of the example was obtained (53% yield).

[0525] LC-MS (method 1): t_R=4.22 min; m/z=430 (MH^+).

Example 8

6-[3-(N-Isobutyl-N-acetylamino)phenyl]-2-[4-(4-morpholino)phenyl]amino-9H-purine

a) N-Isobutyl-3-(4,4,5,5-tetramethyl-1,2,3-dioxaborolan-2-yl)aniline

[0526] To a solution of 3-(4,4,5,5-tetramethyl-1,2,3-dioxaborolan-2-yl)aniline (250 mg, 1.14 mmol) in CH_2Cl_2 (1 mL) under Ar-atmosphere, a solution of isobutyraldehyde (103 μL, 1.14 mmol) in CH_2Cl_2 (2 mL) was added. The resulting mixture was cooled to 0° C. and sodium triacetoxyborohydride (483 mg, 2.28 mmol) was added. The resulting mixture

was stirred at room temperature overnight and diluted with EtOAc. It was treated with 0.2M $NaHCO_3$. The phases were separated and the aqueous phase extracted thrice with EtOAc. The combined organic phases were dried over Na_2SO_4 and concentrated to dryness. The crude product obtained was chromatographed over silica gel using hexane/EtOAc mixtures of increasing polarity as eluent, to afford 280 mg of the title compound (89% yield).

[0527] LC-MS (method 1): t_R=6.32 min; m/z=276 (MH^+).

b) 2-Chloro-6-[3-(N-isobutylamino)phenyl]-9-(tetrahydropyran-2-yl)-9H-purine

[0528] Following a similar procedure to that described in reference example 2, but using the compound obtained in the previous section instead of 2-fluoro-5-pyridylboronic acid, the desired compound was obtained (63% yield).

[0529] LC-MS (method 1): t_R=10.55 min; m/z=386 (MH^+).

c) 2-Chloro-6-[3-(N-isobutyl-N-acetylamino)phenyl]-9-(tetrahydropyran-2-yl)-9H-purine

[0530] To a solution of the compound obtained in the previous section (57 mg, 0.14 mmol) in CH_2Cl_2 (2 mL) under Ar-atmosphere, acetyl chloride (16 μL, 0.22 mmol) and DIEA (77 μL, 0.45 mmol) were added. The resulting mixture was stirred at room temperature overnight and concentrated to dryness. The resulting residue was diluted in a mixture of EtOAc/H_2O (1:1), the phases were separated and the aqueous phase extracted with EtOAc. The combined organic phases were dried over Na_2SO_4 and concentrated to dryness. The crude product obtained was chromatographed over silica gel using EtOAc/MeOH mixtures of increasing polarity as eluent, to afford 30 mg of the desired compound (47% yield).

[0531] LC-MS (method 1): t_R=9.52 min; m/z=428 (MH^+).

d) 6-[3-(N-Isobutyl-N-acetylamino)phenyl]-2-[4-(4-morpholino)phenyl]amino-9-(tetrahydropyran-2-yl)-9H-purine

[0532] Following a similar procedure to that described in example 1 section b, but starting from the compound obtained in the previous section, the desired compound was obtained (25% yield).

[0533] LC-MS (method 1): t_R=9.18 min; m/z=570 (MH^+).

e) Title Compound

[0534] Following a similar procedure to that described in example 1 section c, but using the compound obtained in the previous section, the title compound of the example was obtained (11% yield).

[0535] LC-MS (method 1): t_R=7.03 min; m/z=486 (MH^+).

Example 9

2-(3-Aminophenyl)amino-6-[6-(4-aminopiperidin-1-yl)pyridin-3-yl]-9H-purine

a) 6-{6-[4-(tert-Butoxycarbonyl)aminopiperidin-1-yl]pyridin-3-yl}-2-(3-nitrophenyl)amino-9-(tetrahydropyran-2-yl)-9H-purine

[0536] Following a similar procedure to that described in example 1 section b, but using 3-nitroaniline instead of [4-(4-morpholino)phenyl]amine, the desired compound was obtained (56% yield).

[0537] LC-MS (method 2): t_R=3.45 min; m/z=616 (MH^+).

b) 2-(3-Aminophenyl)amino-6-{6-[4-(tert-butoxycarbonyl)aminopiperidin-1-yl]pyridin-3-yl}-9-(tetrahydropyran-2-yl)-9H-purine

[0538] Following a similar procedure to that described in reference example 7 section b, but starting from the compound obtained in the previous section, the desired compound was obtained (59% yield).

[0539] LC-MS (method 1): t_R=8.82 min; m/z=586 (MH^+).

c) Title Compound

[0540] Following a similar procedure to that described in example 1 section c, but using the compound obtained in the previous section, the title compound of the example was obtained (31% yield).

[0541] LC-MS (method 1): t_R=4.54 min; m/z=402 (MH^+).

Example 10

2-[4-(4-Morpholino)phenyl]amino-6-[6-(piperidin-3-ylamino)pyridin-3-yl]-9H-purine

a) 2-[4-(4-morpholino)phenyl]amino-6-[6-[1-(tert-butoxycarbonyl)piperidin-3-ylamino]pyridin-3-yl]-9-(tetrahydropyran-2-yl)-9H-purine

[0542] Following a similar procedure to that described in example 2 section a, but using the compound obtained in example 5a section a, and 3-amino-1-(tert-butoxycarbonyl) piperidine, 0.027 g of the desired compound was obtained (20% yield).

b) Title Compound

[0543] Following a similar procedure to that described in example 1 section c, but using the compound obtained in the previous section. In this case, the crude product obtained was chromatographed over a SCX-2 column instead of silica gel using MeOH—NH_3(MeOH) mixtures of increasing polarity as eluent. The title compound of the example was obtained (88% yield).

[0544] LC-MS (method 4): t_R=1.28 min; m/z=472 (MH^+).

Following a similar procedure to that described in example 10, but using in each case the corresponding starting materials, these compounds were obtained:

Example	Compound name	reagent for step a)	HPLC method	t_R (min)	m/z
10a	2-[4-(4-morpholino)phenyl]amino-6-[6-(N-propylamino)pyridin-3-yl]-9H-purine	N-propylamine	4	1.55	431
10b	6-[6-(N-dimethylamino)pyridin-3-yl]-2-[4-(4-morpholino)phenyl]amino-9H-purine	N-dimethylamine hydrochloride	4	1.40	417

-continued

Example	Compound name	reagent for step a)	HPLC method	t_R (min)	m/z
10c	6-[6-([1,4]diazepan-1-yl)pyridin-3-yl]-2-[4-(4-morpholino)phenyl]amino-9H-purine	N-tert-butoxycarbonylhomopiperazine	4	1.28	472
10d	6-[6-(3-methoxycarbonylpyrrolidin-1-yl)pyridin-3-yl]-2-[4-(4-morpholino)phenyl]amino-9H-purine	Methyl pyrrolidine-3-carboxylate	4	1.61	501
10e	6-[6-(N-ethylmethylamino)pyridin-3-yl]-2-[4-(4-morpholino)phenyl]amino-9H-purine	N-ethylmethylamine	4	1.52	431
10f	6-[6-(N-butylmethylamino)pyridin-3-yl]-2-[4-(4-morpholino)phenyl]amino-9H-purine	N-butylmethylamine	4	1.88	459
10g	6-[6-N-((2-hydroxyethyl)methylamino)pyridin-3-yl]-2-[4-(4-morpholino)phenyl]amino-9H-purine	2-(methylamino)ethanol	4	1.32	447
10h	6-[6-(N-diethylamino)pyridin-3-yl]-2-[4-(4-morpholino)phenyl]amino-9H-purine	N-diethylamine	4	1.64	445
10i	6-[6-(N-benzylmethylamino)pyridin-3-yl]-2-[4-(4-morpholino)phenyl]amino-9H-purine	N-benzylmethyl amine	4	2.19	493
10j	6-[6-[(2-hydroxy-2-phenylethyl)methylamino]pyridin-3-yl]-2-[4-(4-morpholino)phenyl]amino-9H-purine	2-(methylamino)-1-phenylethanol	4	1.90	523
10k	6-[6-(N-isobutylmethylamino)pyridin-3-yl]-2-[4-(4-morpholino)phenyl]amino-9H-purine	N-isobutymethyll amine	4	1.88	459
10l	6-[6-(N-butylethylamino)pyridin-3-yl]-2-[4-(4-morpholino)phenyl]amino-9H-purine	N-butylethylamine	4	2.03	473
10m	6-[6-((2-hydroxyethyl)propylamino)pyridin-3-yl]-2-[4-(4-morpholino)phenyl]amino-9H-purine	2-(propylamino)ethanol	4	1.61	475
10n	6-[6-(2-methoxyethyl)methylaminopyridin-3-yl]-2-[4-(4-morpholino)phenyl]amino-9H-purine	N-(2-methoxyethyl)methylamine	4	1.55	461
10o	6-[6-(2-hydroxypropyl)methylaminopyridin-3-yl]-2-[4-(4-morpholino)phenyl]amino-9H-purine	1-(methylamino)propan-2-ol	4	1.43	461
10p	6-[6-(N-ethylpropylamino)pyridin-3-yl]-2-[4-(4-morpholino)phenyl]amino-9H-purine	N-ethylpropylamine	4	1.83	459
10q	6-[6-[N-methyl-(prop-2-ynyl)amino]pyridin-3-yl]-2-[4-(4-morpholino)phenyl]amino-9H-purine	N-methylpropar gylamine	4	1.94	441
10r	6-[6-(N-methylamino)pyridin-3-yl]-2-[4-(4-morpholino)phenyl]amino-9H-purine	N-methylamine hydrochloride	4	1.38	403

Example 11

6-[6-(3-Methylaminocarbonylpyrrolidin-1-yl)pyridin-3-yl]-2-[4-(4-morpholino)phenyl]amino-9H-purine

a) 6-[6-(3-Carboxypyrrolidin-1-yl)pyridin-3-yl]-2-[4-(4-morpholino)phenyl]amino-9H-purine

[0545] Following a similar procedure to that described in example 7 section b, but using the compound obtained in example 10d, the title compound was obtained quantitatively.

b) Title Compound

[0546] Following a similar procedure to that described in example 7 section c, but using the compound obtained in the previous section, and N-methylamine hydrochloride instead of 30% aqueous NH_3 solution, the title compound of the example was obtained (20% yield).

[0547] LC-MS (method 4): t_R=1.37 min; m/z=500 (MH^+).

Example 12

2-(3-Aminosulfonylphenyl)amino-6-{(4-[3-(hydroxymethyl)piperidin-1-yl]phenyl}-9H-purine

a) 2-Chloro-6-{4-[3-(hydroxymethyl)piperidin-1-yl]phenyl}-9-(tetrahydropyran-2-yl)-9H-purine

[0548] Following a similar procedure to that described in reference example 2, but using the compound obtained in

reference example 4a instead of 2-fluoro-5-pyridylboronic acid, the desired compound was obtained (39% yield).

[0549] LC-MS (method 5): t_R=2.47 min; m/z=428 (MH^+).

b) 2-[3-(N-tert-Butyl)aminosulfonylphenyl]amino-6-{4-[3-(hydroxymethyl)piperidin-1-yl]phenyl}-9-(tetrahydropyran-2-yl)-9H-purine

[0550] To a solution of the compound obtained in the previous section (150 mg, 0.351 mmol) in tert-butanol (4 mL) under Ar-atmosphere, potassium carbonate (106 mg, 0.768 mmol), X-Phos (17 mg, 0.036 mmol), $Pd_2(dba)_3$ (16 mg, 0.017 mmol) and 3-amino-N-tert-butylbenzenesulfonamide (160 mg, 0.701 mmol) were added at room temperature. The mixture was purgued under Ar-atmosphere and heated at 100° C. overnight. The reaction crude was filtered through a plug of Celite®, washed with methanol and evaporated to dryness. The crude product thus obtained was chromatographed over silica gel using hexane/EtOAc mixtures of increasing polarity as eluent, to afford 99 mg of the desired compound (46% yield).

[0551] LC-MS (method 5): t_R=2.53 min; m/z=620 (MH^+)

c) Title Compound

[0552] The compound obtained in the previous section (60 mg, 0.097 mmol) and a mixture of THF/6N $HCl_{(aq)}$ (3 mL) was stirred at reflux temperature for 4 h under Ar-atmosphere. Afterwards, the mixture was concentrated to dryness and the residue was partitioned and the mixture was concentrated to dryness. The residue was partitioned between 0.2N $NaHCO_3$ and CH_2Cl_2. The organic phase was dried over Na_2SO_4 and concentrated to dryness. The crude product thus obtained was chromatographed over silica gel using $CHCl_3$/MeOH/NH_3 mixtures of increasing polarity as eluent, to afford 22 mg of the desired compound (48% yield).

[0553] LC-MS (method 1): t_R=5.83 min; m/z=480 (MH^+).

Following a similar procedure to that described in example 12, but using the corresponding starting materials, the following compound was obtained:

Example	Compound name	Starting Material	HPLC method	t_R (min)	m/z
13a	2-(3-acetylaminophenyl)-amino-6-[3-(methylsulfinyl)phenyl]-9H-purine	Example 1ch	5	1.37	407

Example 14

2-(3-Aminosulfonylphenyl)amino-6-[4-(ethylaminocarbonyloxy)phenyl]-9H-purine

a) 2-Chloro-6-(4-hydroxyphenyl)-9-(tetrahydropyran-2-yl)-9H-purine

[0556] Following a similar procedure to that described in reference example 2, but using 4-hydroxyphenyl boronic acid instead of 2-fluoro-5-pyridylboronic acid, the desired compound was obtained (21% yield).

[0557] LC-MS (method 5): t_R=2.11 min; m/z=329 (MH^-).

b) 2-Chloro-6-(4-ethylaminocarbonyloxy)phenyl-9-(tetrahydropyran-2-yl)-9H-purine

[0558] A mixture of the compound obtained in the previous section (125 mg, 0.378 mmol), ethyl isocyanate (0.030 mL, 0.380 mmol) and 3 mL of DMF was stirred at 80° C. overnight. The resulting solution was evaporated to dryness and chromatographed over silica gel using hexane/EtOAc mixtures of increasing polarity as eluent, to afford 33 mg of the desired compound (22% yield).

[0559] LC-MS (method 5): t_R=2.36 min; m/z=402 (MH^+)

c) 2-(3-Aminosulfonylphenyl)amino-6-(4-ethylaminocarbonyloxy)phenyl-9-(tetrahydropyran-2-yl)-9H-purine

[0560] Following a similar procedure to that described in example 12 section b, but using the compound obtained in the previous section and 3-aminobenzenesulfonamide instead of 3-amino-N-tert-butylbenzenesulfonamide, the desired compound was obtained.

[0561] LC-MS (method 5): t_R=1.40 min; m/z=538 (MH^+).

d) Title Compound

[0562] A mixture of the compound obtained in the previous section (68 mg, 0.126 mmol), 4M dioxane/$HCl_{(g)}$ (5 mL) and 1 mL of methanol was stirred at room temperature under Ar-atmosphere overnight. The solution was concentrated to dryness and the crude product thus obtained was chromatographed over silica gel using EtOAc/MeOH mixtures of increasing polarity as eluent, to afford 27 mg of the desired compound (47% yield).

[0563] LC-MS (method 1): t_R=3.83 min; m/z=454 (MH^+).

Example	Compound name	a) step reagent	b) step reagent	HPLC method	t_R (min)	m/z
12a	2-(3-aminosufonylphenyl)amino-6-(3-methylsulfanyl)phenyl-9H-purine	3-(methylsulfanyl)phenylboronic acid	3-amino-N-tert-butylbenzenesulfonamide	5	1.84	413

Example 13

2-(3-Aminosulfonylphenyl)amino-6-[3-(methylsulfinyl)phenyl]-9H-purine

[0554] To a solution of the compound of example 12a (50 mg, 0.121 mmol) in 4 mL of a 1:1 mixture of acetic acid and methanol, was added under an Ar-atmosphere 0.04 mL of 30% H_2O_2 and the resulting mixture was stirred at room temperature overnight. The crude product obtained was evaporated to dryness and chromatographed over silica gel using $CHCl_3$/MeOH/NH_3 mixtures of increasing polarity as eluent, to afford 21 mg of the desired compound (41% yield).

[0555] LC-MS (method 5): t_R=1.27 min; m/z=429 (MH^+).

Following a similar procedure to that described in example 13, but using the corresponding starting materials, the following compound was obtained:

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

Example	Compound name	reagent for step a)	reagent for step c)	HPLC method	t_R (min)	m/z
14a	2-[3-aminosulfonylphenyl]amino-6-[4-(ethylaminocarbonylamino)phenyl]-9H-purine	4-aminophenylboronic acid	3-aminobenzenesulfonamide	5	1.43	453

Example 15

2-[3-(Aminosulfonyl)phenyl]amino-6-[4-(methanesulfonylamino)phenyl]-9H-purine

a) 6-(4-Aminophenyl)-2-chloro-9-(tetrahydropyran-2-yl)-9H-purine

[0564] Following a similar procedure to that described in reference example 2, but using 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline instead of 2-fluoro-5-pyridylboronic acid, the desired compound was obtained (33% yield).

[0565] LC-MS (method 5): t_R=2.15 min; m/z=330 (MH^+).

b) 2-Chloro-6-[4-(methanesulfonylamino)phenyl]-9-(tetrahydropyran-2-yl)-9H-purine

[0566] To a mixture of the compound obtained in the previous section (170 mg, 0.52 mmol), a catalytic amount of DMAP, diisopropyethylamine (0.181 mL, 1.04 mmol) and 4 mL dichloromethane, methanesulfonyl chloride (40.3 4, 0.52 mmol) was added and the resulting mixture was stirred at room temperature overnight. The resulting solution was partitioned between H_2O and dichloromethane and the organic phase was dried over Na_2SO_4 and concentrated to dryness. The crude product thus obtained was chromatographed over silica gel using EtOAc/MeOH mixtures of increasing polarity as eluent, to afford 14 mg of the desired compound (7% yield).

[0567] LC-MS (method 5): t_R=2.07 min; m/z=408 (MH^+)

c) 2-(3-Aminosulfonylphenyl)amino-6-[4-(methanesulfonylamino)phenyl]-9-(tetrahydropyran-2-yl)-9H-purine

[0568] Following a similar procedure to that described in example 12 section b, but using the compound obtained in the previous section and 3-aminobenzenesulfonamide instead of 3-amino-N-tert-butylbenzenesulfonamide, the desired compound was obtained.

[0569] LC-MS (method 5): t_R=1.78 min; m/z=544 (MH^+).

d) Title Compound

[0570] Following a similar procedure to that described in example 14 section d, but using the compound obtained in the previous section, the title compound of the example was obtained (26% yield).

[0571] LC-MS (method 5): t_R=1.28 min; m/z=460 (MH^+).

Following a similar procedure to that described in example 15, but using in each case the corresponding starting materials, these compounds were obtained:

Example	Compound name	reagent for step a)	reagent for step b)	reagent for step c)	HPLC method	t_R (min)	m/z
15a	2-(3-aminosulfonylphenyl)amino-6-[4-(N-isobutirylamino)phenyl]-9H-purine	4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline	isobutyril chloride	3-amino-N-tert-butylbenzene sulfonamide	5	1.58	452
15b	6-[4-(N-methylpropionylamino)phenyl]-2-[4-(4-morpholino)phenyl]amino-9H-purine	N-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline	propionyl chloride	[4-(4-morpholino)phenyl]amine	4	2.13	458
15c	6-[4-(N-methylmethanesulfonylamino)-phenyl]-2-[4-(4-morpholino)phenyl]amino-9H-purine	N-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline	methanesulfonyl chloride	[4-(4-morpholino)phenyl]amine	4	2.15	480

-continued

Example	Compound name	reagent for step a)	reagent for step b)	reagent for step c)	HPLC method	t_R (min)	m/z
15d	2-[4-(4-methylpiperazin-1-yl)phenyl]amino-6-[4-(N-methylpropionylamino)phenyl]-9H-purine	N-tert-butoxycarbonyl-N-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1)	propionyl chloride	[4-(4-methylpiperazin-1-yl)phenyl]amine	4	1.64	471
15e	6-[4-(N-methylmethanesulfonylamino)-phenyl]-2-[4-(4-methylpiperazin-1-yl)phenyl]amino-9H-purine	N-tert-butoxycarbonyl-N-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1)	methanesulfonyl chloride	[4-(4-methylpiperazin-1-yl)phenyl]amine	4	1.63	493

(1) Step d was performed after step a

Example 16

6-[6-(N-Methylmethanesulfonylamino)pyridin-3-yl]-2-[4-(4-morpholino)phenyl]amino-9H-purine

a) 6-[6-(N-Methylmethansulfonylamino)pyridin-3-yl]-2-[4-(4-morpholino)phenyl]amino-9-(tetrahydropyran-2-yl)-9H-purine

[0572] Following a similar procedure to that described in example 15 section b, but using the compound obtained in example 10r section b, the desired compound was obtained.

b) Title Compound

[0573] Following a similar procedure to that described in example 14 section d, but using the compound obtained in the previous section, the title compound of the example was obtained.

[0574] LC-MS (method 4): t_R=2.15 min; m/z=481 (MH^+).

Example 17

2-[3-(N-Acetyl)aminosulfonylphenyl]amino-6-[6-(methylpropylamino)pyridin-3-yl]-9H-purine

[0575] A mixture of the compound of example 2r (115 mg, 0.26 mmol), N,N-dimethyaminopyridine (catalytic amount), acetic anhydride (0.025 mL, 0.26 mmol) and pyridine (4 mL) was stirred at room temperature overnight. The resulting solution was evaporated to dryness and chromatographed over silica gel using $CHCl_3$/MeOH/NH_3 mixtures of increasing polarity as eluent, to afford 17 mg of the desired compound (13% yield).

[0576] LC-MS (method 5): t_R=1.49 min; m/z=481 (MH^+).

Example 18

2-(3-Aminosulfonylphenyl)amino-6-[6-(3-hydroxypiperidin-1-yl)pyridin-3-yl]-9H-purine

a) 6-[6-[3-(tert-Butyldimethylsilyloxy)piperidin-1-yl]pyridin-3-yl]-2-chloro-9-(tetrahydropyran-2-yl)-9H-purine

[0577] A mixture of the compound obtained in example 2a section a (1.84 g, 4.42 mmol), imidazole (752 mg, 11.05 mmol), tert-butyldimethylsilyl chloride and DMF (50 mL) was stirred at room temperature overnight. The resulting solution was diluted with dichloromethane (250 mL) and was partitioned between H_2O and dichloromethane. The organic phase was dried over Na_2SO_4 and concentrated to dryness. The crude product thus obtained was chromatographed over silica gel using EtOAc/MeOHI mixtures of increasing polarity as eluent, to afford the desired compound in quantitative yield.

b) 6-[6-[3-(tert-Butyldimethylsilyloxy)piperidin-1-yl]pyridin-3-yl]-2-(3-tert-butylaminosulfonylphenyl) amino-9-(tetrahydropyran-2-yl)-9H-purine

[0578] Following a similar procedure to that described in example 12 section b, but using the compound obtained in the previous section instead of 2-chloro-6-{4-[3-(hydroxymethyl)piperidin-1-yl]phenyl}-9-(tetrahydropyran-2-yl)-9H-purine, the title compound was obtained.

c) 2-(3-tert-Butylaminosulfonylphenyl)amino-6-[6-(3-hydroxypiperidin-1-yl)pyridin-3-yl]-9-(tetrahydropyran-2-yl)-9H-purine

[0579] To a solution of the compound obtained in the previous section (136 mg, 0.19 mmol) and 3.8 mL of THF, tetrabutylammonium fluoride hydrate (148 mg, 056 mmol) was added. The mixture was stirred for 3 h at room temperature and the resulting suspension was evaporated to dryness and chromatographed over silica gel using $CHCl_3$/MeOH/NH_3 mixtures of increasing polarity as eluent, to afford 82 mg of the desired compound (72% yield).

d) Title Compound

[0580] Following a similar procedure to that described in example 12 section c, but using the compound obtained in the previous section, the title compound was obtained.

[0581] LC-MS (method 4): t_R=1.45 min; m/z=467 (MH^+).

Following a similar procedure to that described in example 18, but using in each case the corresponding starting materials, these compounds were obtained:

Example	Compound name	reagent for step b)	HPLC method	t_R (min)	m/z
18a	6-[6-(3-hydroxypiperidin-1-yl)pyridin-3-yl]-2-(3-methylaminosulfonylbenzene)amino-9H-purine	3-amino-N-methylbenzenesulfonamide	4	1.61	481
18b	2-[4-(3-aminopyrrolidin-1-yl)phenyl]amino-6-[6-(3-hydroxypiperidin-1-yl)pyridin-3-yl]-9H-purine	Reference Example 8a	4	1.19	472

Example 19

6-(6-Butoxypyridin-3-yl)-2-[4-(4-morpholino)phenyl]amino-9H-purine

a) 6-(6-Butoxypyridin-3-yl)-2-[4-(4-morpholino) phenyl]amino 9-(tetrahydropyran-2-yl)-9H-purine

[0582] A mixture of the compound obtained in example 5a section a (100 mg, 0.21 mmol) and potassium tert-butoxyde (56 mg, 0.5 mmol) in n-BuOH (2 mL) was irradiated in a monomode microwave at 160° C. for 10 min (160 W). The resulting crude product was evaporated to dryness and was partitioned between H_2O and dichloromethane. The organic phase was dried over Na_2SO_4 and concentrated to dryness and the crude product thus obtained was chromatographed over silica gel using $CHCl_3$/MeOH/NH_3 mixtures of increasing polarity as eluent, to afford 54 mg of the desired compound.

b) Title Compound

[0583] Following a similar procedure to that described in example 1 section c, but using the compound obtained in the previous section, the title compound of the example was obtained.

[0584] LC-MS (method 4): t_R=2.97 min; m/z=446 (MH^+).

Following a similar procedure to that described in example 19, but using the corresponding starting materials, the following compound was obtained:

Example	Compound name	reagent for step b)	HPLC method	t_R (min)	m/z
19a	6-[6-(2-hydroxy)-ethoxypyridin-3-yl]-2-[4-(4-morpholino)-phenyl]amino-9H-purine	ethylene glycol	4	1.70	434

Example 20

2-(3-Aminosulfonylphenyl)amino-6-(2-carboxypyrrole-4-yl)-9H-purine

a) 2-Chloro-9-(tetrahydropyran-2-yl)-6-[2-(methoxycarbonyl)-1-(4-toluoyl)sulfonyl-pyrrole-4-yl]-9H-purine

[0585] Following a similar procedure to that described in reference example 2, but using the compound obtained in reference example 11 instead of 2-fluoro-5-pyridylboronic acid, and using K_2CO_3 instead of Na_2CO_3, the desired compound was obtained (60% yield).

[0586] LC-MS (method 5): t_R=3.02 min; m/z=516 (MH^+).

b) 2-(3-Aminosulfonyl)phenylamino-9-(tetrahydropyran-2-yl)-6-[1-(4-toluoyl)sulfonyl-2-(methoxycarbonyl)pyrrole-4-yl]-9H-purine

[0587] Following a similar procedure to that described in example 12 section b, but using the compound obtained in the previous section instead of 2-chloro-6-{4-[3-(hydroxymethyl)piperidin-1-yl]phenyl}-9-(tetrahydropyran-2-yl)-9H-purine and 3-aminobenzenesulfonamide instead of 3-amino-N-tert-butylbenzenesulfonamide, the desired compound was obtained (72% yield).

[0588] LC-MS (method 5): t_R=2.60 min; m/z=652 (MH^+).

c) Title Compound

[0589] A solution of the compound obtained in the previous section (0.54 g, 0.83 mmol) in 30 mL methanol and 25 mL 1N NaOH was heated at 80° C. during 2 h. A solution of 6N HCl was added dropwise until acidic pH and the solution extracted three times with ethyl acetate. The organic layer was dried over Na_2SO_4 and evaporated to dryness. The crude product thus obtained was filtered over silica gel using $CHCl_3$/MeOH/acetic acid/DMF mixtures as eluent, the solution was evaporated and dried, to afford the title compound (17% yield).

[0590] LC-MS (method 5): t_R=0.82 min; m/z=400 (MH^+).

Example 21

2-(3-Aminophenyl)amino-6-(3-methanesulfonyl) phenyl-9H-purine

a) 2-(3-Aminophenyl)amino-6-(3-methanesulfonyl) phenyl-9-(tetrahydropyran-2-yl)-9H-purine

[0591] Following a similar procedure to that described in reference example 7 section b, but using the compound obtained in 1cu section b, the desired compound was obtained in quantitative yield.

b) Title Compound

[0592] Following a similar procedure to that described in example 1 section c, but using the compound obtained in the

previous section, the title compound of the example was obtained (5% yield).

[0593] LC-MS (method 4): t_R=1.82 min; m/z=381 (MH^+).

Example 22

6-(3-Methylsulfanylphenyl)-2-[4-(4-morpholino) phenyl]amino-9H-purine

a) 2-Chloro-6-[(3-methylsulfanyl)phenyl]-9-(tetrahydropyran-2-yl)-9H-purine

[0594] Following a similar procedure to that described in reference example 2, but using 3-(methylsulfanyl)phenylboronic acid instead of 2-fluoro-5-pyridylboronic acid, the desired compound was obtained (72% yield).

[0595] LC-MS (method 5): t_R=2.18 min; m/z=419 (MH^+).

b) 2-Chloro-6-[(3-methylsulfinyl)phenyl]-9-(tetrahydropyran-2-yl)-9H-purine

[0596] To a solution of the compound obtained in the previous section in dichloromethane (2 mL) 197 mg of m-chloroperbenzoic acid (77%) was added. The mixture was stirred overnight at room temperature and then the solvent was evaporated. The crude product thus obtained was purified over silica gel using hexane/EtOAc mixtures of increasing polarity, to afford 195 mg of the title compound (70% yield).

[0597] LC-MS (method 5): t_R=1.95 min; m/z=377 (MH^+).

c) 6-[(3-Methylsulfinyl)phenyl]-2-[4-(4-morpholino) phenyl]amino-9-(tetrahydropyran-2-yl)-9H-purine

[0598] To a solution of the compound obtained in the previous section (97 mg, 0.258 mmol) in tert-butanol (5 mL), K_2CO_3 (157 mg, 0.567 mmol), X-Phos (25 mg, 0.0258 mmol), $Pd_2(dba)_3$ (24 mg, 0.0129 mmol) and [4-(4-morpholino)phenyl]amine (184 mg, 1.034 mmol) were added at room temperature and the mixture was stirred under Ar-atmosphere at 90° C. overnight. The crude product obtained was filtered over Celite® and concentrated to dryness.

[0599] LC-MS (method 5): t_R=1.99 min; m/z=519 (MH^+).

d) Title Compound

[0600] The crude product obtained in the previous section (0.258 mmol) and a mixture of 4M dioxane/$HCl_{(g)}$ (3 mL) was stirred at room temperature under Ar-atmosphere overnight. The solvent was concentrated and the crude product obtained was chromatographed over silica gel using $CHCl_3$/MeOH/NH_3 mixtures of increasing polarity as eluent, to afford the desired compound (7% yield).

[0601] LC-MS (method 5): t_R=2.18 min; m/z=419 (MH^+).

Example 23

2-(3-Aminosulfonyl)phenylamino-6-(4-pyrazolyl)-9H-purine

a) 2-Chloro-6-(1-tert-butoxycarbonylpyrazol-4-yl)-9-(tetrahydropyran-2-yl)-9H-purine

[0602] Following a similar procedure to that described in reference example 2, but using 2-(1-tert-butoxycarbonyl) pyrazol-4-yl-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane instead of 2-fluoro-5-pyridylboronic acid, the desired compound was obtained.

[0603] LC-MS (method 5): t_R=1.70 min; m/z=303 (MH^-).

b) 2-[(3-Aminosulfonyl)phenyl]amino-6-(4-pyrazolyl)-9-(tetrahydropyran-2-yl)-9H-purine

[0604] Following a similar procedure to that described in example 22 section c, but using the compound obtained in the previous section, and 3-aminobenzenesulfonamide instead of [4-(4-morpholino)phenyl]amine, the desired compound was obtained.

[0605] LC-MS (method 1): t_R=5.63 min; m/z=441 (MH^+).

c) Title Compound

[0606] The compound obtained in the previous section was mixed with Dowex 50w×8 (440 mg) in methanol (4 mL) and DMSO (1 mL) and the mixture was stirred overnight at room temperature. The suspension was filtered and washed with NH_4OH/MeOH (25%) and methanol. Evaporation of the solvent yielded the desired product.

[0607] LC-MS (method 1): t_R=4.01 min; m/z=357 (MH^+).

Following a similar procedure to that described in example 23, but using in each case the corresponding starting materials, the following compounds were obtained:

Example	Compound name	reagent for step a)	reagent for step b)	HPLC method	t_R (min)	m/z
23a	2-[(3-aminosulfonyl)phenyl]amino-6-(1-methyl-4-pyrazolyl)-9H-purine	1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole	3-aminobenzenesulfonamide	5	1.18	371
23b	2-[(3-aminosulfonyl)phenyl]amino-6-(3-furanyl)-9H-purine	3-furanboronic acid	3-aminobenzenesulfonamide	5	5.38	357
23c	2-[(3-aminosulfonyl)phenyl]amino-6-(3-pyrrolyl)-9H-purine	1-(triisopropylsilyl)-1H-pyrrole-3-boronic acid	3-aminobenzenesulfonamide	5	1.18	356

Example 24

6-[1-(Aminocarbonyldimethylmethyl)pyrazol-4-yl]-2-(3-aminosulfonyl)phenylamino-9H-purine

a) 2-Chloro-6-[1-(ethoxycarbonyldimethylmethyl) pyrazol-4-yl]-9-(tetrahydropyran-2-yl)-9H-purine

[0608] To a solution of the compound obtained in example 23, section a in DMF (16 mL), cooled to 0° C., 171 mg (3.938 mmol) of NaH and ethyl-2-bromoisobutyrate (0.442 mL, 2.953 mmol) were added. The mixture was stirred for 3 h at room temperature. The resulting suspension was diluted with a mixture of tert-butylmethyl ether (100 mL), water (20 mL) and NH_4Cl saturated solution (5 mL). The two phases were separated and the aqueous phase was extracted with tert-butylmethyl ether. The combined organic phases were dried over Na_2SO_4 and concentrated to dryness to afford the desired product.

b) 6-[1-(Carboxydimethylmethyl)pyrazol-4-yl]-2-chloro-9-(tetrahydropyran-2-yl)-9H-purine

[0609] To a solution of 378 mg of the compound obtained in the previous section in THF (2 mL), a solution of $LiOH.H_2O$ (75 mg) in 2 mL of water was added. The mixture was stirred overnight at room temperature. The crude product was cooled to 0° C. and 2 mL HCl 1N, 2.5 mL of water and 50 mL of EtOAc were added. The phases were separated and the aqueous phase extracted with EtOAc. The combined organic phases were dried over Na_2SO_4 and concentrated to dryness, to afford. 347 mg of the desired product.

[0610] LC-MS (method 5): t_R=1.41 min; m/z=391 (MH^+).

c) 6-[1-(Aminocarbonyldimethylmethyl)pyrazol-4-yl]-2-chloro-9-(tetrahydropyran-2-yl)-9H-purine

[0611] A mixture of the product obtained in the previous section (144 mg, 0.346 mmol) and CU (100 mg, 0.554 mmol) in 8 mL of DMF was stirred for 3 h at room temperature. Then, triethylamine (0.217 mL, 1.55 mmol) and ammonium chloride (56 mg, 1.04 mmol) were added and the mixture was stirred overnight at room temperature. The resulting suspension was diluted in EtOAc and washed with 1N HCl, water, 1N NaOH and brine. The organic phase was dried over Na_2SO_4 and concentrated to dryness, to afford 112 mg of the desired product.

[0612] LC-MS (method 5): t_R=1.82 min; m/z=390 (MH^+).

d) 6-[1-(Aminocarbonyldimethylmethyl)pyrazol-4-yl]-2-(3-aminosulfonyl)phenylamino-9-(tetrahydropyran-2-yl)-9H-purine

[0613] Following a similar procedure to that described in 22 section c, but using the compound obtained in the previous section, and 3-aminobenzenesulfonamide instead of [4-(4-morpholino)phenyl]amine, the desired compound was obtained.

[0614] LC-MS (method 5): t_R=1.66 min; m/z=526 (MH^+).

e) Title Compound

[0615] A mixture of the compound obtained in the previous section and 4M dioxane/$HCl_{(g)}$ (2 mL) was stirred at room temperature overnight. The suspension was concentrated to dryness and the crude product thus obtained was chromatographed over silica gel using $CHCl_3$/MeOH mixtures of increasing polarity as eluent, to afford the desired compound.

[0616] LC-MS (method 5): t_R=1.24 min; m/z=442 (MH^+).

Following a similar procedure to that described in example 24, but using in each case the corresponding starting materials, the following compound was obtained:

Example	Compound name	reagent for step d)	HPLC method	t_R (min)	m/z
24a	6-[1-(aminocarbonyldimethylmethyl)pyrazol-4-yl]-2-[4-(4-methylpiperazin-1-yl)phenyl]amino-9H-purine	[4-(4-methylpiperazin-1-yl)phenyl]amine	5	1.32	461

Example 25

2-(3-Aminosulfonyl)phenylamino-6-[3-(2,2,2-trifluoroethyl)aminocarbonylphenyl]-9H-purine

a) 6-(3-Carboxy)phenyl-2-chloro-6-(3-carboxy)phenyl-9-(tetrahydropyran-2-yl)-9H-purine

[0617] Following a similar procedure to that described in reference example 2, but using 3-carboxyphenylboronic acid instead of 2-fluoro-5-pyridylboronic acid, the desired compound was obtained (90% yield).

b) 2-Chloro-9-(tetrahydropyran-2-yl)-6-[3-(2,2,2-trifluoroethyl)aminocarbonylphenyl]-9H-purine

[0618] A mixture of the compound obtained in the previous section (420 mg, 1.17 mmol), DIEA (0.92 mL, 5.26 mmol), 2,2,2-trifluoroethylamine hydrochloride (476 mg, 3.51 mmol) and HBTU (533 mg, 1.40 mmol) were stirred at room temperature in 30 mL DMF overnight. The mixture was evaporated to dryness and chromatographed over silica gel using Hexane/Ethyl Acetate mixtures of increasing polarity as eluent, to afford the desired compound (26%).

[0619] LC-MS (method 5): t_R=2.46 min; m/z=440 (MH^+).

c) 2-(3-Aminosulfonyl)phenylamino-9-(tetrahydropyran-2-yl)-6-[3-(2,2,2-trifluoroethyl)aminocarbonylphenyl]-9H-purine

[0620] Following a similar procedure to that described in 12 section b, but using the compound obtained in the previous section, and 3-aminobenzenesulfonamide instead of

3-amino-N-tert-butylbenzenesulfonamide, the desired compound was obtained.

[0621] LC-MS (method 5): t_R=2.14 min; m/z=576 (MH^+).

d) Title Compound

[0622] A mixture of the compound obtained in the previous section (0.305 mmol) and 4M dioxane/$HCl_{(g)}$ (5.2 mL) was stirred at room temperature under Ar-atmosphere overnight. The solution was concentrated to dryness and the crude product thus obtained was chromatographed over silica gel using $CHCl_3$/MeOH/NH_3 mixtures of increasing polarity as eluent, to afford 77 mg of the desired compound (51% yield).

[0623] LC-MS (method 5): t_R=1.71 min; m/z=492 (MH^+).

Example 26

2-(3-Aminosulfonylphenyl)amino-6-(2-methylaminocarbonylpyrrole-4-yl)-9H-purine

[0624] A mixture of the compound obtained in example 20 (20 mg, 0.041 mmol), HBTU (19 mg, 0.050 mmol), and methylamine solution 2.0M in THF (0.1 mL, 0.207 mmol) were stirred in 1 mL of DMF at room temperature overnight. The resulting mixture was evaporated to dryness and purified over preparative HPLC. The title compound was obtained (3%).

[0625] LC-MS (method 5): t_R=1.71 min; m/z=492 (MH^+).

Following a similar procedure to that described in example 26, but using the corresponding starting material, the following compound was obtained:

Example	Compound name	reagent	HPLC method	t_R (min)	m/z
26a	2-(3-aminosulfonylphenyl)amino-6-(2-ethylaminocarbonylpyrrole-4-yl)-9H-purine	Ethylamine (2.0M in THF)	5	1.35	427

Example 27

Biological Assay 1

JAK3 Kinase Inhibition

[0626] In a final volume of 50 μL, 5 μL of the test product dissolved in 10% DMSO (final concentration, 0.001-10 μM), was incubated with 4 μg/mL of human JAK3 781-1124, 1 μg/mL of Poly-L-Ala, L-Glu, L-Lys, L-Tyr and ATP (0.2 μM, approximately 2×10^5 cpm of γ^{33}P-ATP) in HEPES buffer (60 mM, pH 7.5) with Mg^{2+}chloride (3 mM), Mn^{2+} chloride (3 mM), sodium orthovanadate (3 μM) and dithiotreitol (1.2 mM). The reaction was started by adding Mg^{2+}[γ^{33}P-ATP]. After incubation for 50 min at room temperature, the reaction was quenched by the addition of 50 μL of 2% phosphoric acid solution. The reaction mixture was filtered in vacuo and washed three times with a 150 mM phosphoric acid solution. 200 μL of liquid scintillation was added before drying it and counting it.

The compounds of all examples showed more than 50% of inhibition of JAK3 activity at 10 μM in this assay.

Example 28

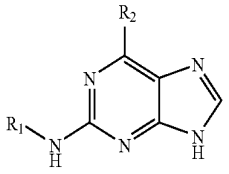
Biological Assay 2

Delayed-Type Hypersensitivity Response (DTH)

[0627] This assay was performed essentially as disclosed in Kudlacz E. et al, see supra. Male C57BL/6J mice received i.v. injections of 1×10^5 sheep red blood cells in a volume of 0.2 mL sterile phosphate buffered saline (PBS). Four days later, sensitized mice received an injection of 1×10^8 sheep red blood cells in a volume of 30 μL sterile PBS into the left footpad. Twenty-four hours later, animals were sacrificed and their footpads removed and weighted. The DTH swelling response was calculated by subtracting the right footpad weight (baseline) from that of the left footpad (experimental). Test compounds or vehicle (0.2% carboxymethylcellulose and 1% Tween 80 in water) were administered p.o. once daily during both sensitization and challenge phases of the DTH response.

Compounds of examples 1 cc, 1cr, 1ct, 5u, 10h and 10p were active in this assay when administered orally.

1. A compound of formula I:



I

wherein:

R_1 is chosen from phenyl and a 5- or 6-membered aromatic heterocycle bonded to the NH group through a C atom, wherein the phenyl or heterocycle is optionally fused to a 5- or 6-membered saturated, partially unsaturated or aromatic carbocyclic or heterocyclic ring, wherein R_1 optionally contains from 1 to 4 heteroatoms chosen from N, O and S, wherein one or more C or S atoms of the 5- or 6-membered fused ring are optionally oxidized forming CO, SO or SO_2 groups, and wherein R_1 is optionally substituted with one or more R_3;

R_2 is chosen from phenyl and a 5- or 6-membered aromatic heterocycle bonded to the purine ring through a C atom, wherein the phenyl or heterocycle is optionally fused to a 5- or 6-membered saturated, partially unsaturated or aromatic carbocyclic or heterocyclic ring, wherein R_2 optionally contains from 1 to 4 heteroatoms chosen from N, O and S, wherein one or more C or S atoms of the 5- or 6-membered fused ring is optionally oxidized forming CO, SO or SO_2 groups, and wherein R_2 is optionally substituted with one or more R_4;

R_3 and R_4 independently are chosen from C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, halogen, —CN, —NO_2, —COR_E, —CO_2R_6, —$CONR_6R_6$, —OR_6, —$OCOR_5$, —$OCONR_5R_5$, —OCO_2R_5, —SR_6, —SO_2R_5, —$SO_2NR_6R_6$, —$SO_2NR_7COR_5$,

—NR_6R_6, —NR_7COR_6, —$NR_7CONR_6R_6$, —$NR_7CO_2R_5$, —$NR_7SO_2R_5$, —C(=N—OH)R_5, and Cy_1, wherein the C_{1-4}alkyl, C_{2-4}alkenyl and C_{2-4}alkynyl groups are optionally substituted with one or more R_8 and Cy_1 is optionally substituted with one or more R_9;

R_5 is chosen from C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, and Cy_2, wherein the C_{1-4}alkyl, C_{2-4}alkenyl and C_{2-4}alkynyl groups are optionally substituted with one or more R_{10} and Cy_2 is optionally substituted with one or more R_{11};

R_6 is chosen from hydrogen and R_5;

R_7 is chosen from hydrogen and C_{1-4}alkyl;

R_8 is chosen from halogen, —CN, —NO_2, —COR_{13}, —CO_2R_{13}, —$CONR_{13}R_{13}$, —OR_{13}, —$OCOR_{12}$, —$OCONR_{12}R_{12}$, —OCO_2R_{12}, —SR_{13}, —SO_2R_{12}, —SOR_{12}, —$SO_2NR_{13}R_{13}$, —$SO_2NR_7COR_{12}$, —$NR_{13}R_{13}$, —NR_7COR_{13}, —$NR_7CONR_{13}R_{13}$, —$NR_7CO_2R_{12}$, —$NR_7SO_2R_{12}$, —C(=N—OH)R_{12} and Cy_2, wherein Cy_2 is optionally substituted with one or more R_{11};

R_9 is chosen from the group of R_{14} and C_{1-4}alkyl, where the C_{1-4}alkyl is optionally substituted with one or more R_{10};

R_{10} is chosen from halogen, —CN, —NO_2, —COR_{16}, —CO_2R_{16}, —$CONR_{16}R_{16}$, —OR_{16}, —$OCOR_{15}$, —$OCONR_{15}R_{15}$, —OCO_2R_{15}, —SR_{16}, —SO_2R_{15}, —SOR_{15}, —$SO_2NR_{16}R_{16}$, —$SO_2NR_7COR_{15}$, —$NR_{16}R_{16}$, —NR_7COR_{16}, —$NR_7CONR_{16}R_{16}$, —$NR_7CO_2R_{15}$, —$NR_7SO_2R_{15}$, —C(=N—OH)R_{15} and Cy_2, wherein Cy_2 is optionally substituted with one or more R_{11};

R_{11} is chosen from C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl, cyanoC_{1-4}alkyl, and R_{14};

R_{12} is chosen from C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl, cyanoC_{1-4}alkyl, Cy_3-C_{1-4}alkyl, and Cy_2, wherein Cy_2 is optionally substituted with one or more R_{11};

R_{13} is chosen from hydrogen and R_{12};

R_{14} is chosen from halogen, —CN, —NO_2, —COR_{18}, —CO_2R_{18}, —$CONR_{18}R_{18}$, —OR_{18}, —$OCOR_{17}$, —$OCONR_{17}R_{17}$, —OCO_2R_{17}, —SR_{18}, —SO_2R_{17}, —SOR_{17}, —$SO_2NR_{18}R_{18}$, —$SO_2NR_7COR_{17}$, —$NR_{18}R_{18}$, —NR_7COR_{18}, —$NR_7CONR_{18}R_{18}$, —$NR_7CO_2R_{17}$, —$NR_7SO_2R_{17}$ and —C(=N—OH)R_{17};

R_{15} is chosen from C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl, cyanoC_{1-4}alkyl, and or Cy_2, wherein Cy_2 is optionally substituted with one or more R_{11};

R_{16} is chosen from hydrogen, and or R_{15};

R_{17} is chosen from C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl and cyanoC_{1-4}alkyl;

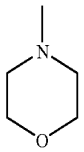
R_{18} is chosen from hydrogen, and R_{17};

or two R_{17} groups or two R_{18} groups on the same N atom are bonded together with the N atom to form a saturated 5- or 6-membered ring, which optionally contains one or two heteroatoms chosen from N, S and O and which is optionally substituted with one or more C_{1-4}alkyl groups;

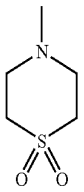
Cy_1 and Cy_2 independently are chosen from a 3- to 7-membered monocyclic and a 8- to 12-membered bicyclic carbocyclic ring that is optionally saturated, partially unsaturated or aromatic, and which optionally contains from 1 to 4 heteroatoms chosen from N, S and O, wherein said ring is optionally bonded 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;

Cy_3 is chosen from rings (a)-(c):

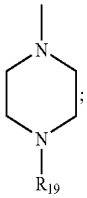
(a)



(b)



(c)



wherein R_{19} is chosen from hydrogen, and C_{1-4}alkyl, or a salt thereof.

2. (canceled)

3. The compound according to claim **1**, wherein R_1 is chosen from phenyl substituted with one or two R_3.

4. The compound according to claim **3**, wherein the groups R_3 are placed at positions 3, 4 and/or 5 of the phenyl ring.

5. (canceled)

6. (canceled)

7. The compound according to claim **1**, wherein:

each R_3 is independently chosen from C_{1-4}alkyl, halogen, hydroxyC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, —OR_6, $Cy_{2a}C_{1-4}$alkyl, —$SO_2NR_6R_6$, —$SO_2NR_7COR_5$, —NR_6R_6, —NR_7COR_6, and Cy_1, wherein Cy_1 is optionally substituted with one or more R_9, and wherein Cy_2 is optionally substituted with one or more R_{11};

Cy_1 is a 5- or 6-membered saturated monocyclic heterocycle which contains 1 or 2 heteroatoms chosen from N, S and O with the proviso that it contains at least one N atom, wherein said heterocycle is bonded to the rest of the molecule through a N atom, wherein one or more C or S ring atoms are optionally oxidized forming CO, SO or SO_2 groups; and

Cy_2 is a 5- or 6-membered saturated monocyclic heterocycle which contains 1 or 2 heteroatoms chosen from N, S and O, wherein said heterocycle is optionally bonded to the rest of the molecule through any available C or N atom, wherein one or more C or S ring atoms are optionally oxidized forming CO, SO or SO_2 groups.

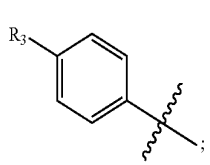
8. (canceled)

9. (canceled)

10. The compound according to claim **7**, wherein R_3 is chosen from $—SO_2NR_6R_6$, $—NR_7COR_6$, and or Cy_2C_{1-4}alkyl, wherein Cy_2 is optionally substituted with one or more R_{11}.

11. The compound according to claim **1**, wherein:

R_1 is a ring of formula R_{1d}:



R_{1d}

wherein R_3 is chosen from C_{1-4}alkyl, $—NR_6R_6$, $—SO_2NR_6R_6$, and Cy_1, wherein the C_{1-4}alkyl group is optionally substituted with one or more R_8 and Cy_1 is optionally substituted with one or more R_9; wherein Cy_2 is optionally substituted with one or more R_{11}; and

Cy_1 is a 5- or 6-membered saturated monocyclic heterocycle which contains 1 or 2 heteroatoms selected from N, S and O with the proviso that it contains at least one N atom, wherein said heterocycle is bonded to the rest of the molecule through a N atom, wherein one or more C or S ring atoms can be optionally oxidized forming CO, SO or SO_2 groups.

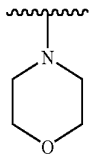
12. The compound according to claim **11**, wherein

R_3 is chosen from hydroxyC_{1-4}alkyl, Cy_2C_{1-4}alkyl, $—NR_6R_6$, $—SO_2NR_6R_6$, and Cy_1, wherein Cy_1 is optionally substituted with one or more R_9 and wherein Cy_2 is optionally substituted with one or more R_{11}; and

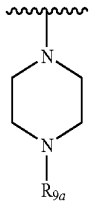
Cy_2 is a 5- or 6-membered saturated monocyclic heterocycle which contains 1 or 2 heteroatoms chosen from N, S and O, wherein said heterocycle is optionally bonded to the rest of the molecule through any available C or N atom, wherein one or more C or S ring atoms are optionally oxidized forming CO, SO or SO_2 groups.

13. The compound according to claim **12**, wherein R_3 is chosen from $—SO_2NR_6R_6$ and Cy_1, wherein Cy_1 is optionally substituted with one or more R_9.

14. The compound according to claim **13**, wherein R_3 is chosen from formulas (i)-(iii)

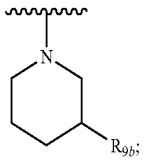


(i)



(ii)

-continued



(iii)

wherein R_{9a} is chosen from hydrogen, and C_{1-4}alkyl; and R_{9b} is chosen from hydrogen, C_{1-4}alkyl and hydroxy.

15. (canceled)

16. (canceled)

17. The compound according to claim **1** wherein R_6 in R_3 is chosen from hydrogen and R_5, wherein R_5 is C_{1-4}alkyl optionally substituted with one or more R_{10}.

18. (canceled)

19. The compound according to claim **1** wherein R_2 is chosen from phenyl and a 5- or 6-membered aromatic heterocycle bonded to the purine ring through a C atom, which is optionally fused to a 5- or 6-membered saturated, partially unsaturated or aromatic carbocyclic or heterocyclic ring, wherein R_2 optionally contains from 1 to 4 heteroatoms chosen from N, O and S, wherein the adjacent atoms to the C atom at the position of attachment to the purine ring are C atoms, wherein one or more C or S atoms of the 5- or 6-membered fused ring are optionally oxidized forming CO, SO or SO_2 groups, and wherein R_2 is optionally substituted with one or more R_4.

20. (canceled)

21. The compound according to claim **19**, wherein R_2 is a 5- or 6-membered aromatic heterocycle bonded to the purine ring through a C atom, which is optionally fused to a 5- or 6-membered saturated, partially unsaturated or aromatic carbocyclic or heterocyclic ring, wherein R_2 contains from 1 to 4 heteroatoms chosen from N, O and S, wherein the adjacent atoms to the C atom at the position of attachment to the purine ring are C atoms, wherein one or more C or S atoms of the 5- or 6-membered fused ring are optionally oxidized forming CO, SO or SO_2 groups, and wherein R_2 is optionally substituted with one or more R_4.

22. (canceled)

23. The compound according to claim **21**, wherein R_2 is 3-pyridyl optionally substituted with one or more R_4.

24. The compound according to claim **23**, wherein R_2 is 3-pyridyl substituted with one or two R_4.

25. (canceled)

26. (canceled)

27. (canceled)

28. (canceled)

29. (canceled)

30. The compound according to claim **1**, wherein

each R_4 is independently chosen from C_{1-4}alkyl, halogen, hydroxyC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, $—CONR_6R_6$, $—SR_6$, $—SOR_5$, $—SO_2R_5$, $—NR_6R_6$, $NR_7SO_2R_5$, $—NR_7CONR_6R_6$, and Cy_1, wherein Cy_1 is optionally substituted with one or more R_9; and

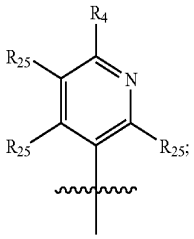
Cy_1 is a 5- or 6-membered saturated monocyclic heterocycle which contains 1 or 2 heteroatoms chosen from N, S and O with the proviso that it contains at least one N atom, wherein said heterocycle is bonded to the rest of

the molecule through a N atom, wherein one or more C or S ring atoms are optionally oxidized forming CO, SO or SO_2 groups.

31. (canceled)

32. The compound according to claim **1**, wherein:

R_2 is a group of formula:



wherein each R_{25} is independently chosen from hydrogen, halogen, and C_{1-4}alkyl.

33. (canceled)

34. (canceled)

35. The compound according to claim **32**, wherein R_4 is $—NR_6R_6$.

36. The compound according to claim **1** wherein R_6 is C_{1-4}alkyl optionally substituted with one or more R_{10}.

37. (canceled)

38. The compound according to claim **1** wherein each R_{25} is hydrogen.

39. (canceled)

40. (canceled)

41. (canceled)

42. (canceled)

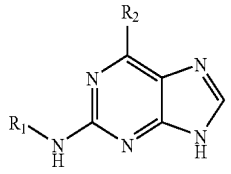
43. (canceled)

44. A pharmaceutical composition comprising at least one compound chosen from compounds of formula I according to claim **1** or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable excipients

45. (canceled)

46. A method for the treatment or prevention of at least one disease chosen from transplant rejection; immune, autoimmune or inflammatory diseases; neurodegenerative diseases; and proliferative disorders, said method comprising administration of a compound of formula I:

I



wherein:

R_1 is chosen from phenyl and a 5- or 6-membered aromatic heterocycle bonded to the NH group through a C atom, wherein the phenyl or heterocycle is optionally fused to a 5- or 6-membered saturated, partially unsaturated or aromatic carbocyclic or heterocyclic ring, wherein R_1 optionally contains from 1 to 4 heteroatoms chosen from N, O and S, wherein one or more C or S atoms of the 5- or 6-membered fused ring are optionally oxidized forming CO, SO or SO_2 groups, and wherein R_1 is optionally substituted with one or more R_3;

R_2 is chosen from phenyl and a 5- or 6-membered aromatic heterocycle bonded to the purine ring through a C atom, wherein the phenyl or heterocycle is optionally fused to a 5- or 6-membered saturated, partially unsaturated or aromatic carbocyclic or heterocyclic ring, wherein R_2 optionally contains from 1 to 4 heteroatoms chosen from N, O and S, wherein one or more C or S atoms of the 5- or 6-membered fused ring are optionally oxidized forming CO, SO or SO_2groups, and wherein R_2 is optionally substituted with one or more R_4;

R_3 and R_4 independently are chosen from C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, halogen, —CN, $—NO_2$—COR_6, $—CO_2R_6$, $—CONR_6R_6$, $—OR_6$, $—OCOR_5$, $—OCONR_5R_5$, $—OCO_2R_5$, $—SR_6$, $—SO_2R_5$, $—SOR_5$, $—SO_2NR_6R_6$, $—SO_2NR_7COR_5$, $—NR_6R_6$, $—NR_7COR_6$, $—NR_7CONR_6R_6$, $—NR_7CO_2R_5$, $—NR_7SO_2R_5$, $—C(=N—OH)R_5$, and Cy_1, wherein the C_{1-4} alkyl, C_{2-4}alkenyl and C_{2-4}alkynyl groups are optionally substituted with one or more R_8 and Cy_1 is optionally substituted with one or more R_9;

R_5 is chosen from C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, and Cy_1, wherein the C_{1-4}alkyl, C_{2-4}alkenyl and C_{2-4}alkynyl groups are optionally substituted with one or more R_{10} and Cy_2 is optionally substituted with one or more R_{11};

R_6 is chosen from hydrogen and R_5;

R_7 is chosen from hydrogen and C_{1-4}alkyl;

R_8 is chosen from halogen, —CN, $—NO_2$—COR_{13}, $—CO_2R_{13}$, $—CONR_{13}R_{13}$, $—OR_{13}$, $—OCOR_{12}$, $—OCONR_{12}R_{12}$, $—OCO_2R_{12}$, $—SR_{13}$, $—SO_2R_{12}$, $—SOR_{12}$, $—SO_2NR_{13}R_{13}$, $—SO_2NR_7COR_{12}$, $—NR_{13}R_{13}$, $—NR_7COR_{13}$, $—NR_7CONR_{13}R_{13}$, $—NR_7CO_2R_{12}$, $—NR_7SO_2R_{12}$, $—C(=N—OH)R_{12}$, and Cy_2, wherein Cy_2 is optionally substituted with one or more R_{11};

R_9 is chosen from R_{14} and C_{1-4}alkyl, where the C_{1-4}alkyl is optionally substituted with one or more R_{10};

R_{10} is chosen from halogen, —CN, $—NO_2$—COR_{16}, $—CO_2R_{16}$, $—CONR_{16}R_{16}$, $—OR_{16}$, $—OCOR_{15}$, $—OCONR_{15}R_{15}$, $—OCO_2R_{15}$, $—SR_{16}$, $—SO_2R_{15}$, $—SOR_{15}$, $—SO_2NR_{16}R_{16}$, $—SO_2NR_7COR_{15}$, $—NR_{16}R_{16}$, $—NR_7COR_{16}$, $—NR_7CONR_{16}R_{16}$, $—NR_7CO_2R_{15}$, $—NR_7SO_2R_{15}$, $—C(=N—OH)R_{15}$, and Cy_2, wherein Cy_2 is optionally substituted with one or more R_{11};

R_{11} is chosen from C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl, cyanoC_{1-4}alkyl, and R_{14};

R_{12} is chosen from C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl, cyanoC_{1-4}alkyl, Cy_3-C_{1-4}alkyl, and Cy_2, wherein Cy_2 is optionally substituted with one or more R_{11};

R_{13} is chosen from hydrogen, and R_{12};

R_{14} is chosen from halogen, —CN, $—NO_2$—COR_{18}, $—CO_2R_{18}$, $—CONR_{18}R_{18}$, $—OR_{18}$, $—OCOR_{17}$, $—OCONR_{17}R_{17}$, $—OCO_2R_{17}$, $—SR_{18}$, $—SO_2R_{17}$, $—SO_2NR_{18}R_{18}$, $—SO_2NR_7COR_{17}$, $—NR_{18}R_{18}$, $—NR_7COR_{18}$—$NR_7CONR_{18}R_{18}$, $—NR_7CO_7R_{17}$, $—NR_7SO_2R_{17}$, and $—C(=N—OH)R_{17}$;

R_{15} is chosen from C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl, cyanoC_{1-4}alkyl, and Cy_2, wherein Cy_2 is optionally substituted with one or more R_{11};

R_{16} is chosen from hydrogen, and R_{15};

R_{17} is chosen from C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl, and cyanoC_{1-4}alkyl;

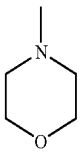
R_{18} is chosen from hydrogen, and R_{17};

or two R_{17} groups or two R_{18} groups on the same N atom are bonded together with the N atom to form a saturated 5- or 6-membered ring, which optionally contains one or two heteroatoms chosen from N, S and O and which are optionally substituted with one or more C_{1-4}alkyl groups;

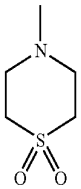
Cy_1 and Cy_2 independently are chosen from a 3- to 7-membered monocyclic and a 8- to 12-membered bicyclic carbocyclic ring that is optionally saturated, partially unsaturated or aromatic, and which optionally contains from 1 to 4 heteroatoms chosen from N, S and O, wherein said ring is optionally bonded to the rest of the molecule through any available C or N atom, and wherein one or more C or S ring atoms is optionally oxidized forming CO, SO or SO_2 groups;

Cy_3 is chosen from rings (a)-(c):

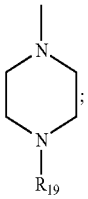
(a)



(b)



(c)



wherein R_{19} is chosen from hydrogen, and C_{1-4}alkyl,

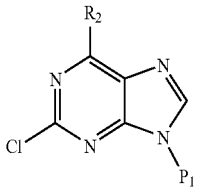
or a salt thereof.

47. (canceled)

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

(a) reacting a compound of formula IV with a compound of formula V

IV



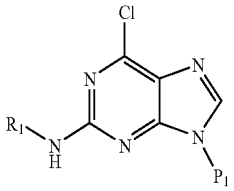
V

R_1NH_2

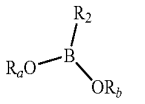
wherein R_1 and R_2 are as defined in claim **1** and P_1 is an amine protecting group, followed if required by the removal of the protecting group; or

(b) reacting a compound of formula X with a compound of formula III

X



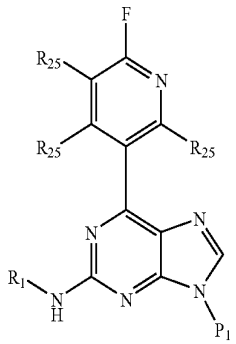
III



wherein R_1 and R_2 are as defined in claim **1**, P_1 is an amine protecting group, and R_a and R_b are chosen from H and C_{1-4}alkyl, or R_a and R_b can be bonded forming together with the B and O atoms a 5- or 6-membered ring that can be optionally substituted with one or more methyl groups, followed if required by the removal of the protecting group; or

(c) reacting a compound of formula XV with a compound of formula XII

XV



XII

R_4*—H

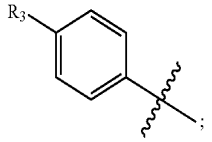
wherein R_4* is chosen from —NR_6R_6 and Cy_1 bonded through a N atom to the pyridine ring, each R_{25} is independently chosen from hydrogen, halogen, C_{1-4}alkoxy, haloC_{1-4}alkoxy, and —SC_{1-4}alkyl, P_1 is an amine protecting group and R_1, Cy_1 and R_6 are as defined in claim **1**, followed if required by the removal of the protecting group; or

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

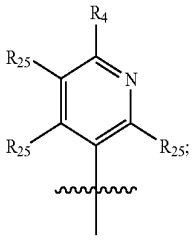
49. The compound according to claim **1**, wherein:

R_1 is a ring of formula R_{1d}:

R_{1d}



R_2 is a group of formula:



R_3 is chosen from C_{1-4}alkyl, $—NR_6R_6$, $—SO_2NR_6R_6$ and Cy_1, wherein the C_{1-4}alkyl group is optionally substituted with one or more R_8 and Cy_1 is optionally substituted with one or more R_9; R_4 is $—NR_6R_6$; Cy_{2a} is optionally substituted with one or more R_{11}; each R_{25} is independently chosen from hydrogen, halogen and C_{1-4}alkyl; and

Cy_1 is a 5- or 6-membered saturated monocyclic heterocycle which contains 1 or 2 heteroatoms chosen from N, S and O with the proviso that it contains at least one N atom, wherein said heterocycle is bonded to the rest of the molecule through a N atom, wherein one or more C or S ring atoms are optionally oxidized forming CO, SO or SO_2 groups.

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