(12) STANDARD PATENT (11) Application No. **AU 2014201789 B2**
(19) AUSTRALIAN PATENT OFFICE

(54) Title
N-containing heteroaryl derivatives as JAK3 kinase inhibitors

(51) International Patent Classification(s)
C07D 519/04 (2006.01) ***A61P 29/00*** (2006.01)
A61K 31/52 (2006.01) ***A61P 35/00*** (2006.01)
A61K 31/522 (2006.01) ***A61P 37/00*** (2006.01)

(21) Application No: **2014201789** (22) Date of Filing: **2014.03.26**

(43) Publication Date: **2014.04.24**
(43) Publication Journal Date: **2014.04.24**
(44) Accepted Journal Date: **2015.07.09**

(62) Divisional of:
2010311378

(71) Applicant(s)
Vectura Limited

(72) Inventor(s)
Almansa Rosales, Carmen;Salas Solana, Jorge;Soliva Soliva, Robert;Rodriguez Escrich, Sergio;Sicre Gonzales, Maria Cristina

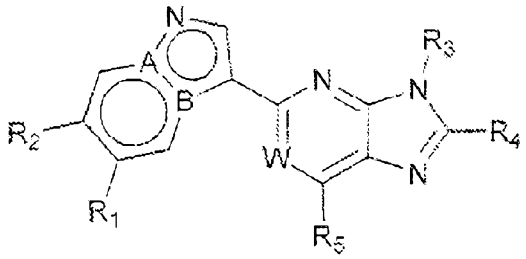
(74) Agent / Attorney
Spruson & Ferguson, L 35 St Martins Tower 31 Market St, Sydney, NSW, 2000

(56) Related Art
US 2009/0203690
EP 1790650
WO 2008/043019
US 2008/0119496

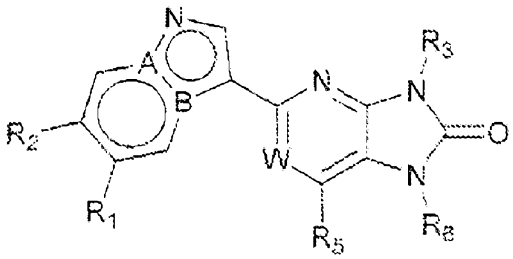
20142017789 26 Mar 2014

N-CONTAINING HETEROARYL DERIVATIVES AS JAK3 KINASE INHIBITORS

Abstract



(I)



(II)

N-containing heteroaryl derivatives of formula I or II, wherein the meanings for the various substituents are as disclosed in the description. These compounds are useful as JAK, particularly JAK3, kinase inhibitors.

26 Mar 2014 2014201789

N-containing heteroaryl derivatives as JAK3 kinase inhibitors

Field of the invention

The present invention relates to a new series of *N*-containing heteroaryl derivatives, as well as to processes for their preparation, to pharmaceutical compositions comprising them and to their use in therapy.

Background of the invention

The Janus kinases (JAKs) are cytoplasmic protein tyrosine kinases that play pivotal roles in pathways that modulate cellular functions in the 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.

Four members of the JAK family have been identified so far: JAK1, JAK2, JAK3 and Tyk2. Unlike JAK1, JAK2 and Tyk2, whose expression is ubiquitous, JAK3 is mainly found in hematopoietic cells. JAK3 is associated in a non-covalent manner with the γc subunit of the receptors of IL-2, IL-4, IL-7, IL-9, IL-13 and IL-15. These cytokines play an important role in the proliferation and differentiation of T lymphocytes. JAK3-deficient mouse T cells do not respond to IL-2. This cytokine is fundamental in the regulation of T lymphocytes. In this regard, it is known that antibodies directed against the IL-2 receptor are able to prevent transplant rejection. In patients with X severe combined immunodeficiency (X-SCID), very low levels of JAK3 expression as well as genetic defects in the γc subunit of the receptor have been identified, which indicates that immunosuppression is a consequence of an alteration in the JAK3 signaling pathway.

Animal studies have suggested that JAK3 not only plays a critical role in T and B lymphocyte maturation, but also that JAK3 is required to maintain lymphocyte function. Modulation of the immunological activity through this new mechanism can prove useful in the treatment of T cell proliferative disorders such as transplant rejection and autoimmune diseases.

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

In conclusion, JAK3 kinase inhibitors have been recognised as a new class of effective immunosuppressive agents useful for transplant rejection prevention and in the treatment of immune, autoimmune, inflammatory and

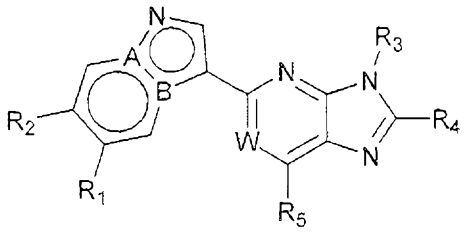
2014201789 26 Mar 2014

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).

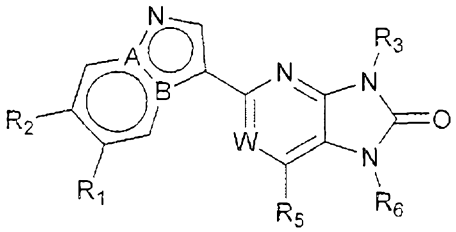
Accordingly, it would be desirable to provide novel compounds that are capable of inhibiting JAK/STAT signaling pathways, and in particular which are capable of inhibiting JAK3 activity, and which are good drug candidates. Compounds should exhibit good activity in *in vitro* and *in vivo* pharmacological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

Description of the invention

One aspect of the invention relates to a compound of formula I or II



I



II

wherein

A is carbon and B is nitrogen, or A is nitrogen and B is carbon;

W is CH or N;

R_1 and R_2 independently are hydrogen, C_{1-4}alkyl, haloC_{1-4}alkyl, hydroxyC_{1-4}alkyl, cyanoC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, halogen, –CN, $-OR_8$ or $-SR_8$;

R_3 is C_{1-4}alkyl, R_9-C_{1-4}alkyl, Cy_1 or Cy_2-C_{1-4}alkyl, wherein Cy_1 and Cy_2 are optionally substituted with one or more R_{10};

R_4 is hydrogen, C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl, cyanoC_{1-4}alkyl, $R_{12}R_7$N-C_{0-4}alkyl, $R_{13}CONR_7$-C_{0-4}alkyl, $R_{13}R_7NCO$-C_{0-4}alkyl, $R_{12}R_7NCONR_7$-C_{0-4}alkyl, $R_{13}CO_2NR_7$-C_{0-4}alkyl, $R_{13}SO_2NR_7$-C_{0-4}alkyl, $-OR_{12}$ or Cy_2-C_{0-4}alkyl; wherein Cy_2 is optionally substituted with one or more R_{11};

R_5 is hydrogen, C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl, cyanoC_{1-4}alkyl, halogen, –CN, $-OR_{12}$, $-NR_7R_{12}$, or Cy_2-C_{0-4}alkyl, wherein Cy_2 is optionally substituted with one or more R_{11};

R_6 is hydrogen, C_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl, $R_{12}R_7$N-C_{1-4}alkyl, $R_{16}CO$-C_{0-4}alkyl, $R_{16}CO_2$-C_{0-4}alkyl, $R_{16}CO$-O-C_{1-4}alkyl, cyanoC_{1-4}alkyl, Cy_1 or Cy_2-C_{1-4}alkyl, wherein Cy_1 and Cy_2 are optionally substituted with one or more R_{11};

R_7 is hydrogen or C_{1-4}alkyl;

R_8 is hydrogen, C_{1-4}alkyl, haloC_{1-4}alkyl, hydroxyC_{1-4}alkyl, or C_{1-4}alkoxyC_{1-4}alkyl;

2014201789 26 Mar 2014

R_9 is halogen, –CN, $–CONR_7R_{12}$, $–COR_{13}$, $–CO_2R_{12}$, $–OR_{12}$, $–OCONR_7R_{12}$, $–SO_2R_{13}$, $–SO_2NR_7R_{12}$, $–NR_7R_{12}$, $–NR_7COR_{12}$, $–NR_7CONR_7R_{12}$, $–NR_7CO_2R_{13}$ or $–NR_7SO_2R_{13}$;

R_{10} is C_{1-4}alkyl or R_9-C_{0-4}alkyl;

R_{11} is C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl, cyanoC_{1-4}alkyl, halogen, –CN, $–CONR_7R_{14}$, $–COR_{14}$, $–CO_2R_{15}$, $–OR_{14}$, $–OCONR_7R_{14}$, $–SO_2R_{15}$, $–SO_2NR_7R_{14}$, $–NR_7R_{14}$, $–NR_7COR_{14}$, $–NR_7CONR_7R_{14}$, $–NR_7CO_2R_{15}$ or $–NR_7SO_2R_{15}$;

R_{12} is hydrogen or R_{13};

R_{13} is C_{1-5}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl, cyanoC_{1-4}alkyl, Cy_2-C_{0-4}alkyl or $R_{14}R_7N$-C_{1-4}alkyl; wherein Cy_2 is optionally substituted with one or more R_{11};

R_{14} is hydrogen or R_{15};

R_{15} is C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl or cyanoC_{1-4}alkyl;

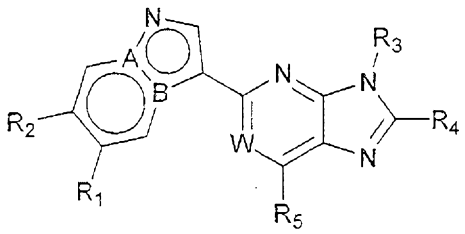
R_{16} is C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl or cyanoC_{1-4}alkyl;

Cy_1 is a 3- to 7-membered monocyclic or 6- to 11-membered bicyclic ring, which is saturated, partially unsaturated or aromatic, and which is carbocyclic or heterocyclic containing from 1 to 4 heteroatoms independently selected from N, S and O, wherein said ring is bonded to the rest of the molecule through any available C atom, and wherein one or more C or S ring atoms are optionally oxidized forming CO, SO or SO_2; and

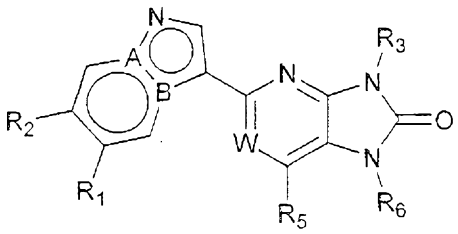
Cy_2 is a 3- to 7-membered monocyclic or 6- to 11-membered bicyclic ring, which is saturated, partially unsaturated or aromatic, and which is carbocyclic or heterocyclic containing from 1 to 4 heteroatoms independently selected from N, S and O, wherein said ring is bonded to the rest of the molecule through any available C or N atom, and wherein one or more C or S ring atoms are optionally oxidized forming CO, SO or SO_2.

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

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



I



II

wherein

A is carbon and B is nitrogen, or A is nitrogen and B is carbon;

W is CH or N;

R_1 and R_2 independently are hydrogen, C_{1-4}alkyl, haloC_{1-4}alkyl, hydroxyC_{1-4}alkyl, cyanoC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, halogen, –CN, $–OR_8$ or $–SR_8$;

R_3 is C_{1-4}alkyl, R_9-C_{1-4}alkyl, Cy_1 or Cy_2-C_{1-4}alkyl, wherein Cy_1 and Cy_2 are optionally substituted with one or more R_{10};

2014201789 26 Mar 2014

R_4 is hydrogen, C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl, cyanoC_{1-4}alkyl, $R_{12}R_7N$-C_{0-4}alkyl, $R_{13}CONR_7$-C_{0-4}alkyl, $R_{13}R_7NCO$-C_{0-4}alkyl, $R_{12}R_7NCONR_7$-C_{0-4}alkyl, $R_{13}CO_2NR_7$-C_{0-4}alkyl, $R_{13}SO_2NR_7$-C_{0-4}alkyl, $-OR_{12}$ or Cy_2-C_{0-4}alkyl; wherein Cy_2 is optionally substituted with one or more R_{11};

R_5 is hydrogen, C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl, cyanoC_{1-4}alkyl, halogen, $-CN$, $-OR_{12}$, $-NR_7R_{12}$, or Cy_2-C_{0-4}alkyl, wherein Cy_2 is optionally substituted with one or more R_{11};

R_6 is hydrogen, C_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl, $R_{12}R_7N$-C_{1-4}alkyl, $R_{16}CO$-C_{0-4}alkyl, $R_{16}CO_2$-C_{0-4}alkyl, $R_{16}CO$-O-C_{1-4}alkyl, cyanoC_{1-4}alkyl, Cy_1 or Cy_2-C_{1-4}alkyl, wherein Cy_1 and Cy_2 are optionally substituted with one or more R_{11};

R_7 is hydrogen or C_{1-4}alkyl;

R_8 is hydrogen, C_{1-4}alkyl, haloC_{1-4}alkyl, hydroxyC_{1-4}alkyl, or C_{1-4}alkoxyC_{1-4}alkyl;

R_9 is halogen, $-CN$, $-CONR_7R_{12}$, $-COR_{13}$, $-CO_2R_{12}$, $-OR_{12}$, $-OCONR_7R_{12}$, $-SO_2R_{13}$, $-SO_2NR_7R_{12}$, $-NR_7R_{12}$, $-NR_7COR_{12}$, $-NR_7CONR_7R_{12}$, $-NR_7CO_2R_{13}$ or $-NR_7SO_2R_{13}$;

R_{10} is C_{1-4}alkyl or R_9-C_{0-4}alkyl;

R_{11} is C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl, cyanoC_{1-4}alkyl, halogen, $-CN$, $-CONR_7R_{14}$, $-COR_{14}$, $-CO_2R_{15}$, $-OR_{14}$, $-OCONR_7R_{14}$, $-SO_2R_{15}$, $-SO_2NR_7R_{14}$, $-NR_7R_{14}$, $-NR_7COR_{14}$, $-NR_7CONR_7R_{14}$, $-NR_7CO_2R_{15}$ or $-NR_7SO_2R_{15}$;

R_{12} is hydrogen or R_{13};

R_{13} is C_{1-5}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl, cyanoC_{1-4}alkyl, Cy_2-C_{0-4}alkyl or $R_{14}R_7N$-C_{1-4}alkyl; wherein Cy_2 is optionally substituted with one or more R_{11};

R_{14} is hydrogen or R_{15};

R_{15} is C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl or cyanoC_{1-4}alkyl;

R_{16} is C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl or cyanoC_{1-4}alkyl;

Cy_1 is a 3- to 7-membered monocyclic or 6- to 11-membered bicyclic ring, which is saturated, partially unsaturated or aromatic, and which is carbocyclic or heterocyclic containing from 1 to 4 heteroatoms independently selected from N, S and O, wherein said ring is bonded to the rest of the molecule through any available C atom, and wherein one or more C or S ring atoms are optionally oxidized forming CO, SO or SO_2; and

Cy_2 is a 3- to 7-membered monocyclic or 6- to 11-membered bicyclic ring, which is saturated, partially unsaturated or aromatic, and which is carbocyclic or heterocyclic containing from 1 to 4 heteroatoms independently selected from N, S and O, wherein said ring is bonded to the rest of the molecule through any available C or N atom, and wherein one or more C or S ring atoms are optionally oxidized forming CO, SO or SO_2;

for use in therapy.

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

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

2014201789 26 Mar 2014

neurodegenerative diseases, or proliferative disorders. In a further preferred embodiment, the disease mediated by JAKs, particularly JAK3, is selected from transplant rejection or immune, autoimmune or inflammatory diseases. In a further preferred embodiment, the disease mediated by JAKs, particularly JAK3, is a proliferative disorder.

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

Another aspect of the present invention relates to the use of a compound of formula I or II 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, inflammatory or autoimmune ocular diseases, leukemias, lymphomas, and thromboembolic and allergic complications associated with leukemias and lymphomas.

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

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

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

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

2014201789 26 Mar 2014

disorders. In a further preferred embodiment, the disease mediated by JAKs, particularly JAK3, is selected from transplant rejection or immune, autoimmune or inflammatory diseases. In a further preferred embodiment, the disease mediated by JAKs, particularly JAK3, is a proliferative disorder.

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

Another aspect of the present invention relates to the use of a compound of formula I or II 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, inflammatory or autoimmune ocular diseases, leukemias, lymphomas, and thromboembolic and allergic complications associated with leukemias and lymphomas.

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

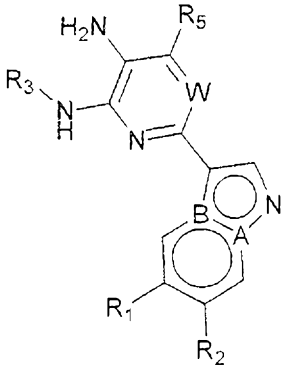
Another aspect of the present invention relates to a method of treating or preventing at least one disease selected from transplant rejection, immune, autoimmune or inflammatory diseases, neurodegenerative diseases, or proliferative disorders in a subject in need thereof, especially a human being, which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

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, inflamamtory or autoimmune ocular diseases, 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 amount of a compound of formula I or II or a pharmaceutically acceptable salt thereof effective to treat said disease.

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

2014201789 26 Mar 2014

(a) for a compound of formula I, reacting a compound of formula VI with a compound of formula III



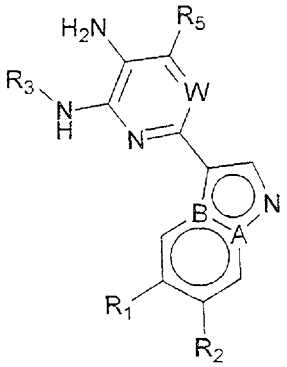
VI

R_4—NCS

III

wherein A, B, W, R_1, R_2, R_3, R_4 and R_5 have the meaning previously described in relation with a compound of formula I or II; or

(b) for a compound of formula I, reacting a compound of formula VI with a compound of formula IV



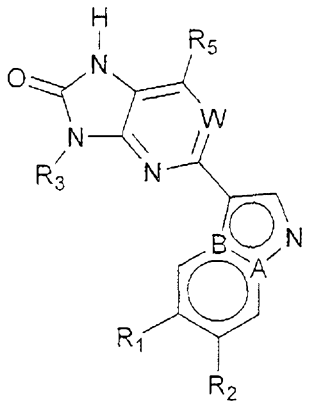
VI

R_4—CHO

IV

wherein A, B, W, R_1, R_2, R_3, R_4 and R_5 have the meaning previously described in relation with a compound of formula I or II; or

(c) when in a compound of formula II R_5 is hydrogen (a compound of formula IIa), reacting a compound of formula VI, as defined above, with a synthetic equivalent for the CO synthon.



IIa

wherein A, B, W, R_1, R_2, R_3 and R_5 have the meaning previously described in relation with a compound of formula I or II; or

2014201789 26 Mar 2014

(d) when in a compound of formula II R_6 is other than hydrogen, reacting a compound of formula IIa with a compound of formula V (R_6-X) in the presence of a base, wherein X is a leaving group; or

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

In the above definitions, the term C_{1-5} alkyl, as a group or part of a group, means a straight or branched alkyl chain which contains from 1 to 5 carbon atoms and includes among others the groups methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *sec*-butyl, *tert*-butyl, pentyl and *iso*-pentyl. Likewise, 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.

A C_{1-4}alkoxy group, as a group or part of a group, means a group of formula -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.

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 as defined above, which can be the same or different. Examples include, among others, the groups methoxymethyl, ethoxymethyl, propoxymethyl, isopropoxymethyl, butoxymethyl, isobutoxymethyl, *sec*-butoxymethyl, *tert*-butoxymethyl, dimethoxymethyl, 1-methoxyethyl, 2-methoxyethyl, 2-ethoxyethyl, 1,2-diethoxyethyl, 1-butoxyethyl, 2-*sec*-butoxyethyl, 3-methoxypropyl, 2-butoxypropyl, 1-methoxy-2-ethoxypropyl, 3-*tert*-butoxypropyl and 4-methoxybutyl.

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

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, nonafluorobutyl, 1-chloro-2-fluoroethyl and 2-bromo-1-chloro-1-fluoropropyl.

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.

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.

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,

2014201789 26 Mar 2014

3-fluoropropoxy, 3-chloropropoxy, 2,2,3,3-tetrafluoropropoxy, 2,2,3,3,3-pentafluoropropoxy, heptafluoropropoxy, 4-fluorobutoxy, nonafluorobutoxy, 1-chloro-2-fluoroethoxy and 2-bromo-1-chloro-1-fluoropropoxy.

The term C_0 alkyl indicates that the alkyl group is absent.

Thus, the term R_9-C_{0-4} alkyl includes R_9 and R_9-C_{1-4} alkyl. The term R_9-C_{1-4} alkyl relates to a group resulting from the substitution of one hydrogen atom of a C_{1-4} alkyl group with one R_9 group.

The terms $R_{12}R_7N$-C_{0-4}alkyl, $R_{13}CONR_7$-C_{0-4}alkyl, $R_{13}R_7NCO$-C_{0-4}alkyl, $R_{12}R_7NCONR_7$-C_{0-4}alkyl, $R_{13}CO_2NR_7$-C_{0-4}alkyl, $R_{13}SO_2NR_7$-C_{0-4}alkyl, $R_{16}CO$-C_{0-4}alkyl and $R_{16}CO_2$-C_{0-4}alkyl include -NR_7R_{12} and $R_{12}R_7N$-C_{1-4}alkyl, -NR_7COR_{13} and $R_{13}CONR_7$-C_{1-4}alkyl, -$CONR_7R_{13}$ and $R_{13}R_7NCO$-C_{1-4}alkyl, -$NR_7CONR_7R_{12}$ and $R_{12}R_7NCONR_7$-C_{1-4}alkyl, -$NR_7CO_2R_{13}$ and $R_{13}CO_2NR_7$-C_{1-4}alkyl, -$NR_7SO_2R_{13}$ and $R_{13}SO_2NR_7$-C_{1-4}alkyl, -COR_{16} and $R_{16}CO$-C_{1-4}alkyl, and -CO_2R_{16} and $R_{16}CO_2$-C_{1-4}alkyl, respectively.

A group $R_{12}R_7N$-C_{1-4}alkyl, $R_{14}R_7N$-C_{1-4}alkyl, $R_{13}CONR_7$-C_{1-4}alkyl, $R_{13}R_7NCO$-C_{1-4}alkyl, $R_{12}R_7NCONR_7$-C_{1-4}alkyl, $R_{13}CO_2NR_7$-C_{1-4}alkyl, $R_{13}SO_2NR_7$-C_{1-4}alkyl, $R_{16}CO$-C_{1-4}alkyl, $R_{16}CO_2$-C_{1-4}alkyl or $R_{16}CO$-O-C_{1-4}alkyl means a group resulting from the replacement of one hydrogen atom from a C_{1-4}alkyl group with one -NR_7R_{12}, -NR_7R_{14}, -NR_7COR_{13}, -$CONR_7R_{13}$, -$NR_7CONR_7R_{12}$, -$NR_7CO_2R_{13}$ -$NR_7SO_2R_{13}$, -COR_{16}, -CO_2R_{16} or –$OCOR_{16}$ group, respectively.

A Cy_1 group refers to a 3- to 7-membered monocyclic or 6- to 11-membered bicyclic carbocyclic or heterocyclic ring, which is saturated, partially unsaturated or aromatic. When heterocyclic, it contains from 1 to 4 heteroatoms independently selected from N, S and O. Bicyclic rings are formed either by two rings fused through two adjacent C or N atoms, or through two non-adjacent C or N atoms forming a bridged ring, or else they are formed by two rings bonded through a single common C atom forming a spiro ring. Cy_1 is bonded to the rest of the molecule through any available C atom. When Cy_1 is saturated or partially unsaturated, one or more C or S atoms of said ring are optionally oxidized forming CO, SO or SO_2 groups. Cy_1 is optionally substituted as disclosed above in the definition of a compound of formula I or II, said substituents can be the same or different and can be placed on any available position of the ring system.

A Cy_2 group refers to a 3- to 7-membered monocyclic or 6- to 11-membered bicyclic carbocyclic or heterocyclic ring, which is saturated, partially unsaturated or aromatic. When heterocyclic, it contains from 1 to 4 heteroatoms independently selected from N, S and O. Bicyclic rings are formed either by two rings fused through two adjacent C or N atoms, or through two non-adjacent C or N atoms forming a bridged ring, or else they are formed by two rings bonded through a single common C atom forming a spiro ring. Cy_2 is bonded to the rest of the molecule through any available C or N atom. When Cy_2 is saturated or partially unsaturated, one or more C or S atoms of said ring are optionally oxidized forming CO, SO or SO_2 groups. Cy_2 is optionally substituted as disclosed above in the definition of a compound of formula I or II, said substituents can be the same or different and can be placed on any available position of the ring system.

Examples of either Cy_1 or Cy_2 include, among others, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, azetidinyl, aziridinyl, oxiranyl, oxetanyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, oxazolidinyl, pyrazolidinyl, pyrrolidinyl, thiazolidinyl, dioxanyl, morpholinyl, thiomorpholinyl, 1,1-dioxothiomorpholinyl, piperazinyl, homopiperazinyl, piperidinyl, pyranyl, tetrahydropyranyl, homopiperidinyl, oxazinyl, oxazolinyl, pyrrolinyl, thiazolinyl,

2014201789 26 Mar 2014

pyrazolinyl, imidazolinyl, isoxazolinyl, isothiazolinyl, 2-oxo-pyrrolidinyl, 2-oxo-piperidinyl, 4-oxo-piperidinyl, 2-oxo-piperazinyl, 2-oxo-1,2-dihydropyridinyl, 2-oxo-1,2-dihydropyrazinyl, 2-oxo-1,2-dihydropyrimidinyl, 3-oxo-2,3-dihydropyridazyl, phenyl, naphthyl, thienyl, furyl, pyrrolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, 1,3,4-oxadiazolyl, 1,3,4-thiadiazolyl, 1,2,4-oxadiazolyl, 1,2,4-thiadiazolyl, pyridyl, pyrazinyl, pyrimidinyl, 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-1*H*-indolyl, 1-oxo-2,3-dihydro-1*H*-isoindolyl, chromanyl, perhydroquinolinyl, 1-oxo-perhydroisoquinolinyl, 1-oxo-1,2-dihydroisoquinolinyl, 4-oxo-3,4-dihydroquinazolinyl, 2-aza-bicyclo[2.2.1]heptanyl, 5-aza-bicyclo[2.1.1]hexanyl, 2*H*-spiro[benzofuran-3,4'-piperidinyl], 3*H*-spiro[isobenzofuran-1,4'-piperidinyl], 1-oxo-2,8-diazaspiro[4.5]decanyl and 1-oxo-2,7-diazaspiro[4.5]decanyl.

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 piperidinyl, tetrahydropyranyl or indolyl, all the available bonding positions are included, unless a limitation is indicated in the corresponding definition for said cyclic group, for example that the ring is bonded through a C atom in Cy_1, in which case such limitation applies. Thus for example, in the definitions of Cy_2, which do not include any limitation regarding the bonding position, the term piperidinyl includes 1-piperidinyl, 2-piperidinyl, 3-piperidinyl and 4-piperidinyl; tetrahydropyranyl includes 2-tetrahydropyranyl, 3-tetrahydropyranyl and 4-tetrahydropyranyl; and indolyl includes 1-indolyl, 2-indolyl, 3-indolyl, 4-indolyl, 5-indolyl, 6-indolyl and 7-indolyl.

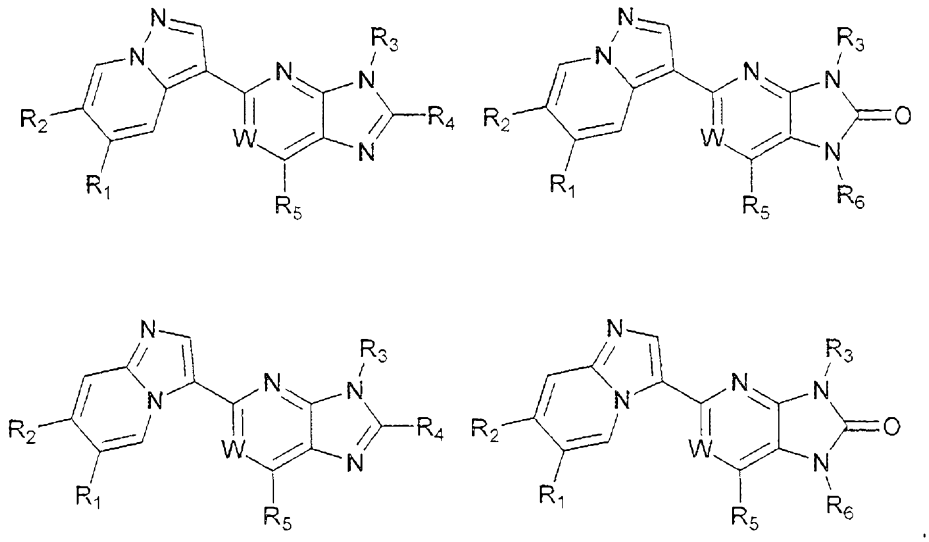
In the above definitions of Cy_1 and Cy_2, when the examples listed refer to a bicycle in general terms, all possible dispositions of the atoms are included. Thus, for example, the term pyrazolopyridinyl includes groups such as 1*H*-pyrazolo[3,4-*b*]pyridinyl, 1*H*-pyrazolo[1,5-*a*]pyridinyl, 1*H*-pyrazolo[3,4-*c*]pyridinyl,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

The term Cy_2-C_{0-4}alkyl includes Cy_2 and Cy_2-C_{1-4}alkyl.

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. Examples include, among others, the groups (piperidinyl-4-yl)methyl, 2-(piperidinyl-4-yl)ethyl, 3-(piperidinyl-4-yl)propyl, 4-(piperidinyl-4-yl)butyl, (tetrahydropyran-4-yl)methyl, 2-(tetrahydropyran-4-yl)ethyl, 3-(tetrahydropyran-4-yl)propyl, 4-(tetrahydropyran-4-yl)butyl, benzyl, phenethyl, 3-phenylpropyl, 4-phenylbutyl, (indolinyl-1-yl)methyl, 2-(indolinyl-1-yl)ethyl, 3-(indolinyl-1-yl)propyl and 4-(indolinyl-1-yl)butyl.

In the definition of a compound of formula I or II, either A is carbon and B is nitrogen, or A is nitrogen and B is carbon. Thus, the compounds of formula I or II include the following types of compounds:

20142017789 26 Mar 2014



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

In certain embodiments of Cy_1 mentioned below, a nitrogen atom that can be substituted means a nitrogen atom that has a hydrogen substituent.

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

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

Any formula given herein is intended to represent unlabeled forms as well as isotopically labeled forms of the compounds. Isotopically labeled compounds have structures depicted by the formulas given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, chlorine, and iodine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, ^{36}Cl, and ^{125}I, respectively. Such isotopically labelled compounds are useful in metabolic studies (preferably with ^{14}C), reaction kinetic studies (with, for example ^{2}H or ^{3}H), detection or imaging techniques [such as positron emission tomography (PET) or single- photon emission computed tomography (SPECT)] including drug or substrate tissue distribution assays, or in radioactive treatment of patients. In particular, an ^{18}F or ^{11}C labeled compound may be particularly preferred for PET or SPECT studies. Further, substitution with heavier isotopes such as deuterium (i.e., ^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements. Isotopically labeled compounds of the invention can generally be prepared by

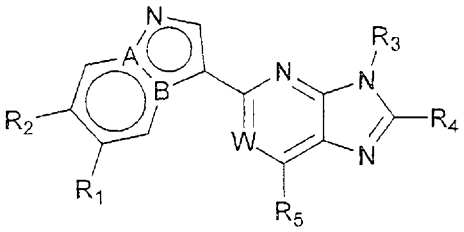
2014201789 26 Mar 2014

carrying out the procedures disclosed in the schemes or in the examples and preparations described below by substituting a readily available isotopically labeled reagent for a non- isotopically labeled reagent. In addition to the unlabeled form, all isotopically labeled forms of the compounds of formula I and II are included within the scope of the invention.

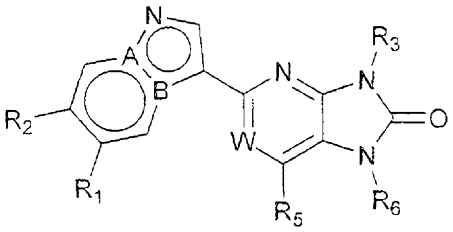
Any formula given herein is also intended to represent the corresponding tautomers forms. "Tautomer" refers to alternate forms of a molecule that differ in the position of a proton. Examples include, among others, enol-keto and imine-enamine tautomers, and the tautomeric forms of heteroaryl groups containing a –N=CH-NH- ring atom arrangement, such as pyrazoles, imidazoles, benzimidazoles, triazoles and tetrazoles.

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

In another embodiment, the invention relates to a compound of formula I or II



I



II

wherein

A is carbon and B is nitrogen, or A is nitrogen and B is carbon;

W is CH or N;

R_1 and R_2 independently are hydrogen, C_{1-4}alkyl, haloC_{1-4}alkyl, hydroxyC_{1-4}alkyl, cyanoC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, halogen, –CN, $-OR_8$ or $-SR_8$;

R_3 is C_{1-4}alkyl, R_9-C_{1-4}alkyl, Cy_1 or Cy_2-C_{1-4}alkyl, wherein Cy_1 and Cy_2 are optionally substituted with one or more R_{10};

R_4 is hydrogen, C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl, cyanoC_{1-4}alkyl, $R_{12}R_7$N-C_{0-4}alkyl, $R_{13}CONR_7$-C_{0-4}alkyl, $R_{13}R_7NCO$-C_{0-4}alkyl, $R_{12}R_7NCONR_7$-C_{0-4}alkyl, $R_{13}CO_2NR_7$-C_{0-4}alkyl, $R_{13}SO_2NR_7$-C_{0-4}alkyl, $-OR_{12}$ or Cy_2-C_{0-4}alkyl; wherein Cy_2 is optionally substituted with one or more R_{11};

R_5 is hydrogen, C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl, cyanoC_{1-4}alkyl, halogen, –CN, $-OR_{12}$, $-NR_7R_{12}$, or Cy_2-C_{0-4}alkyl, wherein Cy_2 is optionally substituted with one or more R_{11};

R_6 is hydrogen, C_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl, $R_{12}R_7$N-C_{1-4}alkyl, Cy_1 or Cy_2-C_{1-4}alkyl, wherein Cy_1 and Cy_2 are optionally substituted with one or more R_{11};

R_7 is hydrogen or C_{1-4}alkyl;

R_8 is hydrogen, C_{1-4}alkyl, haloC_{1-4}alkyl, hydroxyC_{1-4}alkyl, or C_{1-4}alkoxyC_{1-4}alkyl;

R_9 is halogen, –CN, $-CONR_7R_{12}$, $-COR_{13}$, $-CO_2R_{12}$, $-OR_{12}$, $-OCONR_7R_{12}$, $-SO_2R_{13}$, $-SO_2NR_7R_{12}$, $-NR_7R_{12}$, $-NR_7COR_{12}$, $-NR_7CONR_7R_{12}$, $-NR_7CO_2R_{13}$ or $-NR_7SO_2R_{13}$;

R_{10} is C_{1-4}alkyl or R_9-C_{0-4}alkyl;

R_{11} is C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl, cyanoC_{1-4}alkyl, halogen, –CN,

2014201789 26 Mar 2014

$-CONR_7R_{14}$, $-COR_{14}$, $-CO_2R_{15}$, $-OR_{14}$, $-OCONR_7R_{14}$, $-SO_2R_{15}$, $-SO_2NR_7R_{14}$, $-NR_7R_{14}$, $-NR_7COR_{14}$, $-NR_7CONR_7R_{14}$, $-NR_7CO_2R_{15}$ or $-NR_7SO_2R_{15}$;

R_{12} is hydrogen or R_{13};

R_{13} is 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-C_{0-4}alkyl; wherein Cy_2 is optionally substituted with one or more R_{11};

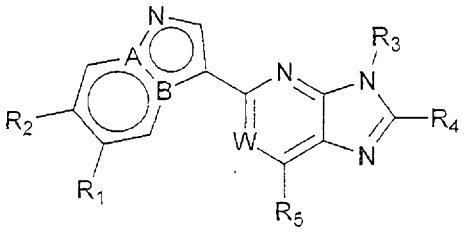
R_{14} is hydrogen or R_{15};

R_{15} is C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl or cyanoC_{1-4}alkyl;

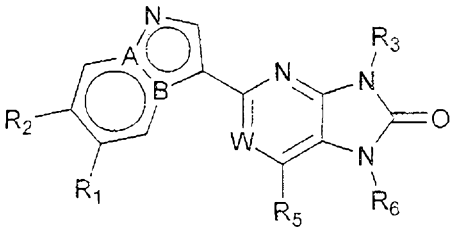
Cy_1 is a 3- to 7-membered monocyclic or 6- to 11-membered bicyclic ring, which is saturated, partially unsaturated or aromatic, and which is carbocyclic or heterocyclic containing from 1 to 4 heteroatoms independently selected from N, S and O, wherein said ring is bonded to the rest of the molecule through any available C atom, and wherein one or more C or S ring atoms are optionally oxidized forming CO, SO or SO_2; and

Cy_2 is a 3- to 7-membered monocyclic or 6- to 11-membered bicyclic ring, which is saturated, partially unsaturated or aromatic, and which is carbocyclic or heterocyclic containing from 1 to 4 heteroatoms independently selected from N, S and O, wherein said ring is bonded to the rest of the molecule through any available C or N atom, and wherein one or more C or S ring atoms are optionally oxidized forming CO, SO or SO_2.

In another embodiment, the invention relates to a compound of formula I or II



I



II

wherein

A is carbon and B is nitrogen, or A is nitrogen and B is carbon;

W is CH or N;

R_1 and R_2 independently are hydrogen, C_{1-4}alkyl, haloC_{1-4}alkyl, hydroxyC_{1-4}alkyl, cyanoC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, halogen, –CN, $-OR_8$ or $-SR_8$;

R_3 is C_{1-4}alkyl, R_9-C_{1-4}alkyl, Cy_1 or Cy_2-C_{1-4}alkyl, wherein Cy_1 and Cy_2 are optionally substituted with one or more R_{10};

R_4 is hydrogen, C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl, cyanoC_{1-4}alkyl, $R_{12}R_7N$-C_{0-4}alkyl, $R_{13}CONR_7$-C_{0-4}alkyl, $R_{13}R_7NCO$-C_{0-4}alkyl, $R_{12}R_7NCONR_7$-C_{0-4}alkyl, $R_{13}CO_2NR_7$-C_{0-4}alkyl, $R_{13}SO_2NR_7$-C_{0-4}alkyl, $-OR_{12}$ or Cy_2-C_{0-4}alkyl; wherein Cy_2 is optionally substituted with one or more R_{11};

R_5 is hydrogen, C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl, cyanoC_{1-4}alkyl, halogen, –CN, $-OR_{12}$, $-NR_7R_{12}$, or Cy_2-C_{0-4}alkyl, wherein Cy_2 is optionally substituted with one or more R_{11};

R_6 is hydrogen, C_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl, $R_{12}R_7N$-C_{1-4}alkyl, $R_{15}CO$-C_{0-4}alkyl, $R_{16}CO_2$-C_{0-4}alkyl, Cy_1 or Cy_2-C_{1-4}alkyl, wherein Cy_1 and Cy_2 are optionally substituted with one or more R_{11};

2014201789 26 Mar 2014

R_7 is hydrogen or C_{1-4}alkyl;

R_8 is hydrogen, C_{1-4}alkyl, haloC_{1-4}alkyl, hydroxyC_{1-4}alkyl, or C_{1-4}alkoxyC_{1-4}alkyl;

R_9 is halogen, –CN, $–CONR_7R_{12}$, $–COR_{13}$, $–CO_2R_{12}$, $–OR_{12}$, $–OCONR_7R_{12}$, $–SO_2R_{13}$, $–SO_2NR_7R_{12}$, $–NR_7R_{12}$, $–NR_7COR_{12}$, $–NR_7CONR_7R_{12}$, $–NR_7CO_2R_{13}$ or $–NR_7SO_2R_{13}$;

R_{10} is C_{1-4}alkyl or R_9-C_{0-4}alkyl;

R_{11} is C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl, cyanoC_{1-4}alkyl, halogen, –CN, $–CONR_7R_{14}$, $–COR_{14}$, $–CO_2R_{15}$, $–OR_{14}$, $–OCONR_7R_{14}$, $–SO_2R_{15}$, $–SO_2NR_7R_{14}$, $–NR_7R_{14}$, $–NR_7COR_{14}$, $–NR_7CONR_7R_{14}$, $–NR_7CO_2R_{15}$ or $–NR_7SO_2R_{15}$;

R_{12} is hydrogen or R_{13};

R_{13} is 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-C_{0-4}alkyl; wherein Cy_2 is optionally substituted with one or more R_{11};

R_{14} is hydrogen or R_{15};

R_{15} is C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl or cyanoC_{1-4}alkyl;

R_{16} is C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl or cyanoC_{1-4}alkyl;

Cy_1 is a 3- to 7-membered monocyclic or 6- to 11-membered bicyclic ring, which is saturated, partially unsaturated or aromatic, and which is carbocyclic or heterocyclic containing from 1 to 4 heteroatoms independently selected from N, S and O, wherein said ring is bonded to the rest of the molecule through any available C atom, and wherein one or more C or S ring atoms are optionally oxidized forming CO, SO or SO_2; and

Cy_2 is a 3- to 7-membered monocyclic or 6- to 11-membered bicyclic ring, which is saturated, partially unsaturated or aromatic, and which is carbocyclic or heterocyclic containing from 1 to 4 heteroatoms independently selected from N, S and O, wherein said ring is bonded to the rest of the molecule through any available C or N atom, and wherein one or more C or S ring atoms are optionally oxidized forming CO, SO or SO_2.

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

In another embodiment, the invention relates to the compounds of formula II.

In another embodiment, the invention relates to the compounds of formula I or II wherein A is carbon and B is nitrogen.

In another embodiment, the invention relates to the compounds of formula I or II wherein A is nitrogen and B is carbon.

In another embodiment, the invention relates to the compounds of formula I or II wherein W is CH.

In another embodiment, the invention relates to the compounds of formula I or II wherein W is N.

In another embodiment, the invention relates to the compounds of formula I or II wherein R_1 and R_2 independently are hydrogen, halogen, –CN, $–OR_8$ or $–SR_8$, preferably hydrogen or –CN.

In another embodiment, the invention relates to the compounds of formula I or II wherein R_2 is hydrogen.

In another embodiment, the invention relates to the compounds of formula I or II wherein R_2 is –CN.

In another embodiment, the invention relates to the compounds of formula I or II wherein R_1 is hydrogen, halogen, –CN, $–OR_8$ or $–SR_8$, more preferably hydrogen or –CN; and R_2 is hydrogen.

In another embodiment, the invention relates to the compounds of formula I or II wherein R_1 is hydrogen or

2014201789 26 Mar 2014

–CN.

In another embodiment, the invention relates to the compounds of formula I or II wherein R_1 is hydrogen.

In another embodiment, the invention relates to the compounds of formula I or II wherein R_1 is hydrogen; and R_2 is hydrogen.

In another embodiment, the invention relates to the compounds of formula I or II wherein R_1 is -CN; and R_2 is hydrogen.

In another embodiment, the invention relates to the compounds of formula I or II wherein R_3 is R_9-C_{1-4}alkyl, Cy_1 or Cy_2-C_{1-4}alkyl, wherein Cy_1 and Cy_2 are optionally substituted with one or more R_{10}.

In another embodiment, the invention relates to the compounds of formula I or II wherein R_3 is R_9-C_{1-4}alkyl.

In another embodiment, the invention relates to the compounds of formula I or II wherein R_3 is Cy_1, which is optionally substituted with one or more R_{10}.

In another embodiment, the invention relates to the compounds of formula I or II wherein R_3 is Cy_1 and Cy_1 is a 3- to 7-membered monocyclic or 6- to 11-membered bicyclic ring, which is saturated, partially unsaturated or aromatic, and which is carbocyclic or heterocyclic containing from 1 to 4 heteroatoms independently selected from N, S and O, wherein said ring is bonded to the rest of the molecule through any available C atom, and wherein one or more C or S ring atoms are optionally oxidized forming CO, SO or SO_2; wherein said Cy_1 is optionally substituted with one or more R_{10} provided that if the ring contains a nitrogen atom that can be substituted, then said nitrogen atom is substituted with one R_{10}.

In another embodiment, the invention relates to the compounds of formula I or II wherein R_3 is Cy_1; and Cy_1 in R_3 is a 3- to 7-membered monocyclic ring, which is saturated, partially unsaturated or aromatic, and which is carbocyclic or heterocyclic containing from 1 to 3 heteroatoms independently selected from N, S and O, wherein said ring is bonded to the rest of the molecule through any available C atom, and wherein one or more C or S ring atoms are optionally oxidized forming CO, SO or SO_2; and wherein said Cy_1 is optionally substituted with one or more R_{10}.

In another embodiment, the invention relates to the compounds of formula I or II wherein R_3 is Cy_1; and Cy_1 in R_3 is a 3- to 7-membered saturated monocyclic ring, which is carbocyclic or heterocyclic containing from 1 to 3 heteroatoms independently selected from N, S and O, wherein said ring is bonded to the rest of the molecule through any available C atom, and wherein one or more C or S ring atoms are optionally oxidized forming CO, SO or SO_2; and wherein said Cy_1 is optionally substituted with one or more R_{10}.

In another embodiment, the invention relates to the compounds of formula I or II wherein R_3 is Cy_1; and Cy_1 in R_3 is a 5- to 6-membered saturated monocyclic ring, which is carbocyclic or heterocyclic containing from 1 to 3 heteroatoms independently selected from N, S and O, wherein said ring is bonded to the rest of the molecule through any available C atom, and wherein one or more C or S ring atoms are optionally oxidized forming CO, SO or SO_2; and wherein said Cy_1 is optionally substituted with one or more R_{10}.

In another embodiment, the invention relates to the compounds of formula I or II wherein R_3 is Cy_1; and Cy_1 in R_3 is a 5- to 6-membered saturated monocyclic ring, which is carbocyclic or heterocyclic containing from 1 to 3 heteroatoms independently selected from N, S and O, at least one of which is N; wherein said ring is bonded to the rest of the molecule through any available C atom, and wherein one or more C or S ring atoms are optionally

2014201789 26 Mar 2014

oxidized forming CO, SO or SO_2; and wherein said Cy_1 is optionally substituted with one or more R_{10}.

In another embodiment, the invention relates to the compounds of formula I or II wherein R_3 is Cy_1; and Cy_1 in R_3 is a 3- to 7-membered, preferably 5- to 6-membered saturated monocyclic ring, which is heterocyclic containing from 1 to 3 heteroatoms independently selected from N, S and O, at least one of which is N; wherein said ring is bonded to the rest of the molecule through any available C atom, and wherein one or more C or S ring atoms are optionally oxidized forming CO, SO or SO_2; and wherein said Cy_1 is optionally substituted with one or more R_{10}.

In another embodiment, the invention relates to the compounds of formula I or II wherein R_3 is piperidinyl or pyrrolidinyl, preferably piperidin-3-yl or pyrrolidin-3-yl, which are optionally substituted with one or more R_{10}.

In another embodiment, the invention relates to the compounds of formula I or II wherein R_3 is piperidinyl or pyrrolidinyl, preferably piperidin-3-yl or pyrrolidin-3-yl, which are substituted with one R_{10} on the N atom of the piperidinyl or pyrrolidinyl ring and which are optionally further substituted with one or more R_{10} groups.

In another embodiment, the invention relates to the compounds of formula II wherein R_3 is piperidinyl or pyrrolidinyl, preferably piperidin-3-yl or pyrrolidin-3-yl, which are optionally substituted with one or more R_{10}.

In another embodiment, the invention relates to the compounds of formula II wherein R_3 is piperidinyl or pyrrolidinyl, preferably piperidin-3-yl or pyrrolidin-3-yl, which are substituted with one R_{10} on the N atom of the piperidinyl or pyrrolidinyl ring and which are optionally further substituted with one or more R_{10} groups.

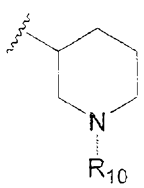
In another embodiment, the invention relates to the compounds of formula I or II wherein R_3 is piperidinyl, preferably piperidin-3-yl, which are optionally substituted with one or more R_{10}.

In another embodiment, the invention relates to the compounds of formula I or II wherein R_3 is piperidinyl, preferably piperidin-3-yl, substituted with one R_{10} on the N atom of the piperidinyl ring and optionally further substituted with one or more R_{10} groups.

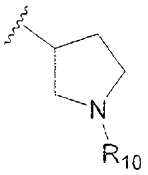
In another embodiment, the invention relates to the compounds of formula II wherein R_3 is piperidinyl, preferably piperidin-3-yl, which are optionally substituted with one or more R_{10}.

In another embodiment, the invention relates to the compounds of formula II wherein R_3 is piperidinyl, preferably piperidin-3-yl, substituted with one R_{10} on the N atom of the piperidinyl ring and optionally further substituted with one or more R_{10} groups.

In another embodiment, the invention relates to the compounds of formula I or II wherein R_3 is a cycle of formula



or

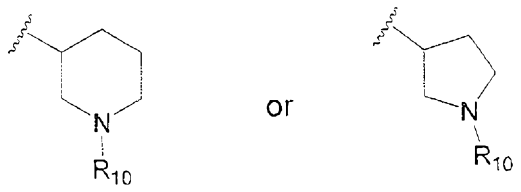


Cy_{1a} Cy_{1b}

wherein Cy_{1a} and Cy_{1b} are optionally substituted with one or more further R_{10}.

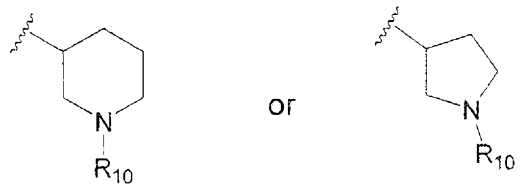
In another embodiment, the invention relates to the compounds of formula I or II wherein R_3 is a cycle of formula

26 Mar 2014
2014201789



Cy_{1a} Cy_{1b}

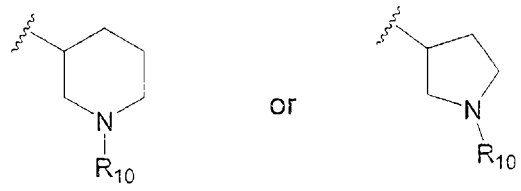
In another embodiment, the invention relates to the compounds of formula II wherein R_3 is a cycle of formula



Cy_{1a} Cy_{1b}

wherein Cy_{1a} and Cy_{1b} are optionally substituted with one or more further R_{10}.

In another embodiment, the invention relates to the compounds of formula II wherein R_3 is a cycle of formula

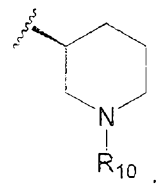


Cy_{1a} Cy_{1b}

In another embodiment, the invention relates to the compounds of formula I or II wherein R_3 is a cycle of formula Cy_{1a}.

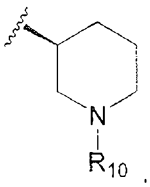
In another embodiment, the invention relates to the compounds of formula II wherein R_3 is a cycle of formula Cy_{1a}.

In another embodiment, the invention relates to the compounds of formula I or II wherein R_3 is a cycle of formula



In another embodiment, the invention relates to the compounds of formula II wherein R_3 is a cycle of formula

2014201789 26 Mar 2014



In another embodiment, the invention relates to the compounds of formula I or II wherein R_3 is a cycle of formula Cy_{1a} and Cy_{1a} has the (S)-stereochemistry.

In another embodiment, the invention relates to the compounds of formula II wherein R_3 is a cycle of formula Cy_{1a} and Cy_{1a} has the (S)-stereochemistry.

In another embodiment, the invention relates to the compounds of formula I or II wherein R_3 is a cycle of formula Cy_{1b}.

In another embodiment, the invention relates to the compounds of formula I or II wherein R_3 is Cy_2-C_{1-4}alkyl, wherein Cy_2 is optionally substituted with one or more R_{10}.

In another embodiment, the invention relates to the compounds of formula I or II wherein R_3 is Cy_2-C_{1-4}alkyl; and Cy_2 is a 3- to 7-membered monocyclic ring, which is saturated, partially unsaturated or aromatic, and which is carbocyclic or heterocyclic containing from 1 to 3 heteroatoms independently selected from N, S and O, wherein said ring is bonded to the rest of the molecule through any available C o N atom, and wherein one or more C or S ring atoms are optionally oxidized forming CO, SO or SO_2; and wherein said Cy_2 is optionally substituted with one or more R_{10}.

In another embodiment, the invention relates to the compounds of formula I or II wherein R_4 is hydrogen, C_{1-4}alkyl, $R_{12}R_7N$-C_{0-4}alkyl or Cy_2-C_{0-4}alkyl, preferably hydrogen, C_{1-4}alkyl, -NR_7R_{12} or Cy_2; wherein Cy_2 is optionally substituted with one or more R_{11}.

In another embodiment, the invention relates to the compounds of formula I or II wherein R_5 is hydrogen or Cy_2; wherein Cy_2 is optionally substituted with one or more R_{11}.

In another embodiment, the invention relates to the compounds of formula I or II wherein R_5 is hydrogen or Cy_2; and Cy_2 is a 3- to 7-membered monocyclic ring, which is saturated, partially unsaturated or aromatic, and which is carbocyclic or heterocyclic containing from 1 to 3 heteroatoms independently selected from N, S and O, wherein said ring is bonded to the rest of the molecule through any available C o N atom, and wherein one or more C or S ring atoms are optionally oxidized forming CO, SO or SO_2; and wherein said Cy_2 is optionally substituted with one or more R_{11}.

In another embodiment, the invention relates to the compounds of formula I or II wherein R_5 is hydrogen.

In another embodiment, the invention relates to the compounds of formula I or II wherein R_6 is C_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl, $R_{12}R_7N$-C_{1-4}alkyl, $R_{16}CO$-C_{0-4}alkyl, $R_{16}CO_2$-C_{0-4}alkyl, $R_{16}CO$-O-C_{1-4}alkyl, cyanoC_{1-4}alkyl, Cy_1 or Cy_2-C_{1-4}alkyl, wherein Cy_1 and Cy_2 are optionally substituted with one or more R_{11}.

In another embodiment, the invention relates to the compounds of formula I or II wherein R_6 is hydrogen, C_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl, $R_{12}R_7N$-C_{1-4}alkyl, $R_{16}CO$-C_{0-4}alkyl, $R_{16}CO_2$-C_{0-4}alkyl, Cy_1 or Cy_2-C_{1-4}alkyl, wherein Cy_1 and Cy_2 are optionally substituted with one or more R_{11}.

In another embodiment, the invention relates to the compounds of formula I or II wherein R_6 is C_{1-4}alkyl, C_{1-}

2014201789 26 Mar 2014

$_4$alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl, $R_{12}R_7N$-C_{1-4}alkyl, $R_{16}CO$-C_{0-4}alkyl, $R_{16}CO_2$-C_{0-4}alkyl, Cy_1 or Cy_2-C_{1-4}alkyl, wherein Cy_1 and Cy_2 are optionally substituted with one or more R_{11}.

In another embodiment, the invention relates to the compounds of formula I or II wherein R_6 is C_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl, $R_{12}R_7N$-C_{1-4}alkyl, $R_{16}CO$-C_{0-4}alkyl, $R_{16}CO_2$-C_{0-4}alkyl or $R_{16}CO$-O-C_{1-4}alkyl.

In another embodiment, the invention relates to the compounds of formula I or II wherein R_6 is hydrogen, C_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl, $R_{12}R_7N$-C_{1-4}alkyl, $R_{16}CO$-C_{0-4}alkyl or $R_{16}CO_2$-C_{0-4}alkyl.

In another embodiment, the invention relates to the compounds of formula I or II wherein R_6 is C_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl, $R_{12}R_7N$-C_{1-4}alkyl, $R_{16}CO$-C_{0-4}alkyl or $R_{16}CO_2$-C_{0-4}alkyl.

In another embodiment, the invention relates to the compounds of formula I or II wherein R_6 is hydrogen, C_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl or $R_{12}R_7N$-C_{1-4}alkyl.

In another embodiment, the invention relates to the compounds of formula I or II wherein R_6 is hydrogen or C_{1-4}alkyl, preferabiy hydrogen, methyl or ethyl.

In another embodiment, the invention relates to the compounds of formula I or II wherein R_6 is C_{1-4}alkyl, preferably methyl or ethyl.

In another embodiment, the invention relates to the compounds of formula II wherein R_6 is C_{1-4}alkyl, preferably methyl or ethyl.

In another embodiment, the invention relates to the compounds of formula II wherein R_6 is methyl.

In another embodiment, the invention relates to the compounds of formula II wherein R_6 is ethyl.

In another embodiment, the invention relates to the compounds of formula I or II wherein R_9 is $-CONR_7R_{12}$, $-COR_{13}$, $-CO_2R_{12}$, $-OR_{12}$, $-OCONR_7R_{12}$, $-SO_2R_{13}$, $-SO_2NR_7R_{12}$, $-NR_7R_{12}$, $-NR_7COR_{12}$, $-NR_7CONR_7R_{12}$, $-NR_7CO_2R_{13}$ or $-NR_7SO_2R_{13}$, preferably R_9 is $-COR_{13}$.

In another embodiment, the invention relates to the compounds of formula I or II wherein R_{10} is R_9-C_{0-4}alkyl, preferably R_9.

In another embodiment, the invention relates to the compounds of formula I or II wherein R_{10} is R_9; and R_9 in R_{10} is $-COR_{13}$ or $-SO_2R_{13}$.In another embodiment, the invention relates to the compounds of formula I or II wherein R_{10} is R_9; and R_9 in R_{10} is $-COR_{13}$.

In another embodiment, the invention relates to the compounds of formula I or II wherein R_{13} is 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-C_{0-4}alkyl; wherein Cy_2 is optionally substituted with one or more R_{11}.

In another embodiment, the invention relates to the compounds of formula I or II wherein R_{13} is C_{1-5}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl or cyanoC_{1-4}alkyl, preferably C_{1-4}alkyl or cyanoC_{1-4}alkyl, more preferably methyl, isopropyl or cyanomethyl, and still more preferably methyl or cyanomethyl.

In another embodiment, the invention relates to the compounds of formula I or II wherein R_{13} is C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl or cyanoC_{1-4}alkyl, preferably C_{1-4}alkyl or cyanoC_{1-4}alkyl, more preferably methyl, isopropyl or cyanomethyl, and still more preferably methyl or cyanomethyl.

In another embodiment, the invention relates to the compounds of formula I or II wherein R_{13} is methyl.

In another embodiment, the invention relates to the compounds of formula I or II wherein R_{13} is isopropyl.

2014201789 26 Mar 2014

In another embodiment, the invention relates to the compounds of formula I or II wherein R_{13} is cyanomethyl.

In another embodiment, the invention relates to the compounds of formula I or II wherein R_{13} is Cy_2-C_{0-4}alkyl wherein Cy_2 is optionally substituted with one or more R_{11}.

In another embodiment, the invention relates to the compounds of formula I or II wherein R_9 is $-CONR_7R_{12}$, $-COR_{13}$, $-CO_2R_{13}$, $-OR_{12}$, $-OCONR_7R_{12}$, $-SO_2R_{13}$, $-SO_2NR_7R_{12}$, $-NR_7R_{12}$, $-NR_7COR_{12}$, $-NR_7CONR_7R_{12}$, $-NR_7CO_2R_{13}$ or $-NR_7SO_2R_{13}$, preferably $-CO_2R_{13}$; and

R_{13} is C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl or cyanoC_{1-4}alkyl, preferably C_{1-4}alkyl or cyanoC_{1-4}alkyl, and more preferably methyl or cyanomethyl.

In another embodiment, the invention relates to the compounds of formula I or II wherein R_{10} is R_9; R_9 in R_{10} is $-COR_{13}$; and R_{13} is C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl or cyanoC_{1-4}alkyl, preferably C_{1-4}alkyl or cyanoC_{1-4}alkyl, and more preferably methyl or cyanomethyl.

In another embodiment, the invention relates to the compounds of formula I or II wherein R_3 is R_9-C_{1-4}alkyl; and

R_9 is $-CONR_7R_{12}$, $-COR_{13}$, $-CO_2R_{12}$, $-OR_{12}$, $-OCONR_7R_{12}$, $-SO_2R_{13}$, $-SO_2NR_7R_{12}$, $-NR_7R_{12}$, $-NR_7COR_{12}$, $-NR_7CONR_7R_{12}$, $-NR_7CO_2R_{13}$ or $-NR_7SO_2R_{13}$.

In another embodiment, the invention relates to the compounds of formula I or II wherein R_3 is R_9-C_{1-4}alkyl;

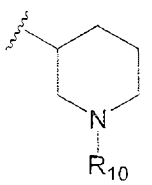
R_9 is $-CONR_7R_{12}$, $-COR_{13}$, $-CO_2R_{13}$, $-OR_{12}$, $-OCONR_7R_{12}$, $-SO_2R_{13}$, $-SO_2NR_7R_{12}$, $-NR_7R_{12}$, $-NR_7COR_{12}$, $-NR_7CONR_7R_{12}$, $-NR_7CO_2R_{13}$ or $-NR_7SO_2R_{13}$; and

R_{13} is C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl or cyanoC_{1-4}alkyl.

In another embodiment, the invention relates to the compounds of formula I or II wherein R_3 is Cy_1, preferably piperidinyl or pyrrolidinyl, more preferably piperidinyl-3-yl or pyrrolidinyl-3yl; wherein Cy_1 in R_3 is optionally substituted with one or more R_{10}; and

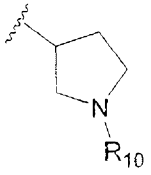
R_{10} is R_9-C_{0-4}alkyl, preferably R_9, more preferably $-COR_{13}$ or $-SO_2R_{13}$.

In another embodiment, the invention relates to the compounds of formula I or II wherein R_3 is a cycle of formula



Cy_{1a}

or

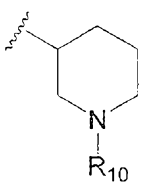


Cy_{1b} ; and

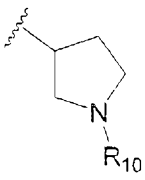
R_{10} is R_9-C_{0-4}alkyl, preferably R_9, more preferably $-COR_{13}$ or $-SO_2R_{13}$.

In another embodiment, the invention relates to the compounds of formula II wherein R_3 is a cycle of formula

2014201789 26 Mar 2014



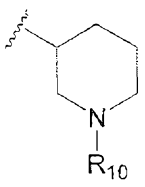
or



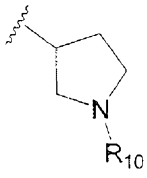
Cy_{1a} Cy_{1b} ; and

R_{10} is R_9-C_{0-4}alkyl, preferably R_9., more preferably –COR_{13} or -SO_2R_{13}.

In another embodiment, the invention relates to the compounds of formula I or II wherein R_3 is a cycle of formula



or



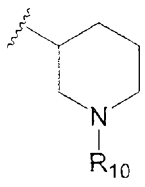
Cy_{1a} Cy_{1b} ;

R_{10} is R_9-C_{0-4}alkyl, preferably R_9;

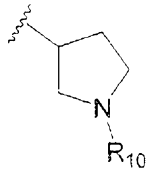
R_9 is—COR_{13} or -SO_2R_{13}; and

R_{13} is C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl or cyanoC_{1-4}alkyl, preferably C_{1-4}alkyl or cyanoC_{1-4}alkyl, and more preferably methyl or cyanomethyl.

In another embodiment, the invention relates to the compounds of formula II wherein R_3 is a cycle of formula



or



Cy_{1a} Cy_{1b} ;

R_{10} is R_9-C_{0-4}alkyl, preferably R_9;

R_9 is –COR_{13} or -SO_2R_{13}; and

R_{13} is C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl or cyanoC_{1-4}alkyl, preferably C_{1-4}alkyl or cyanoC_{1-4}alkyl and more preferably methyl or cyanomethyl.

In another embodiment, the invention relates to the compounds of formula I or II wherein R_3 is a cycle of formula Cy_{1a}; and

R_{10} is R_9-C_{0-4}alkyl, preferably R_9, more preferably –COR_{13} or -SO_2R_{13}, still more preferably –COR_{13}.

In another embodiment, the invention relates to the compounds of formula II wherein R_3 is a cycle of formula Cy_{1a}; and

R_{10} is R_9-C_{0-4}alkyl, preferably R_9, more preferably –COR_{13} or -SO_2R_{13}, still more preferably –COR_{13}.

2014201789 26 Mar 2014

In another embodiment, the invention relates to the compounds of formula I or II wherein R_3 is a cycle of formula Cy_{1a};

R_{10} is R_9-C_{0-4}alkyl, preferably R_9, more preferably $-COR_{13}$ or $-SO_2R_{13}$, still more preferably $-COR_{13}$; and

R_{13} is C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl or cyanoC_{1-4}alkyl, preferably C_{1-4}alkyl or cyanoC_{1-4}alkyl, and more preferably methyl or cyanomethyl.

In another embodiment, the invention relates to the compounds of formula II wherein R_3 is a cycle of formula Cy_{1a};

R_{10} is R_9-C_{0-4}alkyl, preferably R_9, more preferably $-COR_{13}$ or $-SO_2R_{13}$, still more preferably $-COR_{13}$; and

R_{13} is C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl or cyanoC_{1-4}alkyl, preferably C_{1-4}alkyl or cyanoC_{1-4}alkyl, and more preferably methyl or cyanomethyl.

In another embodiment, the invention relates to the compounds of formula I or II wherein R_3 is a cycle of formula Cy_{1a} with (S)-stereochemistry;

R_{10} is R_9-C_{0-4}alkyl, preferably R_9, more preferably $-COR_{13}$ or $-SO_2R_{13}$, still more preferably $-COR_{13}$; and

R_{13} is C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl or cyanoC_{1-4}alkyl, preferably C_{1-4}alkyl or cyanoC_{1-4}alkyl, and more preferably methyl or cyanomethyl.

In another embodiment, the invention relates to the compounds of formula II wherein R_3 is a cycle of formula Cy_{1a} with (S)-stereochemistry;

R_{10} is R_9-C_{0-4}alkyl, preferably R_9, more preferably $-COR_{13}$ or $-SO_2R_{13}$, still more preferably $-COR_{13}$; and

R_{13} is C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl or cyanoC_{1-4}alkyl, preferably C_{1-4}alkyl or cyanoC_{1-4}alkyl, and more preferably methyl or cyanomethyl.

In another embodiment, the invention relates to the compounds of formula I or II wherein R_3 is a cycle of formula Cy_{1b}; and

R_{10} is R_9-C_{0-4}alkyl, preferably R_9, more preferably $-SO_2R_{13}$.

In another embodiment, the invention relates to the compounds of formula II wherein R_3 is a cycle of formula Cy_{1b}; and

R_{10} is R_9-C_{0-4}alkyl, preferably R_9, more preferably $-SO_2R_{13}$.

In another embodiment, the invention relates to the compounds of formula I or II wherein Cy_1 is a 3- to 7-membered monocyclic ring, which is saturated, partially unsaturated or aromatic, and which is carbocyclic or heterocyclic containing from 1 to 3 heteroatoms independently selected from N, S and O, wherein said ring is bonded to the rest of the molecule through any available C atom, and wherein one or more C or S ring atoms are optionally oxidized forming CO, SO or SO_2.

In another embodiment, the invention relates to the compounds of formula I or II wherein Cy_1 is a 3- to 7-membered saturated monocyclic ring, which is carbocyclic or heterocyclic containing from 1 to 3 heteroatoms independently selected from N, S and O, wherein said ring is bonded to the rest of the molecule through any available C atom, and wherein one or more C or S ring atoms are optionally oxidized forming CO, SO or SO_2.

In another embodiment, the invention relates to the compounds of formula I or II wherein Cy_1 is a 5- to 6-membered saturated monocyclic ring, which is carbocyclic or heterocyclic containing from 1 to 3 heteroatoms

independently selected from N, S and O, wherein said ring is bonded to the rest of the molecule through any available C atom, and wherein one or more C or S ring atoms are optionally oxidized forming CO, SO or SO_2.

In another embodiment, the invention relates to the compounds of formula I or II wherein Cy_1 is a 5- to 6-membered saturated monocyclic ring, which is carbocyclic or heterocyclic containing from 1 to 3 heteroatoms independently selected from N, S and O, at least one of which is N; wherein said ring is bonded to the rest of the molecule through any available C atom, and wherein one or more C or S ring atoms are optionally oxidized forming CO, SO or SO_2.

In another embodiment, the invention relates to the compounds of formula I or II wherein Cy_1 is a 5- to 6-membered saturated monocyclic ring, which is heterocyclic containing from 1 to 3 heteroatoms independently selected from N, S and O, at least one of which is N; wherein said ring is bonded to the rest of the molecule through any available C atom, and wherein one or more C or S ring atoms are optionally oxidized forming CO, SO or SO_2.

In another embodiment, the invention relates to the compounds of formula I or II wherein Cy_1 is piperidinyl or pyrrolidinyl, preferably piperidinyl-3-yl or pyrrolidinyl-3-yl.

In another embodiment, the invention relates to the compounds of formula I or II wherein Cy_2 is a 3- to 7-membered monocyclic ring, which is saturated, partially unsaturated or aromatic, and which is carbocyclic or heterocyclic containing from 1 to 3 heteroatoms independently selected from N, S and O, wherein said ring is bonded to the rest of the molecule through any available C o N atom, and wherein one or more C or S ring atoms are optionally oxidized forming CO, SO or SO_2.

In another embodiment, the invention relates to the compounds of formula I or II wherein Cy_2 is a 3- to 7-membered saturated monocyclic ring, which is carbocyclic or heterocyclic containing from 1 to 3 heteroatoms independently selected from N, S and O, wherein said ring is bonded to the rest of the molecule through any available C atom, and wherein one or more C or S ring atoms are optionally oxidized forming CO, SO or SO_2.

In another embodiment, the invention relates to the compounds of formula I or II wherein Cy_2 is a 5- to 6-membered saturated monocyclic ring, which is carbocyclic or heterocyclic containing from 1 to 3 heteroatoms independently selected from N, S and O, wherein said ring is bonded to the rest of the molecule through any available C atom, and wherein one or more C or S ring atoms are optionally oxidized forming CO, SO or SO_2.

In another embodiment, the invention relates to the compounds of formula I or II wherein Cy_2 is a 5- to 6-membered saturated monocyclic ring, which is carbocyclic or heterocyclic containing from 1 to 3 heteroatoms independently selected from N, S and O, at least one of which is N; wherein said ring is bonded to the rest of the molecule through any available C atom, and wherein one or more C or S ring atoms are optionally oxidized forming CO, SO or SO_2.

In another embodiment, the invention relates to the compounds of formula I or II wherein Cy_2 is piperidinyl or pyrrolidinyl.

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

A is nitrogen and B is carbon; and

R_1 and R_2 independently are hydrogen, halogen, –CN, $–OR_8$ or $–SR_8$, preferably hydrogen or –CN.

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

2014201789 26 Mar 2014

A is nitrogen and B is carbon;

R_1 is hydrogen, C_{1-4}alkyl, haloC_{1-4}alkyl, hydroxyC_{1-4}alkyl, cyanoC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, halogen, –CN, $-OR_8$ or $-SR_8$, preferably hydrogen, halogen, –CN, $-OR_8$ or $-SR_8$, and more preferably hydrogen or –CN; and

R_2 is hydrogen.

In another embodiment, the invention relates to the compounds of formula I or II wherein A is nitrogen and B is carbon; R_1 and R_2 are hydrogen.

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

R_1 and R_2 independently are hydrogen, halogen, –CN, $-OR_8$ or $-SR_8$, and more preferably hydrogen or –CN; and

R_3 is R_9-C_{1-4}alkyl, Cy_1 or Cy_2-C_{1-4}alkyl, wherein Cy_1 and Cy_2 are optionally substituted with one or more R_{10}.

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

R_1 is hydrogen, C_{1-4}alkyl, haloC_{1-4}alkyl, hydroxyC_{1-4}alkyl, cyanoC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, halogen, –CN, $-OR_8$ or $-SR_8$, preferably hydrogen, halogen, –CN, $-OR_8$ or $-SR_8$, and more preferably hydrogen or –CN;

R_2 is hydrogen; and

R_3 is R_9-C_{1-4}alkyl, Cy_1 or Cy_2-C_{1-4}alkyl, wherein Cy_1 and Cy_2 are optionally substituted with one or more R_{10}.

In another embodiment, the invention relates to the compounds of formula I or II wherein R_1 and R_2 are hydrogen; and R_3 is R_9-C_{1-4}alkyl, Cy_1 or Cy_2-C_{1-4}alkyl, wherein Cy_1 and Cy_2 are optionally substituted with one or more R_{10}.

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

R_1 is hydrogen, C_{1-4}alkyl, haloC_{1-4}alkyl, hydroxyC_{1-4}alkyl, cyanoC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, halogen, –CN, $-OR_8$ or $-SR_8$, preferably hydrogen, halogen, –CN, $-OR_8$ or $-SR_8$, and more preferably hydrogen or –CN;

R_2 is hydrogen; and

R_3 is R_9-C_{1-4}alkyl.

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

R_1 is hydrogen, C_{1-4}alkyl, haloC_{1-4}alkyl, hydroxyC_{1-4}alkyl, cyanoC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, halogen, –CN, $-OR_8$ or $-SR_8$, preferably hydrogen, halogen, –CN, $-OR_8$ or $-SR_8$, and more preferably hydrogen or –CN;

R_2 is hydrogen; and

R_3 is Cy_1, which is optionally substituted with one or more R_{10}.

In another embodiment, the invention relates to the compounds of formula I or II wherein R_1 and R_2 are hydrogen; and R_3 is Cy_1, which is optionally substituted with one or more R_{10}.

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

R_1 is hydrogen, C_{1-4}alkyl, haloC_{1-4}alkyl, hydroxyC_{1-4}alkyl, cyanoC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, halogen, –CN, $-OR_8$ or $-SR_8$, preferably hydrogen, halogen, –CN, $-OR_8$ or $-SR_8$, and more preferably hydrogen or –CN;

R_2 is hydrogen;

R_3 is Cy_1, wherein Cy_1 in R_3 is a 3- to 7-membered monocyclic ring, which is saturated, partially unsaturated or aromatic, and which is carbocyclic or heterocyclic containing from 1 to 3 heteroatoms independently selected from N, S and O, wherein said ring is bonded to the rest of the molecule through any available C atom, and wherein one

2014201789 26 Mar 2014

or more C or S ring atoms are optionally oxidized forming CO, SO or SO_2; and wherein said Cy_1 is optionally substituted with one or more R_{10}.

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

R_1 is hydrogen, C_{1-4}alkyl, haloC_{1-4}alkyl, hydroxyC_{1-4}alkyl, cyanoC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, halogen, –CN, $-OR_8$ or $-SR_8$, preferably hydrogen, halogen, –CN, $-OR_8$ or $-SR_8$, and more preferably hydrogen or –CN;

R_2 is hydrogen;

R_3 is Cy_1, wherein Cy_1 in R_3 is a 3- to 7-membered, preferably 5- to 6-membered, saturated monocyclic ring, which is carbocyclic or heterocyclic containing from 1 to 3 heteroatoms independently selected from N, S and O, wherein said ring is bonded to the rest of the molecule through any available C atom, and wherein one or more C or S ring atoms are optionally oxidized forming CO, SO or SO_2; and more preferably Cy_1 in R_3 is piperidinyl or pyrrolidinyl, even more preferably piperidin-3-yl or pyrrolidin-3-yl; wherein said Cy_1 is optionally substituted with one or more R_{10}.

In another embodiment, the invention relates to the compounds of formula I or II wherein A is nitrogen and B is carbon;

R_1 is hydrogen, C_{1-4}alkyl, haloC_{1-4}alkyl, hydroxyC_{1-4}alkyl, cyanoC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, halogen, –CN, $-OR_8$ or $-SR_8$, preferably hydrogen, halogen, –CN, $-OR_8$ or $-SR_8$, and more preferably hydrogen or –CN;

R_2 is hydrogen; and

R_3 is R_9-C_{1-4}alkyl, Cy_1 or Cy_2-C_{1-4}alkyl, wherein Cy_1 and Cy_2 are optionally substituted with one or more R_{10}.

In another embodiment, the invention relates to the compounds of formula I or II wherein A is nitrogen and B is carbon; R_1 and R_2 are hydrogen; and R_3 is R_9-C_{1-4}alkyl, Cy_1 or Cy_2-C_{1-4}alkyl, wherein Cy_1 and Cy_2 are optionally substituted with one or more R_{10}.

In another embodiment, the invention relates to the compounds of formula I or II wherein A is nitrogen and B is carbon;

R_1 is hydrogen, C_{1-4}alkyl, haloC_{1-4}alkyl, hydroxyC_{1-4}alkyl, cyanoC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, halogen, –CN, $-OR_8$ or $-SR_8$, preferably hydrogen, halogen, –CN, $-OR_8$ or $-SR_8$, and more preferably hydrogen or –CN;

R_2 is hydrogen; and

R_3 is R_9-C_{1-4}alkyl.

In another embodiment, the invention relates to the compounds of formula I or II wherein A is nitrogen and B is carbon; R_1 and R_2 are hydrogen; and R_3 is R_9-C_{1-4}alkyl.

In another embodiment, the invention relates to the compounds of formula I or II wherein A is nitrogen and B is carbon;

R_1 is hydrogen, C_{1-4}alkyl, haloC_{1-4}alkyl, hydroxyC_{1-4}alkyl, cyanoC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, halogen, –CN, $-OR_8$ or $-SR_8$, preferably hydrogen, halogen, –CN, $-OR_8$ or $-SR_8$, and more preferably hydrogen or –CN;

R_2 is hydrogen; and

R_3 is Cy_1, which is optionally substituted with one or more R_{10}.

In another embodiment, the invention relates to the compounds of formula I or II wherein A is nitrogen and B is carbon; R_1 and R_2 are hydrogen; and R_3 is Cy_1, which is optionally substituted with one or more R_{10}.

2014201789 26 Mar 2014

In another embodiment, the invention relates to the compounds of formula I or II wherein A is nitrogen and B is carbon;

R_1 is hydrogen, C_{1-4}alkyl, haloC_{1-4}alkyl, hydroxyC_{1-4}alkyl, cyanoC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, halogen, –CN, $-OR_8$ or $-SR_8$, preferably hydrogen, halogen, –CN, $-OR_8$ or $-SR_8$, and more preferably hydrogen or –CN;

R_2 is hydrogen; and

R_3 is Cy_1, wherein Cy_1 in R_3 is a 3- to 7-membered monocyclic ring, which is saturated, partially unsaturated or aromatic, and which is carbocyclic or heterocyclic containing from 1 to 3 heteroatoms independently selected from N, S and O, wherein said ring is bonded to the rest of the molecule through any available C atom, and wherein one or more C or S ring atoms are optionally oxidized forming CO, SO or SO_2; and wherein said Cy_1 is optionally substituted with one or more R_{10}.

In another embodiment, the invention relates to the compounds of formula I or II wherein A is nitrogen and B is carbon;

R_1 is hydrogen, C_{1-4}alkyl, haloC_{1-4}alkyl, hydroxyC_{1-4}alkyl, cyanoC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, halogen, –CN, $-OR_8$ or $-SR_8$, preferably hydrogen, halogen, –CN, $-OR_8$ or $-SR_8$, and more preferably hydrogen or –CN;

R_2 is hydrogen; and

R_3 is Cy_1, wherein Cy_1 in R_3 is a 3- to 7-membered, preferably 5- to 6-membered, saturated monocyclic ring, which is carbocyclic or heterocyclic containing from 1 to 3 heteroatoms independently selected from N, S and O, wherein said ring is bonded to the rest of the molecule through any available C atom, and wherein one or more C or S ring atoms are optionally oxidized forming CO, SO or SO_2; and more preferably Cy_1 in R_3 is piperidinyl or pyrrolidinyl, even more preferably piperidin-3-yl or pyrrolidin-3-yl; wherein said Cy_1 is optionally substituted with one or more R_{10}.

In another embodiment, the invention relates to the compounds of formula I or II wherein A is nitrogen and B is carbon;

R_1 is hydrogen, C_{1-4}alkyl, haloC_{1-4}alkyl, hydroxyC_{1-4}alkyl, cyanoC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, halogen, –CN, $-OR_8$ or $-SR_8$, preferably hydrogen, halogen, –CN, $-OR_8$ or $-SR_8$, and more preferably hydrogen or –CN;

R_2 is hydrogen; and

R_3 is a cycle of formula Cy_{1a}, preferably with (S)-stereochemistry.

In another embodiment, the invention relates to the compounds of formula II wherein A is nitrogen and B is carbon;

R_1 is hydrogen, C_{1-4}alkyl, haloC_{1-4}alkyl, hydroxyC_{1-4}alkyl, cyanoC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, halogen, –CN, $-OR_8$ or $-SR_8$, preferably hydrogen, halogen, –CN, $-OR_8$ or $-SR_8$, and more preferably hydrogen or –CN;

R_2 is hydrogen; and

R_3 is a cycle of formula Cy_{1a}, preferably with (S)-stereochemistry.

In another embodiment, the invention relates to the compounds of formula I or II wherein A is nitrogen and B is carbon; and

R_5 is hydrogen.

In another embodiment, the invention relates to the compounds of formula I or II wherein A is nitrogen and

2014201789 26 Mar 2014

B is carbon;

R_1 is hydrogen, halogen, –CN, $–OR_8$ or $–SR_8$, preferably hydrogen or –CN; and R_2 is hydrogen; and

R_5 is hydrogen.

In another embodiment, the invention relates to the compounds of formula I or II wherein A is nitrogen and B is carbon; R_1 and R_2 are hydrogen; and R_5 is hydrogen.

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

R_1 is hydrogen, halogen, –CN, $–OR_8$ or $–SR_8$, preferably hydrogen or –CN; and R_2 is hydrogen;

R_5 is hydrogen; and

R_6 is hydrogen or C_{1-4}alkyl, preferably hydrogen, methyl or ethyl.

In another embodiment, the invention relates to the compounds of formula I or II wherein R_1 and R_2 are hydrogen; R_5 is hydrogen; and R_6 is hydrogen or C_{1-4}alkyl, preferably hydrogen, methyl or ethyl.

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

R_1 is hydrogen, halogen, –CN, $–OR_8$ or $–SR_8$, preferably hydrogen or –CN; and R_2 is hydrogen;

R_5 is hydrogen; and

R_6 is C_{1-4}alkyl, preferably methyl or ethyl.

In another embodiment, the invention relates to the compounds of formula I or II wherein R_1 and R_2 are hydrogen; R_5 is hydrogen; and R_6 is C_{1-4}alkyl, preferably methyl or ethyl.

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

R_1 is hydrogen, halogen, –CN, $–OR_8$ or $–SR_8$, preferably hydrogen or –CN; and R_2 is hydrogen;

R_3 is R_9-C_{1-4}alkyl, Cy_1 or Cy_2-C_{1-4}alkyl, wherein Cy_1 and Cy_2 are optionally substituted with one or more R_{10}; and

R_5 is hydrogen.

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

R_1 and R_2 are hydrogen;

R_3 is R_9-C_{1-4}alkyl, Cy_1 or Cy_2-C_{1-4}alkyl, wherein Cy_1 and Cy_2 are optionally substituted with one or more R_{10}; and

R_5 is hydrogen.

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

R_1 is hydrogen, halogen, –CN, $–OR_8$ or $–SR_8$, preferably hydrogen or –CN; and R_2 is hydrogen;

R_3 is R_9-C_{1-4}alkyl; and

R_5 is hydrogen.

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

R_1 is hydrogen, halogen, –CN, $–OR_8$ or $–SR_8$, preferably hydrogen or –CN; and R_2 is hydrogen;

R_3 is Cy_1, which is optionally substituted with one or more R_{10}; and

R_5 is hydrogen.

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

R_1 and R_2 are hydrogen;

2014201789 26 Mar 2014

R_3 is Cy_1, which is optionally substituted with one or more R_{10}; and

R_5 is hydrogen.

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

R_1 is hydrogen, halogen, –CN, $–OR_8$ or $–SR_8$, preferably hydrogen or –CN; and R_2 is hydrogen;

R_3 is Cy_1, wherein Cy_1 in R_3 is a 3- to 7-membered monocyclic ring, which is saturated, partially unsaturated or aromatic, and which is carbocyclic or heterocyclic containing from 1 to 3 heteroatoms independently selected from N, S and O, wherein said ring is bonded to the rest of the molecule through any available C atom, and wherein one or more C or S ring atoms are optionally oxidized forming CO, SO or SO_2; and wherein said Cy_1 is optionally substituted with one or more R_{10}; and

R_5 is hydrogen.

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

R_1 is hydrogen, halogen, –CN, $–OR_8$ or $–SR_8$, preferably hydrogen or –CN; and R_2 is hydrogen;

R_3 is Cy_1, wherein Cy_1 in R_3 is a 3- to 7-membered, preferably 5- to 6-membered, saturated monocyclic ring, which is carbocyclic or heterocyclic containing from 1 to 3 heteroatoms independently selected from N, S and O, wherein said ring is bonded to the rest of the molecule through any available C atom, and wherein one or more C or S ring atoms are optionally oxidized forming CO, SO or SO_2; and more preferably Cy_1 in R_3 is piperidinyl or pyrrolidinyl, even more preferably piperidin-3-yl or pyrrolidin-3-yl; wherein said Cy_1 is optionally substituted with one or more R_{10}; and

R_5 is hydrogen.

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

R_1 is hydrogen, halogen, –CN, $–OR_8$ or $–SR_8$, preferably hydrogen or –CN; and R_2 is hydrogen;

R_3 is a cycle of formula Cy_{1a}, preferably with (S)-stereochemistry; and

R_5 is hydrogen.

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

R_1 is hydrogen, halogen, –CN, $–OR_8$ or $–SR_8$, preferably hydrogen or –CN; and R_2 is hydrogen;

R_3 is a cycle of formula Cy_{1a}, preferably with (S)-stereochemistry; and

R_5 is hydrogen.

In another embodiment, the invention relates to the compounds of formula I or II wherein A is nitrogen and B is carbon;

R_1 is hydrogen, halogen, –CN, $–OR_8$ or $–SR_8$, preferably hydrogen or –CN; and R_2 is hydrogen;

R_5 is hydrogen; and

R_6 is hydrogen or C_{1-4}alkyl, preferably hydrogen, methyl or ethyl.

In another embodiment, the invention relates to the compounds of formula I or II wherein A is nitrogen and B is carbon;

R_1 and R_2 are hydrogen;

R_5 is hydrogen; and

R_6 is hydrogen or C_{1-4}alkyl, preferably hydrogen, methyl or ethyl.

2014201789 26 Mar 2014

In another embodiment, the invention relates to the compounds of formula I or II wherein A is nitrogen and B is carbon;

R_1 is hydrogen, halogen, –CN, $–OR_8$ or $–SR_8$, preferably hydrogen or –CN; and R_2 is hydrogen;

R_5 is hydrogen; and

R_6 is C_{1-4}alkyl, preferably methyl or ethyl.

In another embodiment, the invention relates to the compounds of formula I or II wherein A is nitrogen and B is carbon;

R_1 and R_2 are hydrogen;

R_5 is hydrogen; and

R_6 is C_{1-4}alkyl, preferably methyl or ethyl.

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

W is CH;

R_1 is hydrogen, halogen, –CN, $–OR_8$ or $–SR_8$, preferably hydrogen or –CN; and R_2 is hydrogen;

R_3 is R_9-C_{1-4}alkyl, Cy_1 or Cy_2-C_{1-4}alkyl, wherein Cy_1 and Cy_2 are optionally substituted with one or more R_{10}; and

R_5 is hydrogen.

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

W is CH;

R_1 and R_2 are hydrogen;

R_3 is R_9-C_{1-4}alkyl, Cy_1 or Cy_2-C_{1-4}alkyl, wherein Cy_1 and Cy_2 are optionally substituted with one or more R_{10}; and

R_5 is hydrogen.

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

W is CH;

R_1 is hydrogen, halogen, –CN, $–OR_8$ or $–SR_8$, preferably hydrogen or –CN; and R_2 is hydrogen;

R_3 is R_9-C_{1-4}alkyl; and

R_5 is hydrogen.

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

W is CH;

R_1 is hydrogen, halogen, –CN, $–OR_8$ or $–SR_8$, preferably hydrogen or –CN, more preferably hydrogen; and R_2 is hydrogen;

R_3 is Cy_1, which is optionally substituted with one or more R_{10}; and

R_5 is hydrogen.

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

W is CH;

R_1 is hydrogen, halogen, –CN, $–OR_8$ or $–SR_8$, preferably hydrogen or –CN, more preferably hydrogen; and R_2 is hydrogen;

R_3 is Cy_1, wherein Cy_1 in R_3 is a 3- to 7-membered monocyclic ring, which is saturated, partially unsaturated or aromatic, and which is carbocyclic or heterocyclic containing from 1 to 3 heteroatoms independently selected from N, S and O, wherein said ring is bonded to the rest of the molecule through any available C atom, and wherein one or more C or S ring atoms are optionally oxidized forming CO, SO or SO_2; and wherein said Cy_1 is optionally substituted with one or more R_{10}; and

R_5 is hydrogen.

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

W is CH;

R_1 is hydrogen, halogen, –CN, $–OR_8$ or $–SR_8$, preferably hydrogen or –CN, more preferably hydrogen; and R_2 is hydrogen;

R_3 is Cy_1, wherein Cy_1 in R_3 is a 3- to 7-membered, preferably 5- to 6-membered, saturated monocyclic ring, which is carbocyclic or heterocyclic containing from 1 to 3 heteroatoms independently selected from N, S and O, wherein said ring is bonded to the rest of the molecule through any available C atom, and wherein one or more C or S ring atoms are optionally oxidized forming CO, SO or SO_2; and more preferably Cy_1 in R_3 is piperidinyl or pyrrolidinyl, even more preferably piperidin-3-yl or pyrrolidin-3-yl; wherein said Cy_1 is optionally substituted with one or more R_{10}; and

R_5 is hydrogen.

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

W is CH;

R_1 is hydrogen, halogen, –CN, $–OR_8$ or $–SR_8$, preferably hydrogen or –CN, more preferably hydrogen; and R_2 is hydrogen;

R_3 is a cycle of formula Cy_{1a}, preferably with (S)-stereochemistry; and

R_5 is hydrogen.

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

W is CH;

R_1 is hydrogen, halogen, –CN, $–OR_8$ or $–SR_8$, preferably hydrogen or –CN, more preferably hydrogen; and R_2 is hydrogen;

R_3 is a cycle of formula Cy_{1a}, preferably with (S)-stereochemistry; and

R_5 is hydrogen.

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

W is N;

R_1 is hydrogen, halogen, –CN, $–OR_8$ or $–SR_8$, preferably hydrogen or –CN; and R_2 is hydrogen;

R_3 is R_9-C_{1-4}alkyl, Cy_1 or Cy_2-C_{1-4}alkyl, wherein Cy_1 and Cy_2 are optionally substituted with one or more R_{10}; and

R_5 is hydrogen.

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

W is N;

2014201789 26 Mar 2014

R_1 and R_2 are hydrogen;

R_3 is R_9-C_{1-4}alkyl, Cy_1 or Cy_2-C_{1-4}alkyl, wherein Cy_1 and Cy_2 are optionally substituted with one or more R_{10}; and

R_5 is hydrogen.

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

W is N;

R_1 is hydrogen, halogen, –CN, $–OR_8$ or $–SR_8$, preferably hydrogen or –CN; and R_2 is hydrogen;

R_3 is R_9-C_{1-4}alkyl; and

R_5 is hydrogen.

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

W is N;

R_1 is hydrogen, halogen, –CN, $–OR_8$ or $–SR_8$, preferably hydrogen or –CN, more preferably hydrogen; and R_2 is hydrogen;

R_3 is Cy_1, which is optionally substituted with one or more R_{10}; and

R_5 is hydrogen.

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

W is N;

R_1 is hydrogen, halogen, –CN, $–OR_8$ or $–SR_8$, preferably hydrogen or –CN, more preferably hydrogen; and R_2 is hydrogen;

R_3 is Cy_1, wherein Cy_1 in R_3 is a 3- to 7-membered monocyclic ring, which is saturated, partially unsaturated or aromatic, and which is carbocyclic or heterocyclic containing from 1 to 3 heteroatoms independently selected from N, S and O, wherein said ring is bonded to the rest of the molecule through any available C atom, and wherein one or more C or S ring atoms are optionally oxidized forming CO, SO or SO_2; and wherein said Cy_1 is optionally substituted with one or more R_{10}; and

R_5 is hydrogen.

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

W is N;

R_1 is hydrogen, halogen, –CN, $–OR_8$ or $–SR_8$, preferably hydrogen or –CN, more preferably hydrogen; and R_2 is hydrogen;

R_3 is Cy_1, wherein Cy_1 in R_3 is a 3- to 7-membered, preferably 5- to 6-membered, saturated monocyclic ring, which is carbocyclic or heterocyclic containing from 1 to 3 heteroatoms independently selected from N, S and O, wherein said ring is bonded to the rest of the molecule through any available C atom, and wherein one or more C or S ring atoms are optionally oxidized forming CO, SO or SO_2; and more preferably Cy_1 in R_3 is piperidinyl or pyrrolidinyl, even more preferably piperidin-3-yl or pyrrolidin-3-yl; wherein said Cy_1 is optionally substituted with one or more R_{10}; and

R_5 is hydrogen.

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

2014201789 26 Mar 2014

A is nitrogen and B is carbon;

R_1 is hydrogen, halogen, –CN, $–OR_8$ or $–SR_8$, preferably hydrogen or –CN; and R_2 is hydrogen;

R_3 is R_9-C_{1-4}alkyl, Cy_1 or Cy_2-C_{1-4}alkyl, wherein Cy_1 and Cy_2 are optionally substituted with one or more R_{10}; and

R_5 is hydrogen.

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

A is nitrogen and B is carbon;

R_1 and R_2 are hydrogen;

R_3 is R_9-C_{1-4}alkyl, Cy_1 or Cy_2-C_{1-4}alkyl, wherein Cy_1 and Cy_2 are optionally substituted with one or more R_{10}; and

R_5 is hydrogen.

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

A is nitrogen and B is carbon;

R_1 is hydrogen, halogen, –CN, $–OR_8$ or $–SR_8$, preferably hydrogen or –CN; and R_2 is hydrogen;

R_3 is R_9-C_{1-4}alkyl; and

R_5 is hydrogen.

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

A is nitrogen and B is carbon;

R_1 is hydrogen, halogen, –CN, $–OR_8$ or $–SR_8$, preferably hydrogen or –CN, more preferably hydrogen; and R_2 is hydrogen;

R_3 is Cy_1, which is optionally substituted with one or more R_{10}; and

R_5 is hydrogen.

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

A is nitrogen and B is carbon;

R_1 is hydrogen, halogen, –CN, $–OR_8$ or $–SR_8$, preferably hydrogen or –CN, more preferably hydrogen; and R_2 is hydrogen;

R_3 is Cy_1, wherein Cy_1 in R_3 is a 3- to 7-membered monocyclic ring, which is saturated, partially unsaturated or aromatic, and which is carbocyclic or heterocyclic containing from 1 to 3 heteroatoms independently selected from N, S and O, wherein said ring is bonded to the rest of the molecule through any available C atom, and wherein one or more C or S ring atoms are optionally oxidized forming CO, SO or SO_2; and wherein said Cy_1 is optionally substituted with one or more R_{10}; and

R_5 is hydrogen.

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

A is nitrogen and B is carbon;

R_1 is hydrogen, halogen, –CN, $–OR_8$ or $–SR_8$, preferably hydrogen or –CN, more preferably hydrogen; and R_2 is hydrogen;

R_3 is Cy_1, wherein Cy_1 in R_3 is a 3- to 7-membered, preferably 5- to 6-membered, saturated monocyclic

2014201789 26 Mar 2014

ring, which is carbocyclic or heterocyclic containing from 1 to 3 heteroatoms independently selected from N, S and O, wherein said ring is bonded to the rest of the molecule through any available C atom, and wherein one or more C or S ring atoms are optionally oxidized forming CO, SO or SO_2; and more preferably Cy_1 in R_3 is piperidinyl or pyrrolidinyl, even more preferably piperidin-3-yl or pyrrolidin-3-yl; wherein said Cy_1 is optionally substituted with one or more R_{10}; and

R_5 is hydrogen.

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

A is nitrogen and B is carbon;

R_1 is hydrogen, halogen, –CN, $–OR_8$ or $–SR_8$, preferably hydrogen or –CN, more preferably hydrogen; and R_2 is hydrogen;

R_3 is a cycle of formula Cy_{1a}, preferably with (S)-stereochemistry; and

R_5 is hydrogen.

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

A is nitrogen and B is carbon;

R_1 is hydrogen, halogen, –CN, $–OR_8$ or $–SR_8$, preferably hydrogen or –CN, more preferably hydrogen; and R_2 is hydrogen;

R_3 is a cycle of formula Cy_{1a}, preferably with (S)-stereochemistry; and

R_5 is hydrogen.

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

R_1 is hydrogen, halogen, –CN, $–OR_8$ or $–SR_8$, preferably hydrogen or –CN; and R_2 is hydrogen;

R_3 is R_9-C_{1-4}alkyl, Cy_1 or Cy_2-C_{1-4}alkyl, wherein Cy_1 and Cy_2 are optionally substituted with one or more R_{10};

R_4 is hydrogen, C_{1-4}alkyl, $R_{12}R_7N$-C_{0-4}alkyl or Cy_2-C_{0-4}alkyl, preferably hydrogen, C_{1-4}alkyl, $-NR_7R_{12}$ or Cy_2; wherein Cy_2 are optionally substituted with one or more R_{11};

R_5 is hydrogen; and

R_6 is hydrogen, C_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl or $R_{12}R_7N$-C_{1-4}alkyl, preferably hydrogen or C_{1-4}alkyl and more preferably hydrogen, methyl or ethyl.

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

R_1 and R_2 are hydrogen;

R_3 is R_9-C_{1-4}alkyl, Cy_1 or Cy_2-C_{1-4}alkyl, wherein Cy_1 and Cy_2 are optionally substituted with one or more R_{10};

R_4 is hydrogen, C_{1-4}alkyl, $R_{12}R_7N$-C_{0-4}alkyl or Cy_2-C_{0-4}alkyl, preferably hydrogen, C_{1-4}alkyl, $-NR_7R_{12}$ or Cy_2; wherein Cy_2 are optionally substituted with one or more R_{11};

R_5 is hydrogen; and

R_6 is hydrogen, C_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl or $R_{12}R_7N$-C_{1-4}alkyl, preferably hydrogen or C_{1-4}alkyl and more preferably hydrogen, methyl or ethyl.

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

R_1 is hydrogen, halogen, –CN, $–OR_8$ or $–SR_8$, preferably hydrogen or –CN; and R_2 is hydrogen;

R_3 is R_9-C_{1-4}alkyl;

2014201789 26 Mar 2014

R_4 is hydrogen, C_{1-4}alkyl, $R_{12}R_7N$-C_{0-4}alkyl or Cy_2-C_{0-4}alkyl, preferably hydrogen, C_{1-4}alkyl, -NR_7R_{12} or Cy_2; wherein Cy_2 are optionally substituted with one or more R_{11};

R_5 is hydrogen; and

R_6 is hydrogen, C_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl or $R_{12}R_7N$-C_{1-4}alkyl, preferably hydrogen or C_{1-4}alkyl and more preferably hydrogen, methyl or ethyl.

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

R_1 is hydrogen, halogen, –CN, $–OR_8$ or $–SR_8$, preferably hydrogen or –CN; and R_2 is hydrogen;

R_3 is Cy_1 which is optionally substituted with one or more R_{10};

R_4 is hydrogen, C_{1-4}alkyl, $R_{12}R_7N$-C_{0-4}alkyl or Cy_2-C_{0-4}alkyl, preferably hydrogen, C_{1-4}alkyl, -NR_7R_{12} or Cy_2; wherein Cy_2 are optionally substituted with one or more R_{11};

R_5 is hydrogen; and

R_6 is hydrogen, C_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl or $R_{12}R_7N$-C_{1-4}alkyl, preferably hydrogen or C_{1-4}alkyl and more preferably hydrogen, methyl or ethyl.

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

R_1 is hydrogen, halogen, –CN, $–OR_8$ or $–SR_8$, preferably hydrogen or –CN; and R_2 is hydrogen;

R_3 is Cy_1, wherein Cy_1 in R_3 is a 3- to 7-membered monocyclic ring, which is saturated, partially unsaturated or aromatic, and which is carbocyclic or heterocyclic containing from 1 to 3 heteroatoms independently selected from N, S and O, wherein said ring is bonded to the rest of the molecule through any available C atom, and wherein one or more C or S ring atoms are optionally oxidized forming CO, SO or SO_2; and wherein said Cy_1 is optionally substituted with one or more R_{10};

R_4 is hydrogen, C_{1-4}alkyl, $R_{12}R_7N$-C_{0-4}alkyl or Cy_2-C_{0-4}alkyl, preferably hydrogen, C_{1-4}alkyl, -NR_7R_{12} or Cy_2; wherein Cy_2 are optionally substituted with one or more R_{11};

R_5 is hydrogen; and

R_6 is hydrogen, C_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl or $R_{12}R_7N$-C_{1-4}alkyl, preferably hydrogen or C_{1-4}alkyl and more preferably hydrogen, methyl or ethyl.

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

R_1 is hydrogen, halogen, –CN, $–OR_8$ or $–SR_8$, preferably hydrogen or –CN; and R_2 is hydrogen;

R_3 is Cy_1, wherein Cy_1 in R_3 is a 3- to 7-membered, preferably 5- to 6-membered, saturated monocyclic ring, which is carbocyclic or heterocyclic containing from 1 to 3 heteroatoms independently selected from N, S and O, wherein said ring is bonded to the rest of the molecule through any available C atom, and wherein one or more C or S ring atoms are optionally oxidized forming CO, SO or SO_2; and more preferably Cy_1 in R_3 is piperidinyl or pyrrolidinyl, even more preferably piperidin-3-yl or pyrrolidin-3-yl; wherein said Cy_1 is optionally substituted with one or more R_{10};

R_4 is hydrogen, C_{1-4}alkyl, $R_{12}R_7N$-C_{0-4}alkyl or Cy_2-C_{0-4}alkyl, preferably hydrogen, C_{1-4}alkyl, -NR_7R_{12} or Cy_2; wherein Cy_2 are optionally substituted with one or more R_{11};

R_5 is hydrogen; and

R_6 is hydrogen, C_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl or $R_{12}R_7N$-C_{1-4}alkyl, preferably hydrogen or

2014201789 26 Mar 2014

C_{1-4}alkyl and more preferably hydrogen, methyl or ethyl.

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

A is nitrogen and B is carbon;

R_1 is hydrogen, halogen, –CN, $–OR_8$ or $–SR_8$, preferably hydrogen or –CN; and R_2 is hydrogen;

R_3 is R_9-C_{1-4}alkyl, Cy_1 or Cy_2-C_{1-4}alkyl, wherein Cy_1 and Cy_2 are optionally substituted with one or more R_{10};

R_4 is hydrogen, C_{1-4}alkyl, $R_{12}R_7N$-C_{0-4}alkyl or Cy_2-C_{0-4}alkyl, preferably hydrogen, C_{1-4}alkyl, $-NR_7R_{12}$ or Cy_2; wherein Cy_2 are optionally substituted with one or more R_{11};

R_5 is hydrogen; and

R_6 is hydrogen, C_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl or $R_{12}R_7N$-C_{1-4}alkyl, preferably hydrogen or C_{1-4}alkyl and more preferably hydrogen, methyl or ethyl.

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

A is nitrogen and B is carbon;

R_1 and R_2 are hydrogen;

R_3 is R_9-C_{1-4}alkyl, Cy_1 or Cy_2-C_{1-4}alkyl, wherein Cy_1 and Cy_2 are optionally substituted with one or more R_{10};

R_4 is hydrogen, C_{1-4}alkyl, $R_{12}R_7N$-C_{0-4}alkyl or Cy_2-C_{0-4}alkyl, preferably hydrogen, C_{1-4}alkyl, $-NR_7R_{12}$ or Cy_2; wherein Cy_2 are optionally substituted with one or more R_{11};

R_5 is hydrogen; and

R_6 is hydrogen, C_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl or $R_{12}R_7N$-C_{1-4}alkyl, preferably hydrogen or C_{1-4}alkyl and more preferably hydrogen, methyl or ethyl.

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

A is nitrogen and B is carbon;

R_1 is hydrogen, halogen, –CN, $–OR_8$ or $–SR_8$, preferably hydrogen or –CN; and R_2 is hydrogen;

R_3 is Cy_1, which is optionally substituted with one or more R_{10};

R_4 is hydrogen, C_{1-4}alkyl, $R_{12}R_7N$-C_{0-4}alkyl or Cy_2-C_{0-4}alkyl, preferably hydrogen, C_{1-4}alkyl, $-NR_7R_{12}$ or Cy_2; wherein Cy_2 are optionally substituted with one or more R_{11};

R_5 is hydrogen; and

R_6 is hydrogen, C_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl or $R_{12}R_7N$-C_{1-4}alkyl, preferably hydrogen or C_{1-4}alkyl and more preferably hydrogen, methyl or ethyl.

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

A is nitrogen and B is carbon;

R_1 is hydrogen, halogen, –CN, $–OR_8$ or $–SR_8$, preferably hydrogen or –CN; and R_2 is hydrogen;

R_3 is Cy_1, wherein Cy_1 in R_3 is a 3- to 7-membered monocyclic ring, which is saturated, partially unsaturated or aromatic, and which is carbocyclic or heterocyclic containing from 1 to 3 heteroatoms independently selected from N, S and O, wherein said ring is bonded to the rest of the molecule through any available C atom, and wherein one or more C or S ring atoms are optionally oxidized forming CO, SO or SO_2; and wherein said Cy_1 is optionally substituted with one or more R_{10};

R_4 is hydrogen, C_{1-4}alkyl, $R_{12}R_7N$-C_{0-4}alkyl or Cy_2-C_{0-4}alkyl, preferably hydrogen, C_{1-4}alkyl, $-NR_7R_{12}$ or Cy_2;

2014201789 26 Mar 2014

wherein Cy_2 are optionally substituted with one or more R_{11};

R_5 is hydrogen; and

R_6 is hydrogen, C_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl or $R_{12}R_7N$-C_{1-4}alkyl, preferably hydrogen or C_{1-4}alkyl and more preferably hydrogen, methyl or ethyl.

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

A is nitrogen and B is carbon;

R_1 is hydrogen, halogen, –CN, $-OR_8$ or $-SR_8$, preferably hydrogen or –CN; and R_2 is hydrogen;

R_3 is Cy_1, wherein Cy_1 in R_3 is a 3- to 7-membered, preferably 5- to 6-membered, saturated monocyclic ring, which is carbocyclic or heterocyclic containing from 1 to 3 heteroatoms independently selected from N, S and O, wherein said ring is bonded to the rest of the molecule through any available C atom, and wherein one or more C or S ring atoms are optionally oxidized forming CO, SO or SO_2; and more preferably Cy_1 in R_3 is piperidinyl or pyrrolidinyl, even more preferably piperidin-3-yl or pyrrolidin-3-yl; wherein said Cy_1 is optionally substituted with one or more R_{10};

R_4 is hydrogen, C_{1-4}alkyl, $R_{12}R_7N$-C_{0-4}alkyl or Cy_2-C_{0-4}alkyl, preferably hydrogen, C_{1-4}alkyl, $-NR_7R_{12}$ or Cy_2; wherein Cy_2 are optionally substituted with one or more R_{11};

R_5 is hydrogen; and

R_6 is hydrogen, C_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl or $R_{12}R_7N$-C_{1-4}alkyl, preferably hydrogen or C_{1-4}alkyl and more preferably hydrogen, methyl or ethyl.

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

A is nitrogen and B is carbon;

R_1 is hydrogen, halogen, –CN, $-OR_8$ or $-SR_8$, preferably hydrogen or –CN; and R_2 is hydrogen;

R_3 is R_9-C_{1-4}alkyl, Cy_1 or Cy_2-C_{1-4}alkyl, wherein Cy_1 and Cy_2 are optionally substituted with one or more R_{10};

R_4 is hydrogen, C_{1-4}alkyl, $R_{12}R_7N$-C_{0-4}alkyl or Cy_2-C_{0-4}alkyl, preferably hydrogen, C_{1-4}alkyl, $-NR_7R_{12}$ or Cy_2; wherein Cy_2 is optionally substituted with one or more R_{11}; and

R_5 is hydrogen.

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

A is nitrogen and B is carbon;

R_1 and R_2 are hydrogen;

R_3 is R_9-C_{1-4}alkyl, Cy_1 or Cy_2-C_{1-4}alkyl, wherein Cy_1 and Cy_2 are optionally substituted with one or more R_{10};

R_4 is hydrogen, C_{1-4}alkyl, $R_{12}R_7N$-C_{0-4}alkyl or Cy_2-C_{0-4}alkyl, preferably hydrogen, C_{1-4}alkyl, $-NR_7R_{12}$ or Cy_2; wherein Cy_2 is optionally substituted with one or more R_{11}; and

R_5 is hydrogen.

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

A is nitrogen and B is carbon;

R_1 is hydrogen, halogen, –CN, $-OR_8$ or $-SR_8$, preferably hydrogen or –CN; and R_2 is hydrogen;

R_3 is Cy_1, which is optionally substituted with one or more R_{10};

R_4 is hydrogen, C_{1-4}alkyl, $R_{12}R_7N$-C_{0-4}alkyl or Cy_2-C_{0-4}alkyl, preferably hydrogen, C_{1-4}alkyl, $-NR_7R_{12}$ or Cy_2;

2014201789 26 Mar 2014

wherein Cy_2 is optionally substituted with one or more R_{11}; and

R_5 is hydrogen.

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

A is nitrogen and B is carbon;

R_1 is hydrogen, halogen, –CN, $–OR_8$ or $–SR_8$, preferably hydrogen or –CN; and R_2 is hydrogen;

R_3 is Cy_1, wherein Cy_1 in R_3 is a 3- to 7-membered monocyclic ring, which is saturated, partially unsaturated or aromatic, and which is carbocyclic or heterocyclic containing from 1 to 3 heteroatoms independently selected from N, S and O, wherein said ring is bonded to the rest of the molecule through any available C atom, and wherein one or more C or S ring atoms are optionally oxidized forming CO, SO or SO_2; and wherein said Cy_1 is optionally substituted with one or more R_{10};

R_4 is hydrogen, C_{1-4}alkyl, $R_{12}R_7N$-C_{0-4}alkyl or Cy_2-C_{0-4}alkyl, preferably hydrogen, C_{1-4}alkyl, $-NR_7R_{12}$ or Cy_2; wherein Cy_2 is optionally substituted with one or more R_{11}; and

R_5 is hydrogen.

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

A is nitrogen and B is carbon;

R_1 is hydrogen, halogen, –CN, $–OR_8$ or $–SR_8$, preferably hydrogen or –CN; and R_2 is hydrogen;

R_3 is Cy_1, wherein Cy_1 in R_3 is a 3- to 7-membered, preferably 5- to 6-membered, saturated monocyclic ring, which is carbocyclic or heterocyclic containing from 1 to 3 heteroatoms independently selected from N, S and O, wherein said ring is bonded to the rest of the molecule through any available C atom, and wherein one or more C or S ring atoms are optionally oxidized forming CO, SO or SO_2; and more preferably Cy_1 in R_3 is piperidinyl or pyrrolidinyl; wherein said Cy_1 is optionally substituted with one or more R_{10};

R_4 is hydrogen, C_{1-4}alkyl, $R_{12}R_7N$-C_{0-4}alkyl or Cy_2-C_{0-4}alkyl, preferably hydrogen, C_{1-4}alkyl, $-NR_7R_{12}$ or Cy_2; wherein Cy_2 is optionally substituted with one or more R_{11}; and

R_5 is hydrogen.

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

A is nitrogen and B is carbon;

R_1 is hydrogen, halogen, –CN, $–OR_8$ or $–SR_8$, preferably hydrogen or –CN; and R_2 is hydrogen;

R_3 is R_9-C_{1-4}alkyl, Cy_1 or Cy_2-C_{1-4}alkyl, wherein Cy_1 and Cy_2 are optionally substituted with one or more R_{10};

R_5 is hydrogen; and

R_6 is hydrogen, C_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl or NR_7R_{12}-C_{1-4}alkyl, preferably hydrogen or C_{1-4}alkyl, more preferably C_{1-4}alkyl and even more preferably methyl or ethyl.

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

A is nitrogen and B is carbon;

R_1 and R_2 are hydrogen;

R_3 is R_9-C_{1-4}alkyl, Cy_1 or Cy_2-C_{1-4}alkyl, wherein Cy_1 and Cy_2 are optionally substituted with one or more R_{10};

R_5 is hydrogen; and

R_6 is hydrogen, C_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl or NR_7R_{12}-C_{1-4}alkyl, preferably hydrogen or

2014201789 26 Mar 2014

C_{1-4}alkyl, more preferably C_{1-4}alkyl and even more preferably methyl or ethyl.

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

A is nitrogen and B is carbon;

R_1 is hydrogen, halogen, –CN, $–OR_8$ or $–SR_8$, preferably hydrogen or –CN, more preferably hydrogen; and R_2 is hydrogen;

R_3 is Cy_1, which is optionally substituted with one or more R_{10};

R_5 is hydrogen; and

R_6 is hydrogen, C_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl or NR_7R_{12}-C_{1-4}alkyl, preferably hydrogen or C_{1-4}alkyl, more preferably C_{1-4}alkyl and even more preferably methyl or ethyl.

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

A is nitrogen and B is carbon;

R_1 is hydrogen, halogen, –CN, $–OR_8$ or $–SR_8$, preferably hydrogen or –CN, more preferably hydrogen; and R_2 is hydrogen;

R_3 is Cy_1, wherein Cy_1 in R_3 is a 3- to 7-membered monocyclic ring, which is saturated, partially unsaturated or aromatic, and which is carbocyclic or heterocyclic containing from 1 to 3 heteroatoms independently selected from N, S and O, wherein said ring is bonded to the rest of the molecule through any available C atom, and wherein one or more C or S ring atoms are optionally oxidized forming CO, SO or SO_2; and wherein said Cy_1 is optionally substituted with one or more R_{10};

R_5 is hydrogen; and

R_6 is hydrogen, C_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl or NR_7R_{12}-C_{1-4}alkyl, preferably hydrogen or C_{1-4}alkyl, more preferably C_{1-4}alkyl and even more preferably methyl or ethyl.

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

A is nitrogen and B is carbon;

R_1 is hydrogen, halogen, –CN, $–OR_8$ or $–SR_8$, preferably hydrogen or –CN; and R_2 is hydrogen;

R_3 is Cy_1, wherein Cy_1 in R_3 is a 3- to 7-membered, preferably 5- to 6-membered, saturated monocyclic ring, which is carbocyclic or heterocyclic containing from 1 to 3 heteroatoms independently selected from N, S and O, wherein said ring is bonded to the rest of the molecule through any available C atom, and wherein one or more C or S ring atoms are optionally oxidized forming CO, SO or SO_2; and more preferably Cy_1 in R_3 is piperidinyl or pyrrolidinyl, even more preferably piperidin-3-yl or pyrrolidin-3-yl; wherein said Cy_1 is optionally substituted with one or more R_{10};

R_5 is hydrogen; and

R_6 is hydrogen, C_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl or NR_7R_{12}-C_{1-4}alkyl, preferably hydrogen or C_{1-4}alkyl, more preferably C_{1-4}alkyl, and even more preferably methyl or ethyl.

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

A is nitrogen and B is carbon;

R_1 is hydrogen or –CN, preferably hydrogen; and R_2 is hydrogen;

R_3 is a cycle of formula Cy_{1a} or Cy_{1b};

2014201789 26 Mar 2014

R_5 is hydrogen; and

R_6 is hydrogen, C_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl, $R_{12}R_7N$-C_{1-4}alkyl, $R_{16}CO$-C_{0-4}alkyl or $R_{16}CO_2$-C_{0-4}alkyl, preferably C_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl, $R_{12}R_7N$-C_{1-4}alkyl, $R_{16}CO$-C_{0-4}alkyl or $R_{16}CO_2$-C_{0-4}alkyl, more preferably C_{1-4}alkyl, and even more preferably methyl or ethyl.

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

A is nitrogen and B is carbon;

R_1 is hydrogen or –CN, preferably hydrogen; and R_2 is hydrogen;

R_3 is a cycle of formula Cy_{1a}, preferably with (S)-stereochemistry;

R_5 is hydrogen; and

R_6 is hydrogen, C_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl, $R_{12}R_7N$-C_{1-4}alkyl, $R_{16}CO$-C_{0-4}alkyl or $R_{16}CO_2$-C_{0-4}alkyl, preferably C_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl, $R_{12}R_7N$-C_{1-4}alkyl, $R_{16}CO$-C_{0-4}alkyl or $R_{16}CO_2$-C_{0-4}alkyl, more preferably C_{1-4}alkyl, and even more preferably methyl or ethyl.

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

R_3 is a cycle of formula Cy_{1a} or Cy_{1b};

R_5 is hydrogen;

R_{10} is -COR_{13} or –SO_2R_{13} and

R_{13} is C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl or cyanoC_{1-4}alkyl, preferably C_{1-4}alkyl or cyanoC_{1-4}alkyl, and more preferably methyl or cyanomethyl.

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

R_3 is a cycle of formula Cy_{1a}, preferably with (S)-stereochemistry;

R_5 is hydrogen;

R_{10} is -COR_{13}; and

R_{13} is C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl or cyanoC_{1-4}alkyl, preferably C_{1-4}alkyl or cyanoC_{1-4}alkyl, and more preferably methyl or cyanomethyl.

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

W is CH;

R_3 is a cycle of formula Cy_{1a} , preferably with (S)-stereochemistry;

R_5 is hydrogen;

R_{10} is -COR_{13}; and

R_{13} is C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl or cyanoC_{1-4}alkyl, preferably C_{1-4}alkyl or cyanoC_{1-4}alkyl, and more preferably methyl or cyanomethyl.

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

W is N;

R_3 is a cycle of formula Cy_{1a}, preferably with (S)-stereochemistry;

R_5 is hydrogen;

R_{10} is -COR_{13}; and

R_{13} is C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl or cyanoC_{1-4}alkyl, preferably C_{1-4}alkyl or

2014201789 26 Mar 2014

cyanoC_{1-4}alkyl, and more preferably methyl or cyanomethyl.

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

A is nitrogen and B is carbon;

R_1 is hydrogen or –CN, preferably hydrogen; and R_2 is hydrogen;

R_3 is a cycle of formula Cy_{1a}, preferably with (S)-stereochemistry;

R_5 is hydrogen; and

R_{10} is -COR_{13}.

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

A is nitrogen and B is carbon;

R_1 is hydrogen or –CN, preferably hydrogen; and R_2 is hydrogen;

R_3 is a cycle of formula Cy_{1a}, preferably with (S)-stereochemistry;

R_5 is hydrogen;

R_{10} is -COR_{13}; and

R_{13} is C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl or cyanoC_{1-4}alkyl, preferably C_{1-4}alkyl or cyanoC_{1-4}alkyl, and more preferably methyl or cyanomethyl.

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

R_3 is a cycle of formula Cy_{1a} or Cy_{1b};

R_5 is hydrogen;

R_6 is hydrogen, C_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl, $R_{12}R_7N$-C_{1-4}alkyl, $R_{16}CO$-C_{0-4}alkyl or $R_{16}CO_2$-C_{0-4}alkyl, preferably C_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl, $R_{12}R_7N$-C_{1-4}alkyl, $R_{16}CO$-C_{0-4}alkyl or $R_{16}CO_2$-C_{0-4}alkyl, more preferably C_{1-4}alkyl, and even more preferably methyl or ethyl;

R_{10} is -COR_{13} or –SO_2R_{13}; and

R_{13} is C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl or cyanoC_{1-4}alkyl, preferably C_{1-4}alkyl or cyanoC_{1-4}alkyl, and more preferably methyl or cyanomethyl.

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

R_3 is a cycle of formula Cy_{1a}, preferably with (S)-stereochemistry;

R_5 is hydrogen;

R_6 is hydrogen, C_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl, $R_{12}R_7N$-C_{1-4}alkyl, $R_{16}CO$-C_{0-4}alkyl or $R_{16}CO_2$-C_{0-4}alkyl, preferably C_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl, $R_{12}R_7N$-C_{1-4}alkyl, $R_{16}CO$-C_{0-4}alkyl or $R_{16}CO_2$-C_{0-4}alkyl, more preferably C_{1-4}alkyl, and even more preferably methyl or ethyl;

R_{10} is -COR_{13}; and

R_{13} is C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl or cyanoC_{1-4}alkyl, preferably C_{1-4}alkyl or cyanoC_{1-4}alkyl, and more preferably methyl or cyanomethyl.

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

A is nitrogen and B is carbon;

R_1 is hydrogen or –CN, preferably hydrogen; and R_2 is hydrogen;

R_3 is a cycle of formula Cy_{1a} or Cy_{1b};

2014201789 26 Mar 2014

R_5 is hydrogen;

R_6 is hydrogen, C_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl, $R_{12}R_7N$-C_{1-4}alkyl, $R_{16}CO$-C_{0-4}alkyl or $R_{16}CO_2$-C_{0-4}alkyl, preferably C_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl, $R_{12}R_7N$-C_{1-4}alkyl, $R_{16}CO$-C_{0-4}alkyl or $R_{16}CO_2$-C_{0-4}alkyl, more preferably C_{1-4}alkyl, and even more preferably methyl or ethyl; and

R_{10} is -COR_{13} or –SO_2R_{13}.

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

A is nitrogen and B is carbon;

R_1 is hydrogen or –CN, preferably hydrogen; and R_2 is hydrogen;

R_3 is a cycle of formula Cy_{1a}, preferably with (S)-stereochemistry;

R_5 is hydrogen;

R_6 is hydrogen, C_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl, $R_{12}R_7N$-C_{1-4}alkyl, $R_{16}CO$-C_{0-4}alkyl or $R_{16}CO_2$-C_{0-4}alkyl, preferably C_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl, $R_{12}R_7N$-C_{1-4}alkyl, $R_{16}CO$-C_{0-4}alkyl or $R_{16}CO_2$-C_{0-4}alkyl, more preferably C_{1-4}alkyl, and even more preferably methyl or ethyl;

R_{10} is -COR_{13}; and

R_{13} is C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl or cyanoC_{1-4}alkyl, preferably C_{1-4}alkyl or cyanoC_{1-4}alkyl, and more preferably methyl or cyanomethyl.

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

A is nitrogen and B is carbon;

W is CH;

R_1 is hydrogen or –CN, preferably hydrogen; and R_2 is hydrogen;

R_3 is a cycle of formula Cy_{1a}, preferably with (S)-stereochemistry;

R_5 is hydrogen;

R_6 is hydrogen, C_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl, $R_{12}R_7N$-C_{1-4}alkyl, $R_{16}CO$-C_{0-4}alkyl or $R_{16}CO_2$-C_{0-4}alkyl, preferably C_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl, $R_{12}R_7N$-C_{1-4}alkyl, $R_{16}CO$-C_{0-4}alkyl or $R_{16}CO_2$-C_{0-4}alkyl, more preferably C_{1-4}alkyl, and even more preferably methyl or ethyl;

R_{10} is -COR_{13}; and

R_{13} is C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl or cyanoC_{1-4}alkyl, preferably C_{1-4}alkyl or cyanoC_{1-4}alkyl and more preferably methyl or cyanomethyl.

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

A is nitrogen and B is carbon;

W is N;

R_1 is hydrogen or –CN, preferably hydrogen; and R_2 is hydrogen;

R_3 is a cycle of formula Cy_{1a}, preferably with (S)-stereochemistry;

R_5 is hydrogen;

R_6 is hydrogen, C_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl, $R_{12}R_7N$-C_{1-4}alkyl, $R_{16}CO$-C_{0-4}alkyl or $R_{16}CO_2$-C_{0-4}alkyl, preferably C_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl, $R_{12}R_7N$-C_{1-4}alkyl, $R_{16}CO$-C_{0-4}alkyl or $R_{16}CO_2$-C_{0-4}alkyl, more preferably C_{1-4}alkyl, and even more preferably methyl or ethyl;

2014201789 26 Mar 2014

R_{10} is -COR_{13}; and

R_{13} is C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl or cyanoC_{1-4}alkyl, preferably C_{1-4}alkyl or cyanoC_{1-4}alkyl, and more preferably methyl or cyanomethyl.

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

A is nitrogen and B is carbon;

R_1 is hydrogen or –CN, preferably hydrogen; and R_2 is hydrogen;

R_3 is a cycle of formula Cy_{1a}, preferably with the (S)-stereochemistry;

R_5 is hydrogen;

R_6 is C_{1-4}alkyl, preferably methyl or ethyl;

R_{10} is -COR_{13}; and

R_{13} is C_{1-4}alkyl or cyanoC_{1-4}alkyl, preferably methyl or cyanomethyl.

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

A is nitrogen and B is carbon;

W is CH;

R_1 is hydrogen or –CN, preferably hydrogen; and R_2 is hydrogen;

R_3 is a cycle of formula Cy_{1a}, preferably with the (S)-stereochemistry;

R_5 is hydrogen;

R_6 is C_{1-4}alkyl, preferably methyl or ethyl;

R_{10} is -COR_{13}; and

R_{13} is C_{1-4}alkyl or cyanoC_{1-4}alkyl, preferably methyl or cyanomethyl.

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

A is nitrogen and B is carbon;

W is N;

R_1 is hydrogen or –CN, preferably hydrogen; and R_2 is hydrogen;

R_3 is a cycle of formula Cy_{1a}, preferably with the (S)-stereochemistry;

R_5 is hydrogen;

R_6 is C_{1-4}alkyl, preferably methyl or ethyl;

R_{10} is -COR_{13}; and

R_{13} is C_{1-4}alkyl or cyanoC_{1-4}alkyl, preferably methyl or cyanomethyl.

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

A is nitrogen and B is carbon;

R_1 is hydrogen and R_2 is hydrogen;

R_3 is a cycle of formula Cy_{1a} with the (S)-stereochemistry;

R_5 is hydrogen;

R_6 is C_{1-4}alkyl, preferably methyl or ethyl;

R_{10} is -COR_{13}; and

R_{13} is C_{1-4}alkyl or cyanoC_{1-4}alkyl, preferably methyl or cyanomethyl.

2014201789 26 Mar 2014

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

A is nitrogen and B is carbon;

R_1 is hydrogen or –CN, preferably hydrogen; and R_2 is hydrogen;

R_3 is a cycle of formula Cy_{1b};

R_5 is hydrogen;

R_6 is C_{1-4}alkyl, preferably methyl or ethyl; and

R_{10} is $-SO_2R_{13}$.

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

In another embodiment, the invention relates to a compound of formula I or II selected from the list of compounds described in examples 1 to 37.

In another embodiment, the invention relates to a compound of formula I or II that 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 38.

In an additional embodiment, the invention relates to a compound according to formula I or II that provides more than 50% inhibition of JAK2 activity at 10 μM, more preferably at 1 μM and still more preferably at 0.1 μM, in a JAK2 assay such as the one described in example 39.

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.

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

The salts of a compound of formula I or II 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 or II with a sufficient amount of the desired acid or base to give the salt in the conventional manner. The salts of the compounds of formula I or II can be converted into other salts of the compounds of formula I or II by ion exchange using ionic exchange resins.

The compounds of formula I or II and their salts may differ in some physical properties but they are

2014201789 26 Mar 2014

equivalent for the purposes of the present invention. All salts of the compounds of formula I or II are included within the scope of the invention.

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

The compounds of formula I or II 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 or II, including all polymorphic forms ("polymorphs") thereof, are included within the scope of the invention.

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

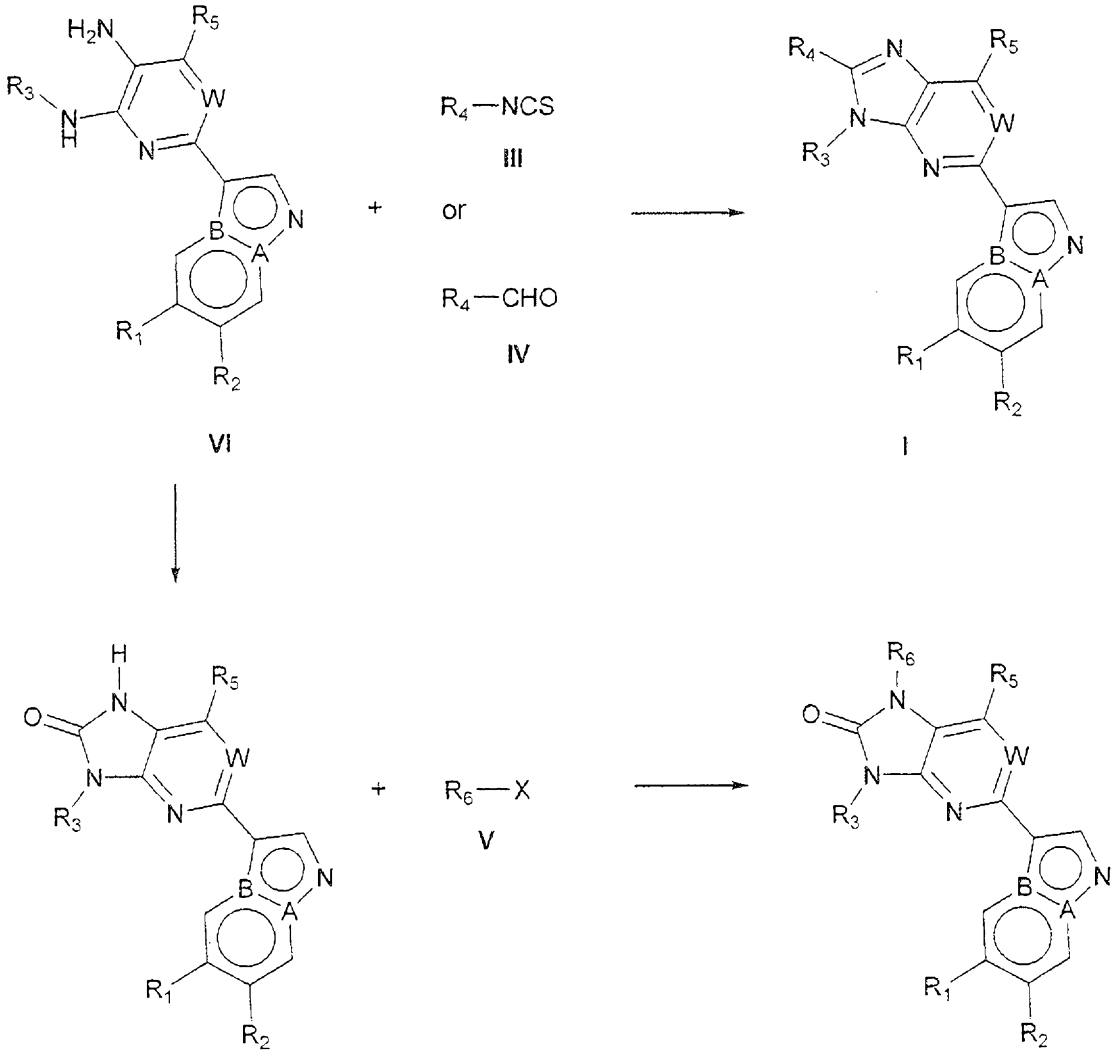
The present invention further covers all unlabeled and isotopically labeled forms of the compounds of formula I or II.

The present invention further covers all tautomeric forms of the compounds of formula I or II.

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

In general, compounds of formula I or II can be obtained from a compound of formula VI, as shown in the following scheme:

20142017789 26 Mar 2014



IIa (II, wherein R_6 is H) **IIb** (II, wherein R_6 is different from H)

wherein A, B, W, R_1, R_2, R_3, R_4 and R_5 have the meaning previously described in relation with a compound of formula I or II; R_6 in a compound of formula V or **IIb** has the meaning previously described in relation with a compound of formula I or II, except hydrogen; and X is a leaving group.

The compounds of formula I can be obtained by reacting a compound of formula VI with either the corresponding isothiocyanate III or aldehyde IV.

The reaction with an isothiocyanate III may be performed in the presence of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide, in a suitable solvent such as dichloromethane, and heating at a suitable temperature usually comprised between 100 and 200 °C. The heating may be thermal or by irradiating with microwaves at a wattage that allows reaching the temperature mentioned above.

The reaction between compounds of formula VI and IV can be carried out in a suitable solvent such as ethanol, butanol, *N*,*N*-dimethylformamide or dimethylacetamide, in the presence of an acid such as acetic acid, *p*-toluenesulfonic acid or sodium bisulfite, and heating, preferably at a temperature comprised between 100 and 200 °C. The heating may be thermal or by irradiating with microwaves at a wattage that allows reaching the temperature mentioned above. When required, the reaction can be completed by subsequent addition of water.

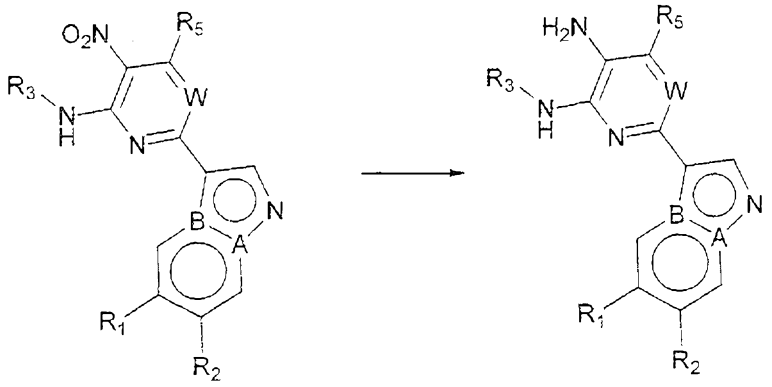
2014201789 26 Mar 2014

The compounds of formula **II** (i.e. compounds of formula **IIa** and **IIb**) can be obtained from a compound of formula **VI**.

The compounds of formula **IIa** (i.e. a compound of formula **II** wherein R_6 is hydrogen) can be obtained by reaction of a compound of formula **VI** with a synthetic equivalent for the CO synthon. Any such synthetic equivalent disclosed in the literature can in principle be used, for example 1,1'-carbonyldiimidazole (CDI), phosgene, diphosgene or triphosgene. The reaction is conducted in the presence of a base such as *N,N*-diisopropylethylamine; and in a suitable solvent such as tetrahydrofuran (THF), and preferably at room temperature. The reaction can be completed by subsequent addition of water.

The compounds of formula **IIb** (i.e. a compound of formula **II** wherein R_6 is different from hydrogen) can be obtained by alkylation of a compound of formula **IIa** with an alkylating agent R_6-X (**V**), wherein X represents a leaving group and R_6 is different from H; suitable examples of X include among others halogen such as Cl, Br or I, mesylate, tosylate or triflate. This reaction may be carried out in the presence of a base such as Cs_2CO_3, K_2CO_3, NaOH, *tert*-BuOK or NaH, in a suitable solvent, such as acetone, toluene, 1,2-dimethoxyethane, and preferably dimethylformamide, at a suitable temperature, comprised between 0 °C and reflux.

The compounds of formula **VI** can be obtained by reduction of a compound of formula **VII** as shown in the following scheme:



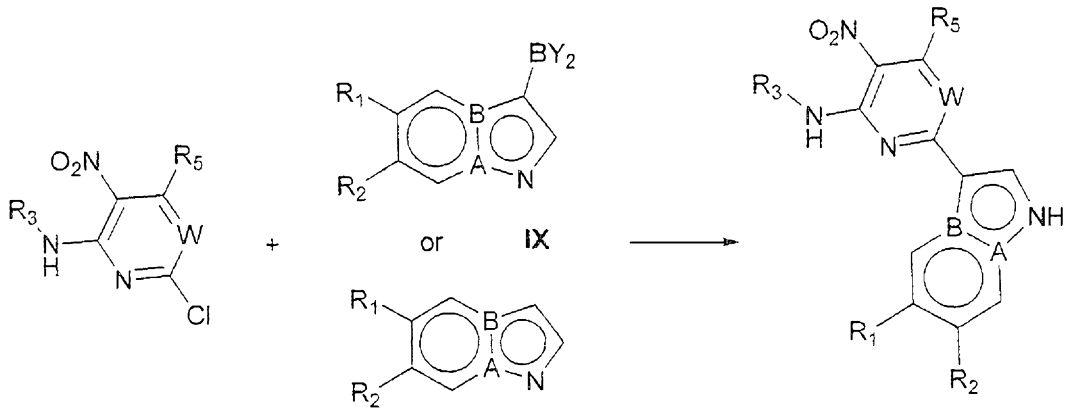
VII **VI**

wherein A, B, W, R_1, R_2, R_3 and R_5 have the meaning previously described in relation with a compound of formula **I** or **II**.

The reaction may be carried out with hydrogen gas, using a platinum catalyst, such as Pt/C in the presence of thiophene in diisopropylethylamine; in a suitable solvent such as EtOH and preferably at room temperature.

The compounds of formula **VII** can be obtained by reacting a compound of formula **VIII** with either a compound of formula **IX** or **X**, as shown in the following scheme:

2014201789 26 Mar 2014



VIII X VII

wherein A, B, W, R_1, R_2, R_3 and R_5 has the meaning previously described in relation with a compound of formula I or II; and BY_2 is a boronic acid or ester.

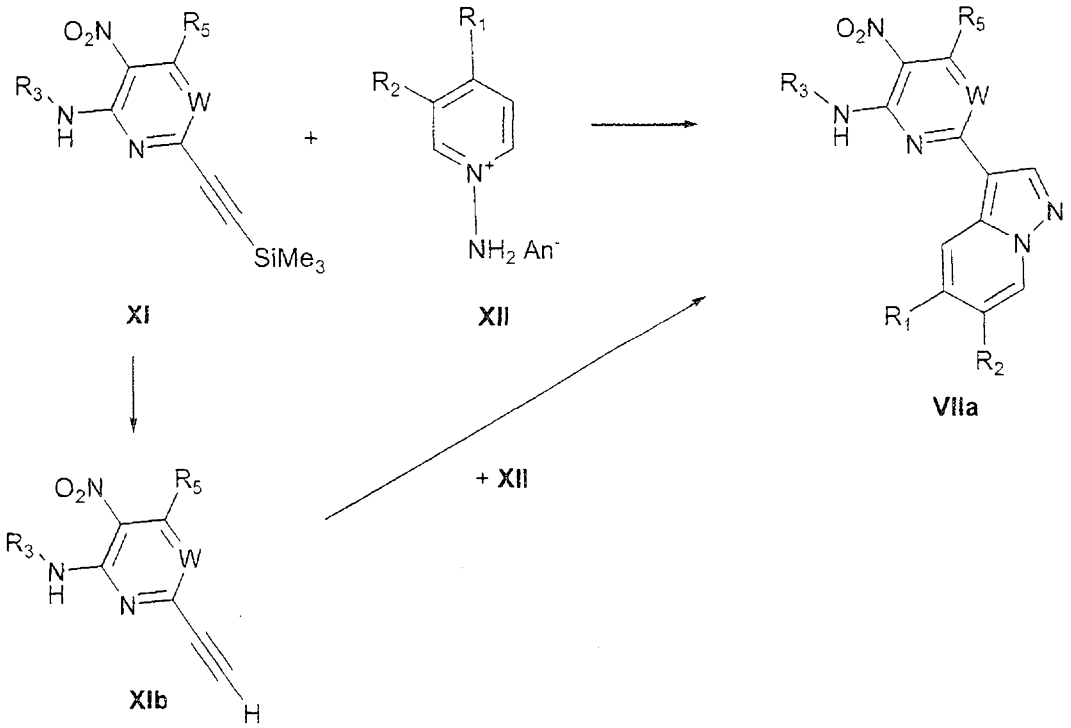
The reaction between compounds of formula VIII and IX may be carried out using the conditions described in the literature for Suzuki's coupling reactions. For example, the reaction may be carried out in the presence of a Pd catalyst such as $Pd(PPh_3)_4$; in the presence of a base such as Na_2CO_3; in a mixture of solvents such as a dimethoxyethane and water; and heating.

The direct coupling between compounds of formula VIII and X can be performed using a palladium catalyst such as for example tetrakis (triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$) and preferably paladium (II) acetate $Pd(OAc)_2$ in the presence of triphenylphosphine, and a base, such as for example triethylamine and preferably potassium acetate. The reaction is usually carried out under anhydrous and anaerobic conditions. The reaction may be carried out in a solvent such as dioxane, *N,N*-dimethylformamide, toluene and preferably in dimethylacetamide and heating at a temperature usually comprised between 60°C-100°C.

Compounds of formula IX and formula X can be easily obtained from commercial compounds by known methods.

Additionaly, the compounds of formula VII wherein A is nitrogen and B is carbon (i.e. VIIa) can be obtained by reacting a compound of formula XI with a compound of formula XII, as shown in the following scheme:

20142014789 26 Mar 2014

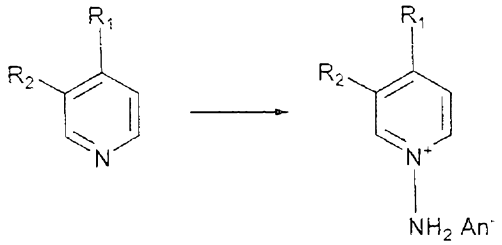


wherein W, R_1, R_2, R_3 and R_5 have the meaning previously described in relation with a compound of formula I or II; and An is iodine, 2,4-dinitrophenolate, p-toluensulphonate or 2,4,6-trimethylbencenosulphonate.

The reaction may be carried out in the presence of tetra-*n*-butylammonium fluoride (TBAF) in THF and of a base such as 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) or 1,4-diazabicyclo[2.2.2]octane (DABCO), preferably 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), in a solvent such as N,N-dimethylformamide, dimethylsulfoxide, dichloromethane, toluene or acetonitrile, preferably acetonitrile, and at a temperature comprised between -78 °C and room temperature.

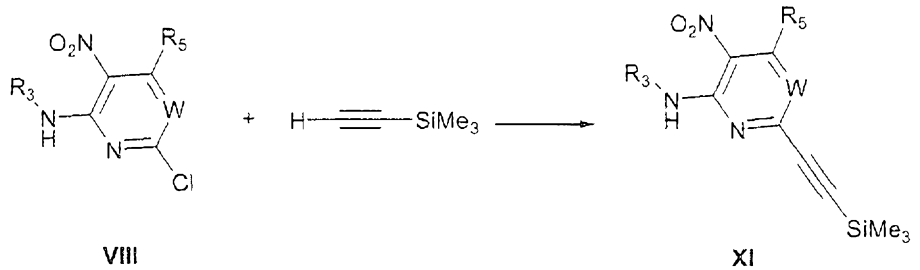
Alternatively the compounds of formula **VIIa** can be obtained by reacting a compound of formula **XII** with the deprotected derivative of the compound of formula **XI** (**XIb**) obtained by using standard conditions.

The compounds of formula **XII** can be obtained by reaction of a compound of formula **XIII** with aminosulfonic acid in the presence of a HI aqueous solution; and of a base such as K_2CO_3, NaOH or KOH; in a solvent such as dichloromethane, tetrahydrofuran, water, ethanol, methanol, isopropanol or acetonitrile; and heating preferably at reflux, as shown in the following scheme:



wherein R_1 and R_2 have the meaning previously described in relation with a compound of formula I or II; and An has the meaning described above.

The compounds of formula XI can be obtained by reaction of a compound of formula VIII with trimethylsilylacetylene, as shown in the following scheme:

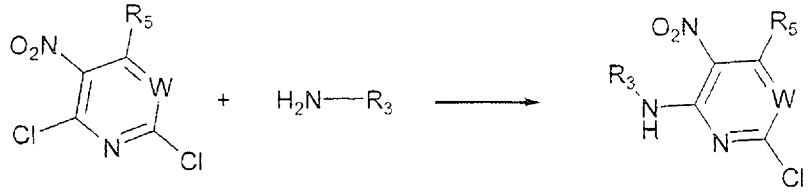


VIII XI

wherein W, R_3 and R_5 have the meaning previously described in relation with a compound of formula I or II.

The reaction with trimethylsilylacetylene may be carried out under Sonogashira conditions, using a palladium catalyst such as for example tetrakis (triphenylphosphino)palladium(0) ($Pd(PPh_3)_4$), preferably bis(triphenylphosphino)dichloropalladium(II) ($Pd(Ph_3P)_2Cl_2$) in the presence of triphenylphospine, a Cu (I) catalyst as a cocatalyst, such as CuI, and a base, such as diethylamine, *N,N*-diisopropylethylamine, triethylamine or isopropylethylamine. The reaction is usually carried out under anhydrous and anaerobic conditions. The reaction may be carried out in a solvent such as dioxane, *N,N*-dimethylformamide, tetrahydrofuran or toluene, at room temperature or by heating.

The compounds of formula VIII can be obtained by reaction of a compound of formula XIV with a compound of formula XV, as shown in the following scheme:



XIV XV VIII

wherein W, R_3 and R_5 have the meaning previously described in relation with a compound of formula I or II.

The reaction between the compounds of formula XIV and XV may be carried out in the presence of a base such as diisopropylethylamine, diethylamine or triethylamine, in a suitable solvent such as THF or acetonitrile, and at a temperature comprised between -78 °C and room temperature.

The compounds of formula XIV and XV are commercial or may be easily obtained from commercial compounds using standard procedures.

Furthermore, some compounds of the present invention can also be obtained from other compounds of formula I or II by appropriate conversion reactions of functional groups in one or several steps, using well-known reactions in organic chemistry under the standard experimental conditions. Said transformations can be carried out for example upon R_3 and include, for example the substitution of a primary or secondary amine by treatment with an alkylating agent, the reaction of an acid or ester with an amine to obtain the corresponding amide, the conversion of an amine into a sulfonamide and the hydrolysis of an ester to obtain a carboxylic acid. In some of these conversions it may be necessary or advisable to protect the reactive or unstable groups by means of conventional protective

groups.

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

As mentioned above, the compounds of the present invention act by inhibiting JAK/STAT signaling pathways, particularly by inhibiting JAK3 activity. Therefore, the compounds of the invention are expected to be useful to treat or prevent diseases in which JAKs, particularly JAK3, play a role in mammals, including human beings. These diseases include, but are not limited to, transplant rejection; immune, autoimmune and inflammatory diseases; neurodegenerative diseases; and proliferative disorders (see e.g. O'Shea J.J. et al, Nat. Rev. Drug. Discov. 2004, 3(7):555-64; Cetkovic-Cvrlje M. et al, Curr. Pharm. Des. 2004, 10(15):1767-84; Cetkovic-Cvrlje M. et al, Arch. Immunol. Ther. Exp. (Warsz), 2004, 52(2):69-82).

Acute or chronic transplant rejection reactions that can be treated or prevented with the compounds of the present invention include any kind of cell, tissue or organ xenotransplants or allografts, such as of heart, lung, liver, kidney, pancreas, uterus, joints, pancreatic islets, bone marrow, limbs, cornea, skin, hepatocytes, pancreatic beta cells, pluripotential cells, neuronal cells and myocardial cells, as well as graft-versus-host reactions (see e.g. Rousvoal G. et al, Transpl. Int. 2006, 19(12):1014-21; Borie DC. 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; Säemann MD. et al, Transpl Int. 2004, 17(9):481-89; Silva Jr HT. et al, Drugs 2006, 66(13):1665-1684).

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, mast cell-mediated allergic reactions such as asthma, angiodema, anaphylaxis, bronchitis, rhinitis and sinusitis, and inflammatory or autoimmune ocular diseases such as dry eye syndrome, glaucoma, Sjögren's syndrome, uveitis and retinopathy of prematurity (see e.g. Sorbera LA. 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 JG. et al, Ann. Rheum. Dis. 2006, 65(2):149-56; Milici AJ. et al, Arthritis Rheum .2006, 54 (9, Suppl): abstr 789; Kremer JM. 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, West K., Curr Opin Inventig Drugs 2009:10(5):491-504, Huang Y. et al., Exp Eye res 2007:85(5):684-95, Killedar SY et al ,Laboratory Investigation

2006:86:1243-1260, Egwuagu C.E., Cytokine 2009:47(3):149-156, Byfield G., Investigative Ophtalmology &Viral Science 2009:50:3360).

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

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 EA. et al, Clin. Cancer Res. 1999, 5(6):1569-82; Narla RK. et al, Clin. Cancer Res. 1998, 4(10):2463-71; Lin Q. et al, Am J. Pathol. 2005, 167(4):969-80; Tibbles HE. et al, J. Biol. Chem. 2001, 276(21):17815-22).

It has been found that certain compounds of formula I or II, besides inhibiting JAK3 activity, also inhibit JAK2 kinase to varying degrees, and therefore can also be useful for the treatment or prevention of any disease mediated by JAK2 kinase. A group of such JAK2-mediated diseases are myeloproliferative disorders, including polycythemia vera, essential thrombocytosis, idiopathic myelofibrosis, chronic myelogenous leukemia, hypereosinophilic syndrome, chronic neutrophilic leukemia, chronic myelomonocytic leukemia, myelofibrosis with myeloid metaplasia, chronic basophilic leukemia, chronic eosinophilic leukemia, systemic mastocytosis and myelodisplastic syndrome (see e.g. Geron I. et al, Cancer cell 2008, 13:321-330; Pardanani A. et al, Leukemia 2007, 21(8):1658-68; Mathur A. et al, Biochem Pharmacol 2009, 78(4):382-9; Manshouri T. et al, Cancer Sci. 2008, 99(6):1265-73; Wernig G. et al, Cancer cell 2008, 13(4):311-20. Elizabeth O. et al, Blood, 111(12: 5663-5671).

Compounds of formula I or II wherein R_1 and R_2 are hydrogen have been found to be particularly useful as JAK2 inhibitors, and thus can be particularly useful, in addition to treating or preventing all the diseases mentioned in the preceding paragraphs, also for the treatment or prevention of myeloproliferative disorders (MPD).

Thus, another aspect of the invention relates to a compound of formula I or II, or a pharmaceutically acceptable salt thereof for use in the treatment or prevention of a disease mediated by JAK2. More preferably, the disease mediated by JAK2 is a myeloproliferative disorder. In a preferred embodiment, the compounds of formula I or II are those wherein R_1 and R_2 are hydrogen.

Another aspect of the present invention relates to the use of a compound of formula I or II or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment or prevention of a disease mediated by JAK2. More preferably, the disease mediated by JAK2 is a myeloproliferative disorder. In a preferred embodiment, the compounds of formula I or II are those wherein R_1 and R_2 are hydrogen.

Another aspect of the present invention relates to a method of treating or preventing a disease mediated by JAK2 in a subject in need thereof, especially a human being, which comprises administering to said subject a compound of formula I or II, or a pharmaceutically acceptable salt thereof. More preferably, the disease mediated by JAK2 is a myeloproliferative disease. In a preferred embodiment, the compounds of formula I or II are those wherein R_1 and R_2 are hydrogen

Another aspect of the invention relates to a compound of formula I or II, or a pharmaceutically acceptable salt thereof for use in the treatment or prevention of a myeloproliferative disorder. In a preferred embodiment, the

2014201789 26 Mar 2014

myeloproliferative disorder is selected from polycythemia vera, essential thrombocytosis, idiopathic myelofibrosis, chronic myelogenous leukemia, hypereosinophilic syndrome, chronic neutrophilic leukemia, chronic myelomonocytic leukemia, myelofibrosis with myeloid metaplasia, chronic basophilic leukemia, chronic eosinophilic leukemia, systemic mastocytosis and myelodisplastic syndrome. In a preferred embodiment, the compounds of formula I or II are those wherein R_1 and R_2 are hydrogen.

Another aspect of the invention relates to the use of a compound of formula I or II or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment or prevention of a myeloproliferative disorder. In a preferred embodiment, the myeloproliferative disorder is selected from polycythemia vera, essential thrombocytosis, idiopathic myelofibrosis, chronic myelogenous leukemia, hypereosinophilic syndrome, chronic neutrophilic leukemia, chronic myelomonocytic leukemia, myelofibrosis with myeloid metaplasia, chronic basophilic leukemia, chronic eosinophilic leukemia, systemic mastocytosis and myelodisplastic syndrome. In a preferred embodiment, the compounds of formula I or II are those wherein R_1 and R_2 are hydrogen.

Another aspect of the present invention relates to a method of treating or preventing a myeloproliferative disorder in a subject in need thereof, especially a human being, which comprises administering to said subject a compound of formula I or II or a pharmaceutically acceptable salt thereof. In a preferred embodiment, the myeloproliferative disorder is selected from polycythemia vera, essential thrombocytosis, idiopathic myelofibrosis, chronic myelogenous leukemia, hypereosinophilic syndrome, chronic neutrophilic leukemia, chronic myelomonocytic leukemia, myelofibrosis with myeloid metaplasia, chronic basophilic leukemia, chronic eosinophilic leukemia, systemic mastocytosis and myelodisplastic syndrome. In a preferred embodiment, the compounds of formula I or II are those wherein R_1 and R_2 are hydrogen.

Biological assays that can be used to determine the ability of a compound to inhibit JAKs, particularly JAK3 and JAK2, are well known in the art. For example, a compound to be tested can be incubated in the presence of the desired JAK, such as JAK3 or JAK2, to determine whether inhibition of JAK enzymatic activity occurs, as described in the assay of examples 38 and 39 for JAK3 and JAK2, respectively. Other *in vitro* useful assays that can be used to measure JAK3-inhibitory activity include cellular assays, for example IL-2-induced proliferation of human T lymphocytes. The immunosuppressive activity of the compounds of the invention can be tested using standard *in vivo* animal models for immune and autoimmune diseases, which are well known in the art. For example, the following assays can be used: delayed-type hypersensitivity (DTH) (see e.g. the method disclosed in Kudlacz E. et al, Am J. Transplant. 2004, 4(1):51-7, the contents of which are incorporated herein by reference), rheumatoid arthritis models such as collagen-induced arthritis (see e.g. the method disclosed in 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 of transplant rejection, incorporated herein by reference). The antiproliferative activity of the compounds of the invention can be tested using standard *in vivo* animal models well known in the art, such as xenograft studies (see e.g Mohammad RH. et al, Pancreas. 1998; 16(1):19).

2014201789 26 Mar 2014

For selecting active compounds for JAK3, testing at 10 μM must result in an activity of more than 50% inhibition of JAK3 activity in the test provided in example 38. More preferably, when tested in this assay compounds should exhibit more than 50% inhibition at 1 μM, and still more preferably, they should exhibit more than 50% inhibition at 0.1 μM.

For selecting active compounds for JAK2, testing at 10 μM must result in an activity of more than 50% inhibition of JAK2 activity in the test provided in example 39 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.

Assays that can be used to predict the PK profile of a compound are well known in the art. For example, a Caco-2 assay can be used to determine *in vitro* the potential for oral absorption of a compound. To show a good PK profile the compound must also exhibit a suitable clearance, as determined in a standard test using for example human liver microsomes in an assay such as the one described in example 40.

Standard assays can be used to assess potential toxic effects of drug candidates, all of which are well known in the art. Such tests include e.g. viability assays in different cell lines such as human hepatocyte carcinoma cells (Hep G2), which can be performed following standard procedures.such as the one described in example 41.

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

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

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

2014201789 26 Mar 2014

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

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

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

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

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

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

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

The following examples illustrate the scope of the invention.

Examples

The following abbreviations have been used in the examples:

AcOH: acetic acid

AcN: acetonitrile

DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene

DIPEA: N,N-diisopropylethylamine

26 Mar 2014
2014201789

DMAC: N,N-dimethylacetamide

DMF: *N,N*-dimethylformamide

EDC: N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide

EtOAc: ethyl acetate

EtOH: ethanol

HATU: 2-(1H-7-Azabenzotriazol-1-yl)--1,1,3,3-tetramethyl uronium hexafluorophosphate Methanaminium

HOBt: 1-hydroxybenzotriazole

HPLC: high performance liquid chromatography

LC-MS: liquid chromatography-mass spectroscopy

MeI: iodomethane

MeOH: methanol

PTSA: para-toluene sulfonic acid

TBAF: tetrabutylammonium fluoride

TBME: *tert*-butyl methyl ether

TEA: triethylamine

TFA: trifluoroacetic acid

THF: tetrahydrofurane

TLC: thin layer cromatography

t_R: retention time

One of the following methods was used to determine the LC-MS spectrums:

Method 1: Column SunFire C18 3.5 µm, (100 mm x 2.1), flow rate: 0.3 mL/min, eluent A = CH3CN:MeOH 1:1 B = NH_4Ac 5 mM pH 7, gradient : 0 min 10 % A; 17 min 95 % A; 10 min 95 % A.

Method 2 : Column XBridge, 3.5 µm (50 mm x 4.6), temperature: 30 °C, flow rate: 2 mL/min, eluent A = NH_4HCO_3 10 mM (pH = 9), B = AcN, gradient: 0 min 5% B; 4.8 min 100% B;

Method 3 : Column XBridge, 3.5 µm (50 mm x 4.6), temperature: 50 °C, flow rate: 1.6 mL/min, eluent A = NH_4HCO_3 10 mM (pH = 9), B = AcN, gradient: 0 min 5% B; 3.5 min 1005% B;

Method 4 (Palau): Column Waters Acquity UPLC BEH C18 (1.7 µm, 2.1 mm x 50 mm), temperature: 40 °C, flow: 0.5 mL/min, eluent: ACN (A) / ammonium bicarbonate 10mM (B), gradient: 0 min 10% A – 3,75 min 90% A

Method 5 :: Column YMC, 3.5 µm (50 mm x 4.6), temperature: 50 °C, flow rate: 1.3 mL/min, eluent A =H_2O (0.1% HCOOH), B = AcN (0.1% HCOOH), gradient: 0 min 5% B; 3.5 min 100% B.

REFERENCE EXAMPLE 1

1-Amino-4-trifluoromethylpyridinium 2,4,6-trimethylbenzenesulfonate

To a solution of 4-trifluoromethylpyridine (2.23 g, 15.2 mmol) in CH_2Cl_2 (66 mL) at 0 °C, O-(mesitylsulfonyl)hydroxylamine (3.27 g, 15.2 mmol) was added. The reaction mixture was stirred at room temperature for 18 h. The reaction mixture was filtered to afford the desired product with quantitative yield.
LC-MS (method 4): t_R = 1.07 min; m/z = 199 (MH^+).

REFERENCE EXAMPLE 2

(S)-3-(4-(1-Acetylpiperidin-3-ylamino)-5-aminopyrimidin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile

Following a similar procedure to that described in example 1 (section a to d), but using (S)-1-acetyl-3-aminopiperidine instead of tetrahydro-2*H*-pyran-4-amine, the desired compound was obtained .
LC-MS (method 3): t_R = 1.59 min; m/z = 377 (MH^+).

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

Reference example	Name	Starting Materials	HPLC method	t_R (min)	m/z
2a	(S)-tert-butyl 3-(5-amino-2-(5-methylpyrazolo[1,5-a]pyridin-3-yl)pyrimidin-4-ylamino)piperidine-1-carboxylate	1-amino-4-methylpyridinium 2,4,6-trimethylbenzenesulfonate (1), ,(S)-3-amino-(1-tert-butoxycarbonyl)piperidine and 2,4-dichloro-5-nitropyrimidine	3	2.32	424
2b	tert-butyl 4-(5-amino-2-(pyrazolo[1,5-a]pyridin-3-yl)pyrimidin-4-ylamino)piperidine-1-carboxylate	1-aminopyridinium iodide,, 4-amino-(1-tert-butoxycarbonyl)piperidine and 2,4-dichloro-5-nitropyrimidine	4	2.00	410

2014201789 26 Mar 2014

2c	2-(pyrazolo[1,5-a]pyridin-3-yl)-N4-(tetrahydro-2H-pyran-4-yl)pyrimidine-4,5-diamine	1-aminopyridinium iodide, tetrahydro-2*H*-pyran-4-amine and 2,4-dichloro-5-nitropyrimidine	3	1.55	311
2d	(S)-tert-butyl 3-(3-amino-6-(pyrazolo[1,5-a]pyridin-3-yl)pyridin-2-ylamino)piperidine-1-carboxylate	1-aminopyridinium iodide , (S)-3-amino-(1-tert-butoxycarbonyl)piperidine and 2,6-dichloro-3-nitropyridine	3	2.43	409
2e	3-(5-amino-4-(8-fluorochroman-4-ylamino)pyrimidin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	1-amino-4-cyanopyridinium 2,4,6-trimethylbenzenesulfonate, 8-fluorochroman-4-amine and 2,4-dichloro-5-nitropyrimidine	1	9.28	402
2f	(S)-3-(6-(1-acetylpiperidin-3-ylamino)-5-aminopyridin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	1-amino-4-cyanopyridinium 2,4,6-trimethylbenzenesulfonate, (S)-1-acetyl-3-aminopiperidin and 2,6-dichloro-3-nitropyridine	3	1.58	377
2g	6-(pyrazolo[1,5-a]pyridin-3-yl)-N2-(tetrahydro-2H-pyran-4-yl)pyridine-2,3-diamine	1-aminopyridinium iodide, tetrahydro-2*H*-pyran-4-amine and 2,6-dichloro-3-nitropyridine	5	1.68	310

2014201789 26 Mar 2014

2h	(S)-tert-butyl 3-(3-amino-6-(5-cyanopyrazolo[1,5-a]pyridin-3-yl)pyridin-2-ylamino)piperidine-1-carboxylate	1-amino-4-cyanopyridinium 2,4,6-trimethylbenzenesulfonate, (S)-3-amino-(1-tert-butoxycarbonyl)piperidine and 2,6-dichloro-3-nitropyridine	3	2.50	434
2i	3-(5-amino-4-(*trans*-4-hydroxycyclohexylamino)pyrimidin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	1-amino-4-cyanopyridinium 2,4,6-trimethylbenzenesulfonate, *trans*-4-aminocyclohexanol and 2,6-dichloro-3-nitropyridine,	3	1.45	350

(1) described by Zhang et al Journal of Heterocyclic Chemistry; 44; 4; 2007; 919-922

EXAMPLE 1

3-(8-Oxo-9-tetrahydro-2*H*-pyran-4-yl-8,9-dihydro-7*H*-purin-2-yl)pyrazolo[1,5-*a*]pyridine-5-carbonitrile

a) 2-Chloro-5-nitro-*N*-tetrahydro-2*H*-pyran-4-ylpyrimidin-4-amine

To a solution of 2,4-dichloro-5-nitropyrimidine (1.03 g, 5.15 mmol) in THF (40 mL) at -78 °C, DIPEA (2.0 mL, 11.86 mmol) and tetrahydro-2*H*-pyran-4-amine (0.54 mL, 5.15 mmol) were added. The reaction mixture was stirred from -78 to -50 °C for 5 h. The crude mixture was quenched with H_2O (50 mL), extracted with EtOAc (3x40 mL) and the combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product thus obtained was chromatographed over silica gel using EtOAc/hexanes mixtures of increasing polarity as eluent, to afford 1.04 g of the desired compound (78% yield).

b) 5-Nitro-*N*-(tetrahydro-2*H*-pyran-4-yl)-2-[(trimethylsilyl)ethynyl]pyrimidin-4-amine

To a suspension of the compound obtained in the previous section (1.01 g, 3.90 mmol), $Pd(PPh_3)_2Cl_2$ (137 mg, 0.19 mmol) and CuI (37 mg, 0.19 mmol) in toluene (40 mL), TEA (1.6 mL, 11.7 mmol) and trimethylsilylacetylene (0.7 mL, 5.07 mmol) were added. The reaction mixture was stirred at room temperature for 18 h, quenched with saturated NH_4Cl aqueous solution (70 mL) and extracted with EtOAc (3x40 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated. The crude residue was cromatographed on a silica gel flash system (SP1 Biotage) using EtOAc/hexanes mixtures of increasing polarity as eluent to afford 0.96 g of the desired product (77% yield).

c) 3-[5-Nitro-4-(tetrahydro-2*H*-pyran-4-ylamino)pyrimidin-2-yl]pyrazolo[1,5-*a*]pyridine-5-carbonitrile

To a suspension of the compound obtained in the previous section (500 mg, 1.56 mmol) and 1-amino-4-cyanopyridinium 2,4,6-trimethylbenzenesulfonate (498 mg, 1.56 mmol) in AcN (30 mL), at 0 °C, 1 M TBAF solution in THF (1.56 mL, 1.56 mmol) and a solution of DBU (0.47 mL, 3.12 mmol) in AcN (10 mL) were added. The reaction mixture was stirred at 0 °C for 5 min and 3 h at room temperature. The reaction mixture was evaporated to dryness. The crude product thus obtained was chromatographed over silica gel using EtOAc/hexanes mixtures of increasing polarity as eluent, to afford 227 mg of the desired compound (48% yield).

d) 3-[5-Amino-4-(tetrahydro-2*H*-pyran-4-ylamino)pyrimidin-2-yl]pyrazolo[1,5-*a*]pyridine-5-carbonitrile

A mixture of the compound obtained in the previous section (119 mg, 0.32 mmol) in EtOH (12 mL) was hydrogenated with Pt/C 5% (149 mg, 0.02 mmol) as a catalyst in the presence of thiophene in DIPEA (4%v/v, 9 drops). The reaction mixture was stirred under H_2 (g) atmosphere at room temperature for 1.5 h. The reaction mixture was filtered through a plug of Celite® and the solvent was concentrated off to afford 78 mg of the desired product (71% yield).

e) 3-(8-Oxo-9-tetrahydro-2*H*-pyran-4-yl-8,9-dihydro-7*H*-purin-2-yl)pyrazolo[1,5-*a*]pyridine-5-carbonitrile

To a solution of the compound obtained in the previous section (78 mg, 0.23 mmol) in THF (7 mL), 1,1´-carbonyldiimidazole (188 mg, 1.16 mmol) was added. The reaction mixture was stirred at room temperature for 4 h, quenched with saturated NaCl aqueous solution (15 mL) and extracted with EtOAc (3x15 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product thus obtained was chromatographed over silica gel using MeOH/CH_2Cl_2 mixtures of increasing polarity as eluent, to afford 5.1 mg of the desired compound (61% yield).

LC-MS (method 1): t_R = 14.25 min; m/z = 362 (MH^+).

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

Example	Name	Starting Material	HPLC method	t_R (min)	m/z
1a	methyl (2*R*)-2-[2-(5-cyanopyrazolo[1,5-*a*]pyridin-3-yl)-8-oxo-7,8-dihydro-9*H*-purin-9-yl]propanoate	D-alanine methyl ester hydrochloride	1	14.48	364

2014201789 26 Mar 2014

1b	(*S*)-*tert*-butyl 3-(2-(5-cyanopyrazolo[1,5-a]pyridin-3-yl)-8-oxo-7*H*-purin-9(8H)-yl)piperidine-1-carboxylate	(*S*)-*tert*-butyl 3-aminopiperidine-1-carboxylate	2	2.23	461
1c	(*R*)-*tert*-butyl 3-(2-(5-cyanopyrazolo[1,5-a]pyridin-3-yl)-8-oxo-7H-purin-9(8H)-yl)piperidine-1-carboxylate	(*R*)-*tert*-butyl 3-aminopiperidine-1-carboxylate	2	2.23	461
1d	(*S*)-3-(9-(1-methoxypropan-2-yl)-8-oxo-8,9-dihydro-7H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	(*S*)-1-methoxypropan-2-amine	2	1.82	350
1e	3-(9-(4,4-difluorocyclohexyl)-8-oxo-8,9-dihydro-7H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	4,4-difluorocyclohexanamine	2	2.03	396
1f	3-(9-(1,1-dioxotetrahydrothien-3-yl)-8-oxo-8,9-dihydro-7H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	3-amino-1,1-dioxotetrahydrothiophene	2	1.43	396
1g	3-(9-(2-fluorobenzyl)-8-oxo-8,9-dihydro-7H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	2-fluorobenzylamine	1	16.58	386
1h	3-(9-(4-methoxybut-1-yl)-8-oxo-8,9-dihydro-7H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	4-methoxybutan-1-amine	1	15.15	396
1i	methyl (2*S*)-2-[2-(5-cyanopyrazolo[1,5-a]pyridin-3-yl)-8-oxo-7,8-dihydro-9*H*-purin-9-yl]propanoate	L-alanine methyl ester hydrochloride	3	1.83	436
1j	9-(1-acetylpiperidin-4-yl)-2-(5-(trifluoromethyl)pyrazolo[1,5-a]pyridin-3-yl)-7H-purin-8(9H)-one (1)	1-acetyl-4-aminopiperidine hydrochloride	4	1.68	446

20142017789 26 Mar 2014

1k	(S)-tert-butyl 3-(2-(5-cyanopyrazolo[1,5-a]pyridin-3-yl)-8-oxo-7H-purin-9(8H)-yl)pyrrolidine-1-carboxylate	(S)-tert-butyl 3-aminopyrrolidine-1-carboxylate	5	2.72	447
1l	(R)-tert-butyl 3-(2-(5-cyanopyrazolo[1,5-a]pyridin-3-yl)-8-oxo-7H-purin-9(8H)-yl)pyrrolidine-1-carboxylate	(R)-tert-butyl 3-aminopyrrolidine-1-carboxylate	3	2.25	447
1m	(S)-tert-butyl 3-(2-(5-methylpyrazolo[1,5-a]pyridin-3-yl)-8-oxo-7H-purin-9(8H)-yl)piperidine-1-carboxylate (2)	*(S)-tert*-butyl 3-aminopiperidine-1-carboxylate	3	2.47	450
1n	ethyl 2-(2-(5-cyanopyrazolo[1,5-a]pyridin-3-yl)-8-oxo-7H-purin-9(8H)-yl)acetate	ethyl 2-aminoacetate	3	1.82	364
1o	3-(9-(*trans*-4-hydroxycyclohexyl)-8-oxo-8,9-dihydro-7H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	*trans*-4-aminocyclohexanol	3	1.55	376
1p	3-(9-(8-fluorochroman-4-yl)-8-oxo-8,9-dihydro-7H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	8-fluorochroman-4-amine	1	15.43	428
1q	tert-butyl 4-(2-(5-cyanopyrazolo[1,5-a]pyridin-3-yl)-8-oxo-7H-purin-9(8H)-yl)piperidine-1-carboxylate	tert-butyl 4-aminopiperidine-1-carboxylate	3	2.33	461
1r	tert-butyl 3-(2-(5-cyanopyrazolo[1,5-a]pyridin-3-yl)-8-oxo-7H-purin-9(8H)-yl)azetidine-1-carboxylate	tert-butyl 3-aminoazetidine-1-carboxylate	3	2.20	433
1s	9-(1-acetylpiperidin-4-yl)-2-(5-methylpyrazolo[1,5-a]pyridin-3-yl)-7H-purin-8(9H)-one (2)	1-acetyl-4-aminopiperidine hydrochloride	4	1.38	392

(1) step c) was performed using reference example 1 instead of 1-amino-4-cyanopyridinium 2,4,6-trimethylbenzenesulfonate

(2) step c) was performed using 1-amino-4-methylpyridinium 2,4,6-trimethylbenzenesulfonate (described by Zhang et al Journal of Heterocyclic Chemistry; 44; 4; 2007; 919-922) instead of 1-amino-4-cyanopyridinium 2,4,6-trimethylbenzenesulfonate

EXAMPLE 2

3-(2-Oxo-3-(tetrahydro-2*H*-pyran-4-yl)-2,3-dihydro-*1H*-imidazo[4,5-b]pyridin-5-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile

a) **6-Chloro-3-nitro-*N*-(tetrahydro-2*H*-pyran-4-yl)pyridin-2-amine**

To a suspension of 2,6-dichloro-3-nitropyridine (6 g, 31.1 mmol) in AcN (200 mL) at 0 °C, TEA (9 mL, 62.2 mmol) and tetrahydro-2*H*-pyran-4-amine (3.15 g, 31.1 mmol) were added. The reaction mixture was stirred at 0 °C for 1.5 h. The reaction crude was tempered and stirred at room temperature for 18 h.

The reaction mixture was evaporated under reduced pressure, dissolved in EtOAc, and washed thrice with saturated $NaHCO_3$ aqueous solution. The combined organic phases were dried over $MgSO_4$ and concentrated to dryness.

The crude residue was cromatographed on a silica gel flash system (ISCO Combiflash) using hexanes/TBME mixtures of increasing polarity as eluent to afford 5.23 g of the desired product (65% yield).

b) **3-Nitro-*N*-(tetrahydro-2*H*-pyran-4-yl)-6-((trimethylsilyl)ethynyl)pyridin-2-amine**

Following a similar procedure to that described in example 1, section b, but using the compound obtained in previous section as starting material, the desired compound was obtained (87% yield).

c) **3-(5-Nitro-6-(tetrahydro-2*H*-pyran-4-ylamino)pyridin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile**

Following a similar procedure to that described in example 1, section c, but using the compound obtained in previous section as starting material, the desired compound was obtained (16% yield).

d) **3-(5-Amino-6-(tetrahydro-2*H*-pyran-4-ylamino)pyridin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile**

Following a similar procedure to that described in example 1, section d, but using the compound obtained in previous section as starting material, the desired compound was obtained (19% yield).

e) **Title compound**

Following a similar procedure to that described in example 1, section e, but using the compound obtained in previous section as starting material, the desired compound was obtained (23% yield).

LC-MS (method 3): t_R = 1.83 min; m/z = 361 (MH^+)

Following a similar procedure to that described in example 2, but using in each case the corresponding starting

materials, the following compounds were obtained:

Example	Name	Starting Material	HPLC method	t_R (min)	m/z (MH^+)
2a	(S)-tert-butyl 3-(2-oxo-5-(pyrazolo[1,5-a]pyridin-3-yl)-1H-imidazo[4,5-b]pyridin-3(2H)-yl)piperidine-1-carboxylate	(S)-3-amino-(1-tert-butoxycarbonyl)piperidine and 1-aminopyridinium iodide	3	2.47	435
2b	(R)-tert-butyl 3-(2-oxo-5-(pyrazolo[1,5-a]pyridin-3-yl)-1H-imidazo[4,5-b]pyridin-3(2H)-yl)pyrrolidine-1-carboxylate	(R)-tert-butyl 3-aminopyrrolidine-1-carboxylate and 1-aminopyridinium iodide	3	2.27	421
2c	(S)-tert-butyl 3-(2-oxo-5-(pyrazolo[1,5-a]pyridin-3-yl)-1H-imidazo[4,5-b]pyridin-3(2H)-yl)pyrrolidine-1-carboxylate	(S)-tert-butyl 3-aminopyrrolidine-1-carboxylate and 1-aminopyridinium iodide	3	2.27	421
2d	(S)-tert-butyl 3-(5-(5-cyanopyrazolo[1,5-a]pyridin-3-yl)-2-oxo-1H-imidazo[4,5-b]pyridin-3(2H)-yl)piperidine-1-carboxylate	(S)-3-amino-(1-tert-butoxycarbonyl)piperidine and 1-amino-4-cyanopyridinium 2,4,6-trimethylbenzenesulfonate	3	2.50	434
2e	5-(pyrazolo[1,5-a]pyridin-3-yl)-3-(tetrahydro-2H-pyran-4-yl)-1H-imidazo[4,5-b]pyridin-2(3H)-one	tetrahydro-2*H*-pyran-4-amine and 1-aminopyridinium iodide	3	1.80	336
2f	(R)-tert-butyl 3-(2-oxo-5-(pyrazolo[1,5-a]pyridin-3-yl)-1H-imidazo[4,5-b]pyridin-3(2H)-yl)piperidine-1-carboxylate	(R)-3-amino-(1-tert-butoxycarbonyl)piperidine and 1-aminopyridinium iodide	4	2.15	435

EXAMPLE 3

2-(Pyrazolo[1,5-*a*]pyridin-3-yl)-9-(tetrahydro-2*H*-pyran-4-yl)-7*H*-purin-8(*9H*)-one

Following a similar procedure to that described in example 1, but using 1-aminopyridinium iodide instead of 1-amino-4-cyanopyridinium 2,4,6-trimethylbenzenesulfonate, the desired compound was obtained (84% yield).

LC-MS (method 3): t_R = 1.62 min; m/z = 337 (MH^+).

Following a similar procedure to that described in example 3, but using in each case the corresponding starting materials, the following compounds were obtained:

Example	Name	Starting Material	HPLC method	t_R (min)	m/z (MH^+)
3a	2-(pyrazolo[1,5-*a*]pyridin-3-yl)-9-((tetrahydro-2*H*-pyran-4-yl)methyl)-7*H*-purin-8(*9H*)-one	(tetrahydro-2*H*-pyran-4-yl)methanamine	2	1.63	351
3b	*(S)-tert*-butyl 3-(8-oxo-2-(pyrazolo[1,5-*a*]pyridin3-yl)-7*H*-purin-9(8*H*)-yl)piperidine-1-carboxylate	*(S)-tert*-butyl-3-aminopiperidine-1-carboxylate	2	2.33	436
3c	9-(2-methoxyethyl)-2-(pyrazolo[1,5-*a*]pyridin-3-yl)-7*H*-purin-8(*9H*)-one	2-methoxyethylamine	2	1.55	311
3d	9-(8-fluorochroman-4-yl)-2-(pyrazolo[1,5-a]pyridin-3-yl)-7*H*-purin-8(9H)-one	8-fluorochroman-4-amine	1	16.07	403
3e	methyl (2S)-2-(8-oxo-2-(pyrazolo[1,5-a]pyridin-3-yl)-7,8-dihydro-9H-purin-9-yl)propanoate	L-alanine methyl ester hydrochloride	3	1.73	339
3f	(S)-tert-butyl 3-(8-oxo-2-(pyrazolo[1,5-a]pyridin-3-yl)-7H-purin-9(8H)-yl)pyrrolidine-1-carboxylate	(S)-tert-butyl 3-aminopyrrolidine-1-carboxylate	3	2.13	422
3g	tert-butyl 4-(8-oxo-2-(pyrazolo[1,5-a]pyridin-3-yl)-7H-purin-9(8H)-yl)piperidine-1-carboxylate	tert-butyl 4-aminopiperidine-1-carboxylate	3	2.35	461

26 Mar 2014 20142017789

3h	9-(1-methylpiperidin-4-yl)-2-(pyrazolo[1,5-a]pyridin-3-yl)-7H-purin-8(9H)-one	1-methylpiperidin-4-amine	4	1.38	350
3i	5-(pyrazolo[1,5-a]pyridin-3-yl)-3-(2,2,6,6-tetramethylpiperidin-4-yl)-1H-imidazo[4,5-b]pyridin-2(3H)-one	2,2,6,6-tetramethylpiperidin-4-amine	4	1.48	391

EXAMPLE 4

3-(7-Methyl-8-oxo-9-tetrahydro-2*H*-pyran-4-yl-8,9-dihydro-7*H*-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile

To a solution of example 1 (48 mg, 0.13 mmol) in DMF (6 mL), 55-65% NaH dispersion in mineral oil (7.3 mg, 0.18 mmol) was added and the resulting solution was stirred at room temperature for 10 min. Then MeI (0.015 mL, 0.25 mmol) was added and the reaction mixture was stirred for 15 h at room temperature. The reaction mixture was quenched with saturated NaCl aqueous solution (10 mL) and extracted with EtOAc (3x10 mL) and CH_2Cl_2 (2x10 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product thus obtained was chromatographed over silica gel using MeOH/CH_2Cl_2 mixtures of increasing polarity as eluent, to afford 50 mg of the desired compound (quantitative yield).

LC-MS (method 1): t_R = 15.48 min; m/z = 376 (MH^+).

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

Example	Name	Starting Material	HPLC method	t_R (min)	m/z
4a	*(S)-tert*-butyl 3-(2-(5-cyanopyrazolo[1,5-a]pyridin-3-yl)-7-methyl-8-oxo-*7H*-purin-9(*8H*)-yl)piperidine-1-carboxylate	Example 1b	2	3.22	475
4b	*(R)-tert*-butyl 3-(2-(5-cyanopyrazolo[1,5-a]pyridin-3-yl)-7-methyl-8-oxo-*7H*-purin-9(8H)-yl)piperidine-1-carboxylate	Example 1c	2	3.22	475
4c	9-(8-fluorochroman-4-yl)-7-methyl-2-(pyrazolo[1,5-a]pyridin-3-yl)-*7H*-purin-8(9H)-one	Example 3d	1	16.83	417

EXAMPLE 5

(*S*)-*tert*-Butyl 3-(7-methyl-8-oxo-2-(pyrazolo[1,5-*a*]pyridine-3-yl)-7*H*-purin-9(8*H*)-yl)piperidine-1-carboxylate

To a solution of example 3b (70 mg, 0.160 mmol) in DMF (3.5 mL), at 0°C, ^{t}BuOK (27 mg, 0.24 mmol) and MeI (0.019 mL, 0.32 mmol) were added. The reaction mixture was stirred at room temperature for 20 min and evaporated to dryness. The crude residue was chromatographed on a silica gel flash system (ISCO Rf) using CH_2Cl_2/ MeOH mixtures of increasing polarity as eluent to afford 64 mg of the desired product (89% yield).

LC-MS (method 3): t_R = 2.58 min; m/z = 450 (MH^+).

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

Example	Name	Starting Material	HPLC method	t_R (min)	m/z (MH^+)
5a	7-methyl-2-(pyrazolo[1,5-*a*]pyridin-3-yl)-9-(tetrahydro-2*H*-pyran-4-yl)-7*H*-purin-8(9*H*)-one	example 3	2	1.83	351
5b	3-(1-methyl-2-oxo-3-(tetrahydro-2*H*-pyran-4-yl)-2,3-dihydro-1*H*-imidazo[4,5-b]pyridin-5-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	example 2	2	2.62	375
5c	9-(2-methoxyethyl)-7-methyl-2-(pyrazolo[1,5-*a*]pyridin-3-yl)-7*H*-purin-8(9*H*)-one	Example 3c	2	1.77	325
5d	7-methyl-2-(pyrazolo[1,5-a]pyridin-3-yl)-9-[(tetrahydro-2H-pyran-4-yl)methyl]-7H-purin-8(9H)-one	Example 3a	2	1.87	365
5e	3-(9-(4,4-difluorocyclohexyl)-7-methyl-8-oxo-8,9-dihydro-7H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	Example 1e	2	2.32	410
5f	3-(9-(1,1-dioxotetrahydrothien-3-yl)-8,9-dihydro-7-methyl-8-oxopurin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile.	Example 1f	2	1.75	410

2014201789 26 Mar 2014

5g	(S)-tert-butyl 3-(5-(5-cyanopyrazolo[1,5-a]pyridin-3-yl)-1-methyl-2-oxo-1H-imidazo[4,5-b]pyridin-3(2H)-yl)piperidine-1-carboxylate	Example 2d	2	2.54	474
5h	3-(9-(2-fluorobenzyl)-7-methyl-8-oxo-8,9-dihydro-7H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	Example 1g	1	17.66	400
5i	9-(1-acetylpiperidin-4-yl)-7-methyl-2-(5-(trifluoromethyl)pyrazolo[1,5-a]pyridin-3-yl)-7H-purin-8(9H)-one	Example 1j	4	1.85	460
5j	(S)-tert-butyl 3-(1-methyl-2-oxo-5-(pyrazolo[1,5-a]pyridin-3-yl)-1H-imidazo[4,5-b]pyridin-3(2H)-yl)piperidine-1-carboxylate	Example 2a	3	2.73	449
5k	(S)-tert-butyl 3-(2-(5-cyanopyrazolo[1,5-a]pyridin-3-yl)-7-methyl-8-oxo-7H-purin-9(8H)-yl)pyrrolidine-1-carboxylate	Example 1k	3	2.52	461
5l	(R)-tert-butyl 3-(2-(5-cyanopyrazolo[1,5-a]pyridin-3-yl)-7-methyl-8-oxo-7H-purin-9(8H)-yl)pyrrolidine-1-carboxylate	Example 1l	3	2.50	461
5m	(S)-tert-butyl 3-(7-methyl-8-oxo-2-(pyrazolo[1,5-a]pyridin-3-yl)-7H-purin-9(8H)-yl)pyrrolidine-1-carboxylate	Example 3f	3	2.40	436
5n	(R)-tert-butyl 3-(1-methyl-2-oxo-5-(pyrazolo[1,5-a]pyridin-3-yl)-1H-imidazo[4,5-b]pyridin-3(2H)-yl)pyrrolidine-1-carboxylate	Example 2b	3	2.50	435
5o	(S)-tert-butyl 3-(1-methyl-2-oxo-5-(pyrazolo[1,5-a]pyridin-3-yl)-1H-imidazo[4,5-b]pyridin-3(2H)-yl)pyrrolidine-1-carboxylate	Example 2c	5	2.98	436

20142017789 26 Mar 2014

5p	(S)-tert-Butyl 3-(1-ethyl-2-oxo-5-(pyrazolo[1,5-a]pyridin-3-yl)-1H-imidazo[4,5-b]pyridin-3(2H)-yl)piperidine-1-carboxylate(1)	Example 2a	4	2.57	463
5q	tert-butyl 4-(7-methyl-8-oxo-2-(pyrazolo[1,5-a]pyridin-3-yl)-7H-purin-9(8H)-yl)piperidine-1-carboxylate	Example 3g	3	2.68	475
5r	(S)-tert-butyl 3-(7-methyl-8-oxo-2-(pyrazolo[1,5-a]pyridin-3-yl)-7H-purin-9(8H)-yl)piperidine-1-carboxylate	Example 3b	3	2.62	450
5s	1-methyl-5-(pyrazolo[1,5-a]pyridin-3-yl)-3-(tetrahydro-2H-pyran-4-yl)-1H-imidazo[4,5-b]pyridin-2(3H)-one	Example 2e	3	2.02	350
5t	(R)-tert-butyl 3-(1-methyl-2-oxo-5-(pyrazolo[1,5-a]pyridin-3-yl)-1H-imidazo[4,5-b]pyridin-3(2H)-yl)piperidine-1-carboxylate	Example 2f	3	2.73	449
5u	tert-butyl 4-(2-(5-cyanopyrazolo[1,5-a]pyridin-3-yl)-7-methyl-8-oxo-7H-purin-9(8H)-yl)piperidine-1-carboxylate	Example 1q	3	2.68	475
5v	tert-butyl 3-(2-(5-cyanopyrazolo[1,5-a]pyridin-3-yl)-7-methyl-8-oxo-7H-purin-9(8H)-yl)azetidine-1-carboxylate	Example 1r	3	2.47	447

(1) ethyl iodide instead of methyl iodide as starting material.

EXAMPLE 6

(*S*)-3-(8-Oxo-9-(piperidin-3-yl)-8,9-dihydro-7*H*-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile hydrochloride

To a solution of example 1b (45 mg, 0.10 mmol) in dioxane (3 mL), 4 M HCl solution in dioxane (2 mL, 8.0 mmol) was added. The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was evaporated to dryness to give 48 mg of the desired compound (100% yield).

LC-MS (method 2): t_R = 1.73 min; m/z = 361 (MH^+).

Following a similar procedure to that described in example 6, but using in each case the corresponding starting materials, the following compounds were obtained:

Example	Compound name	Starting material	HPLC method	t_R (min)	m/z (MH^+)
6a	(*R*)-3-(8-oxo-9-(piperidin-3-yl)-8,9-dihydro-7*H*-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile hydrochloride	Example 1c	2	1.73	361
6b	(*R*)-3-(7-methyl-8-oxo-9-(piperidin-3-yl)-8,9-dihydro-7*H*-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile hydrochloride	Example 4b	2	2.05	375
6c	(*S*)-3-(7-methyl-8-oxo-9-(piperidin-3-yl)-8,9-dihydro-7*H*-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile hydrochloride	Example 4a	2	2.05	375
6d	9-(piperidin-4-yl)-2-(pyrazolo[1,5-*a*]pyridin-3-yl)-7*H*-purin-8(9*H*)-one	Example 3g	2	1.28	336
6e	(*S*)-3-(2-oxo-3-(piperidin-3-yl)-2,3-dihydro-1H-imidazo[4,5-b]pyridin-5-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile hydrochloride	Example 2d	2	1.54	360
6f	(S)-3-(1-methyl-2-oxo-3-(piperidin-3-yl)-2,3-dihydro-1H-imidazo[4,5-b]pyridin-5-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile hydrochloride	Example 5g	2	1.68	374
6g	(S)-1-methyl-3-(piperidin-3-yl)-5-(pyrazolo[1,5-a]pyridin-3-yl)-1H-imidazo[4,5-b]pyridin-2(3H)-one hydrochloride	Example 5j	1	12.46	349

6h	(S)-3-(7-methyl-8-oxo-9-(pyrrolidin-3-yl)-8,9-dihydro-7H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile hydrochloride	Example 5k	3	1.62	361
6i	(R)-3-(7-methyl-8-oxo-9-(pyrrolidin-3-yl)-8,9-dihydro-7H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile hydrochloride	Example 5l	3	1.62	361
6j	(S)-2-(pyrazolo[1,5-a]pyridin-3-yl)-9-(pyrrolidin-3-yl)-7H-purin-8(9H)-one hydrochloride	Example 3f	3	1.23	322
6k	(S)-7-methyl-2-(pyrazolo[1,5-a]pyridin-3-yl)-9-(pyrrolidin-3-yl)-7H-purin-8(9H)-one hydrochloride	Example 5m	3	1.48	336
6l	(S)-3-(8-oxo-9-(pyrrolidin-3-yl)-8,9-dihydro-7H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile hydrochloride (1)	Example 1k	3	1.35	347
6m	(R)-1-methyl-5-(pyrazolo[1,5-a]pyridin-3-yl)-3-(pyrrolidin-3-yl)-1H-imidazo[4,5-b]pyridin-2(3H)-one hydrochloride	Example 5n	3	1.57	335
6n	(R)-5-(pyrazolo[1,5-a]pyridin-3-yl)-3-(pyrrolidin-3-yl)-1H-imidazo[4,5-b]pyridin-2(3H)-one hydrochloride (1)	Example 2b	3	1.40	321
6o	(R)-3-(8-oxo-9-(pyrrolidin-3-yl)-8,9-dihydro-7H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile hydrochloride (1)	Example 1l	3	1.33	347
6p	(S)-2-(pyrazolo[1,5-a]pyridin-3-yl)-9-(pyrrolidin-3-yl)-7H-purin-8(9H)-one hydrochloride	Example 2c	3	1.40	321

2014201789 26 Mar 2014

6q	(S)-1-methyl-5-(pyrazolo[1,5-a]pyridin-3-yl)-3-(pyrrolidin-3-yl)-1H-imidazo[4,5-b]pyridin-2(3H)-one hydrochloride	Example 5o	3	1.57	335
6r	(S)-2-(5-methylpyrazolo[1,5-a]pyridin-3-yl)-9-(piperidin-3-yl)-7H-purin-8(9H)-one hydrochloride	Example 1m	3	1.57	350
6s	(S)-1-ethyl-3-(piperidin-3-yl)-5-(pyrazolo[1,5-a]pyridin-3-yl)-1H-imidazo[4,5-b]pyridin-2(3H)-one hydrochloride	Example 5p	4	1.56	363
6t	7-methyl-9-(piperidin-4-yl)-2-(pyrazolo[1,5-a]pyridin-3-yl)-7H-purin-8(9H)-one hydrochloride	Example 5q	4	1.23	350
6u	(S)-7-methyl-9-(piperidin-3-yl)-2-(pyrazolo[1,5-a]pyridin-3-yl)-7H-purin-8(9H)-one hydrochloride	Example 5r	3	1.67	350
6v	(S)-9-(piperidin-3-yl)-2-(pyrazolo[1,5-a]pyridin-3-yl)-7H-purin-8(9H)-one hydrochloride	Example 3b	3	1.43	336
6w	(R)-1-methyl-3-(piperidin-3-yl)-5-(pyrazolo[1,5-a]pyridin-3-yl)-1H-imidazo[4,5-b]pyridin-2(3H)-one	Example 5t	3	1.77	349
6x	(S)-3-(piperidin-3-yl)-5-(pyrazolo[1,5-a]pyridin-3-yl)-1H-imidazo[4,5-b]pyridin-2(3H)-one hydrochloride	Example 2a	3	1.60	335
6y	3-(7-methyl-8-oxo-9-(piperidin-4-yl)-8,9-dihydro-7H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile hydrochloride	Example 5u	3	1.67	375
6z	(S)-3-(3-(piperidin-3-yl)-3H-imidazo[4,5-b]pyridin-5-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile hydrochloride	Example 18e	3	1.68	3.44

2014201789 26 Mar 2014

6aa	(S)-3-(2-methyl-3-(piperidin-3-yl)-3H-imidazo[4,5-b]pyridin-5-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile hydrochloride	Example 18f	3	1.72	358
6ab	3-(8-oxo-9-(piperidin-4-yl)-8,9-dihydro-7H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile (1)	Example 1q	1	11.13	361
6ac	3-(9-(azetidin-3-yl)-7-methyl-8-oxo-8,9-dihydro-7H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile hydrochloride	Example 5v	3	1.50	347
6ad	(S)-3-(piperidin-3-yl)-5-(pyrazolo[1,5-a]pyridin-3-yl)-3H-imidazo[4,5-b]pyridine hydrochloride	Example 18i	3	1.65	319
6ae	(S)-2-methyl-3-(piperidin-3-yl)-5-(pyrazolo[1,5-a]pyridin-3-yl)-3H-imidazo[4,5-b]pyridine hydrochloride	Example 21m	3	1.48	333

(1) reaction performed with TFA/CH_2Cl_2 instead of 4 M HCl solution in dioxane, and washed with with saturated $NaHCO_3$ aqueous solution.

EXAMPLE 7

(*S*)-3-(9-(1-(2-Cyanoacetyl)piperidin-3-yl)-8-oxo-8,9-dihydro-7*H*-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile

To a solution of the compound obtained in example 6 (45 mg, 0.095 mmol) in anhydrous DMF (3 mL), 2,5-dioxopyrrolidin-1-yl 2-cyanoacetate (69 mg, 0.38 mmol) and anhydrous TEA (0.09 mL, 0.665 mmol) were added. The reaction mixture was stirred at room temperature for 18 h, and the solvent was concentrated off. It was quenched with saturated $NaHCO_3$ aqueous solution (15 mL) and extracted with EtOAc (3x15 mL). The combined organic phases were dried over anhydrous Mg_2SO_4, filtered and concentrated. The crude residue was flash chromatographed on a silica gel flash system (ISCO Rf) using hexanes/acetone mixtures of increasing polarity as eluent to afford 11.7 mg of the desired compound (29% yield).

LC-MS (method 2): t_R = 1.93 min; m/z = 428 (MH^+).

Following a similar procedure to that described in example 7, but using in each case the corresponding starting materials, the following compounds were obtained:

2014201789 26 Mar 2014

Example	Compound name	Starting material	HPLC method	t_R (min)	m/z (MH^+)
7a	(*R*)-3-(9-(1-(2-cyanoacetyl)piperidin-3-yl)-8-oxo-8,9-dihydro-7*H*-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	Example 6a	2	1.93	428
7b	(*R*)-3-(9-(1-(2-cyanoacetyl)piperidin-3-yl)-7-methyl-8-oxo-8,9-dihydro-7*H*-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	Example 6b	2	2.30	442
7c	(*S*)-3-(9-(1-(2-cyanoacetyl)piperidin-3-yl)-7-methyl-8-oxo-8,9-dihydro-7*H*-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	Example 6c	2	2.30	442
7d	3-(9-(1-(2-cyanoacetyl)pyrrolidin-3-yl)-7-methyl-8-oxo-8,9-dihydro-7*H*-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	3-(7-methyl-8-oxo-9-(pyrrolidin-3-yl)-8,9-dihydro-7*H*-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile hydrochloride(1)	2	1.68	428
7e	3-(9-((1-(2-cyanoacetyl)piperidin-4-yl)methyl)-7-methyl-8-oxo-8,9-dihydro-7*H*-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	3-(7-methyl-8-oxo-9-(piperidin-4-ylmethyl)-8,9-dihydro-7*H*-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile hydrochloride (2)	2	1.80	456
7f	(*S*)-3-oxo-3-(3-(8-oxo-2-(pyrazolo[1,5-a]pyridin-3-yl)-7H-purin-9(8H)-yl)piperidin-1-yl)propanenitrile	Example 6v	2	2.05	403
7g	(*S*)-3-(3-(7-methyl-8-oxo-2-(pyrazolo[1,5-a]pyridin-3-yl)-7*H*-purin-9(8*H*)-yl)piperidin-1-yl)-3-oxopropanenitrile	Eample 6u	2	2.58	417

2014201789 26 Mar 2014

7h	(S)-3-(3-(1-(2-cyanoacetyl)piperidin-3-yl)-2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-5-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	Example 6e	2	1.64	427
7i	(S)-3-(3-(1-methyl-2-oxo-5-(pyrazolo[1,5-a]pyridin-3-yl)-1H-imidazo[4,5-b]pyridin-3(2H)-yl)piperidin-1-yl)-3-oxopropanenitrile	Example 6g	5	1.95	416
7j	3-(9-(1-(2-cyanoacetyl)azetidin-3-yl)-7-methyl-8-oxo-8,9-dihydro-7H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	Example 6ac	2	2.10	414
7k	(S)-3-(3-(2-(5-methylpyrazolo[1,5-a]pyridin-3-yl)-8-oxo-7H-purin-9(8H)-yl)piperidin-1-yl)-3-oxopropanenitrile	Example 6r	3	1.73	417
7l	(S)-3-(3-(1-ethyl-2-oxo-5-(pyrazolo[1,5-a]pyridin-3-yl)-1H-imidazo[4,5-b]pyridin-3(2H)-yl)piperidin-1-yl)-3-oxopropanenitrile	Example 6s	4	1.87	430
7m	3-oxo-3-(4-(8-oxo-2-(pyrazolo[1,5-a]pyridin-3-yl)-7H-purin-9(8H)-yl)piperidin-1-yl)propanenitrile	Example 6d	4	1.32	403
7n	(S)-3-(3-(1-(2-cyanoacetyl)piperidin-3-yl)-1-methyl-2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-5-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	Example 6f	3	2.02	441
7o	(R)-3-(3-(1-methyl-2-oxo-5-(pyrazolo[1,5-a]pyridin-3-yl)-1H-imidazo[4,5-b]pyridin-3(2H)-yl)piperidin-1-yl)-3-oxopropanenitrile	Example 6w	4	1.71	416

2014201789 26 Mar 2014

7p	(S)-3-oxo-3-(3-(2-oxo-5-(pyrazolo[1,5-a]pyridin-3-yl)-1H-imidazo[4,5-b]pyridin-3(2H)-yl)piperidin-1-yl)propanenitrile	Example 6x	3	1.75	402
7q	3-(9-(1-(2-cyanoacetyl)piperidin-4-yl)-7-methyl-8-oxo-8,9-dihydro-7H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	Example 6y	3	1.82	442
7r	(S)-3-(3-(1-(2-cyanoacetyl)piperidin-3-yl)-3H-imidazo[4,5-b]pyridin-5-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	Example 6z	5	2.20	411
7s	(S)-3-(3-(1-(2-cyanoacetyl)piperidin-3-yl)-2-methyl-3H-imidazo[4,5-b]pyridin-5-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	Example 6aa	5	2.09	425
7t	(S)-3-(3-(2-methyl-5-(pyrazolo[1,5-a]pyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)piperidin-1-yl)-3-oxopropanenitrile	Example 6ae	3	1.85	400
7u	(S)-3-oxo-3-(3-(5-(pyrazolo[1,5-a]pyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)piperidin-1-yl)propanenitrile	Example 6ad	3	1.77	386

(1) obtained as example 6, but using *tert*-butyl 3-aminopyrrolidine-1-carboxylate as starting material.

(2) obtained as example 6, but using *tert*-butyl 4-(aminomethyl)piperidine-1-carboxylate as starting material.

EXAMPLE 8

(*S*)-3-(9-(1-Acetylpiperidin-3-yl)-8-oxo-8,9-dihydro-7*H*-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile

To a solution of the compound obtained in example 6 (31 mg, 0.063 mmol) in anhydrous DMF (3 mL), acetic anhydride (0.007 mL, 0.08 mmol) and anhydrous TEA (0.02 mL, 0.127 mmol) were added. The reaction mixture was stirred at room temperature for 18 h, and the solvent was concentrated off. It was quenched with saturated $NaHCO_3$ aqueous solution (15 mL) and extracted with EtOAc (3x15 mL). The combined organic phases were dried over anhydrous Mg_2SO_4, filtered and concentrated. The crude residue was flash chromatographed on a silica gel flash system (ISCO Rf) using hexanes/acetone mixtures of increasing polarity as eluent to afford 14.5 mg of the desired compound (57% yield).

LC-MS (method 2): t_R = 1.87 min; m/z = 403 (MH^+).

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

Example	Compound name	Starting material	HPLC method	t_R (min)	m/z (MH^+)
8a	(*S*)-9-(1-acetylpiperidin-3-yl)-2-(pyrazolo[1,5-*a*]pyridin-3-yl)-7*H*-purin-8(9*H*)-one	Example 6v	2	1.55	378
8b	3-(9-(1-acetylpiperidin-4-yl)-8-oxo-8,9-dihydro-7H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	Example 6ab	1	13.31	403
8c	9-(1-acetylpiperidin-4-yl)-2-(pyrazolo[1,5-a]pyridin-3-yl)-7H-purin-8(9H)-one	Example 6d	4	1.30	378
8d	(S)-3-(1-isobutyrylpiperidin-3-yl)-5-(pyrazolo[1,5-a]pyridin-3-yl)-1H-imidazo[4,5-b]pyridin-2(3H)-one (1)	Example 6x	3	2.00	405
8e	(S)-3-(9-(1-acetylpiperidin-3-yl)-7-methyl-8-oxo-8,9-dihydro-7H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	Example 6c	3	1.88	417
8f	(S)-3-(1-acetylpiperidin-3-yl)-5-(pyrazolo[1,5-a]pyridin-3-yl)-1H-imidazo[4,5-b]pyridin-2(3H)-one	Example 6x	3	1.72	377
8g	3-(9-(1-acetylpiperidin-4-yl)-7-methyl-8-oxo-8,9-dihydro-7H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	Example 6y	3	1.78	417
8h	3-(9-(1-acetylazetidin-3-yl)-7-methyl-8-oxo-8,9-dihydro-7H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	Example 6ac	3	1.62	389

(1) using isobutyryl chloride instead of acetic anhydride as starting material.

EXAMPLE 9

(*S*)-3-(9-(1-(Methylsulfonyl)piperidin-3-yl)-8-oxo-8,9-dihydro-7*H*-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile

To a solution of the compound obtained in example 6 (31 mg, 0.063 mmol) in anhydrous DMF (3 mL), methanesulphonic anhydride (13 mg, 0.08 mmol) and anhydrous TEA (0.02 mL, 0.127 mmol) were added. The reaction mixture was stirred at room temperature for 18 h, and the solvent was concentrated off. It was quenched with saturated $NaHCO_3$ aqueous solution (15 mL) and extracted with EtOAc (3x15 mL). The combined organic phases were dried over anhydrous Mg_2SO_4, filtered and concentrated. The crude residue was chromatographed on a silica gel flash system (ISCO Rf) using hexanes/acetone mixtures of increasing polarity as eluent to afford 14.3 mg of the titled compound (52% yield).

LC-MS (method 1 PCB): t_R = 2.08 min; m/z = 439 (MH^+).

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

Example	Compound name	Starting material	HPLC method	t_R (min)	m/z (MH^+)
9a	(*S*)-9-(1-(methylsulfonyl)piperidin-3-yl)-2-(pyrazolo[1,5-*a*]pyridin-3-yl)-7*H*-purin-8(9*H*)-one	Example 6v and methanesulphonyl chloride	2	1.70	414
9b	(S)-3-(8-oxo-9-(1-(propylsulfonyl)piperidin-3-yl)-8,9-dihydro-7H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	Example 6 and propane-1-sulfonyl chloride	5	2.48	467
9c	(S)-3-(8-oxo-9-(1-(2,2,2-trifluoroethylsulfonyl)piperidin-3-yl)-8,9-dihydro-7H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	Example 6 and 2,2,2-trifluoroethanesulfonyl chloride	5	2.55	507
9d	(S)-3-(9-(1-(isobutylsulfonyl)piperidin-3-yl)-8-oxo-8,9-dihydro-7H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	Example 6 and 2-methylpropane-1-sulfonyl chloride	3	2.70	481

2014201789 26 Mar 2014

9e	(S)-3-(8-oxo-9-(1-(3,3,3-trifluoropropylsulfonyl)piperidin-3-yl)-8,9-dihydro-7H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	Example 6 and 3,3,3-trifluoropropane-1-sulfonyl chloride	3	2.70	521
9f	(S)-1-methyl-3-(1-(methylsulfonyl)piperidin-3-yl)-5-(pyrazolo[1,5-a]pyridin-3-yl)-1H-imidazo[4,5-b]pyridin-2(3H)-one	Example 6g and methanesulphonyl chloride	4	1.81	427
9g	(S)-2-(5-methylpyrazolo[1,5-a]pyridin-3-yl)-9-(1-(methylsulfonyl)piperidin-3-yl)-7H-purin-8(9H)-one	Example 6r and methanesulphonyl chloride	3	1.87	428
9h	7-(2-oxopropyl)-9-(1-(2-oxopropyl)piperidin-4-yl)-2-(pyrazolo[1,5-a]pyridin-3-yl)-7H-purin-8(9H)-one	Example 6d and 1-chloropropan-2-one	4	1.66	448
9i	9-(1-acetylpiperidin-4-yl)-7-methyl-2-(pyrazolo[1,5-a]pyridin-3-yl)-7H-purin-8(9H)-one	Example 6t and acetyl choride	4	1.42	392
9j	(S)-3-(3-(1-isobutyrylpiperidin-3-yl)-2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-5-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	Example 6e and isobutyryl chloride	5	2.52	430
9k	(S)-3-(3-(1-(methylsulfonyl)piperidin-3-yl)-2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-5-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	Example 6e and methanesulphonyl chloride	3	1.92	438
9l	(S)-3-(7-methyl-9-(1-(methylsulfonyl)piperidin-3-yl)-8-oxo-8,9-dihydro-7H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	Example 6c and methanesulphonyl chloride	3	2.05	453

2014201789 26 Mar 2014

9m	(S)-3-(9-(1-(ethylsulfonyl)piperidin-3-yl)-8-oxo-8,9-dihydro-7H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	Example 6 and ethylsulphonyl chloride	3	1.90	453
9n	(S)-3-(9-(1-isobutyrylpiperidin-3-yl)-8-oxo-8,9-dihydro-7H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	Example 6 and isobutyryl chloride	3	1.95	431
9o	3-(7-methyl-9-(1-(methylsulfonyl)piperidin-4-yl)-8-oxo-8,9-dihydro-7H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	Example 6y and methanesulphonyl chloride	3	1.95	453
9p	3-(9-(1-(methylsulfonyl)piperidin-4-yl)-8-oxo-8,9-dihydro-7H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	Example 6ab and methanesulphonyl chloride	1	14.06	439
9q	(S)-3-(1-(methylsulfonyl)piperidin-3-yl)-5-(pyrazolo[1,5-a]pyridin-3-yl)-1H-imidazo[4,5-b]pyridin-2(3H)-one	Example 6x and methanesulphonyl chloride	3	1.85	413
9r	3-(7-methyl-9-(1-(methylsulfonyl)azetidin-3-yl)-8-oxo-8,9-dihydro-7H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	Example 6ac and methanesulphonyl chloride	3	2.30	425
9s	(S)-3-(3-(1-acetylpiperidin-3-yl)-2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-5-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	Example 6e and acetyl chloride	5	2.25	402
9t	(S)-3-(1-(2-methoxyacetyl)piperidin-3-yl)-1-methyl-5-(pyrazolo[1,5-a]pyridin-3-yl)-1H-imidazo[4,5-b]pyridin-2(3H)-one	Example 6g and 2-methoxyacetyl chloride	4	1.68	421

9u	(S)-1-methyl-5-(pyrazolo[1,5-a]pyridin-3-yl)-3-(1-(2,2,2-trifluoroethylsulfonyl)piperidin-3-yl)-1H-imidazo[4,5-b]pyridin-2(3H)-one	Example 6g and 2,2,2-trifluoroethanesulfonyl chloride	4	2.17	495

EXAMPLE 10

(*S*)-3-(9-(1-(2-(Dimethylamino)acetyl)piperidin-3-yl)-8-oxo-8,9-dihydro-7*H*-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile

To a solution of N,N-dimethylglicine (10 mg, 0.095 mmol) in anhydrous DMF (2 mL), HOBt.H_2O was added. After 15 min, EDC.HCl (24 mg, 0.126 mmol) and the compound obtained in example 6 (31 mg, 0.063 mmol) were added. The reaction mixture was stirred at room temperature for 2.5 h and the solvent was concentrated off. It was quenched with saturated $NaHCO_3$ aqueous solution (15 mL) and extracted with EtOAc (3x15 mL). The combined organic phases were dried over anhydrous Mg_2SO_4, filtered and concentrated. The crude residue was chromatographed on a silica gel flash system (ISCO Rf) using hexanes/acetone mixtures of increasing polarity as eluent to afford 8.2 mg of the titled compound (29% yield).

LC-MS (method 3): t_R = 1.67 min; m/z = 446 (MH^+).

Following a similar procedure to that described in example 10, but using the corresponding starting material, the following compound was obtained:

Example	Name	Starting Material	HPLC method	t_R (min)	m/z (MH^+)
10a	(*S*)-3-(9-(1-(2-hydroxyacetyl)piperidin-3-yl)-8-oxo-8,9-dihydro-7*H*-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	Example 6 and glicolic acid	3	1.52	419
10b	(S)-3-(9-(1-(2-hydroxy-2-methylpropanoyl)piperidin-3-yl)-8-oxo-8,9-dihydro-7H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	Example 6 and 2-hydroxy-2-methylpropanoic acid	3	1.75	447

20142017789 26 Mar 2014

10c	3-(8-oxo-9-((S)-1-((S)-tetrahydrofuran-2-carbonyl)piperidin-3-yl)-8,9-dihydro-7H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	Example 6 and (S)-tetrahydrofuran-2-carboxylic acid	3	1.75	459
10d	(S)-3-(9-(1-(2-methoxyacetyl)piperidin-3-yl)-8-oxo-8,9-dihydro-7H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	Example 6 and 2-methoxyacetic acid	3	1.65	433
10e	(S)-3-(9-(1-(2-ethylbutanoyl)piperidin-3-yl)-8-oxo-8,9-dihydro-7H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	Example 6 and 2-ethylbutanoic acid	3	2.20	459
10f	(S)-3-(9-(1-(2-(3-methylisoxazol-5-yl)acetyl)piperidin-3-yl)-8-oxo-8,9-dihydro-7H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	Example 6 and 2-(3-methylisoxazol-5-yl)acetic acid	3	1.82	484
10g	3-(9-((S)-1-((S)-2-methoxypropanoyl)piperidin-3-yl)-8-oxo-8,9-dihydro-7H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	Example 6 and *(S)*-2-methoxypropanoic acid	5	2.23	447
10h	(S)-3-(8-oxo-9-(1-(3,3,3-trifluoropropanoyl)piperidin-3-yl)-8,9-dihydro-7H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	Example 6 and 3,3,3-trifluoropropanoic acid	3	1.97	471
10i	(S)-2-(5-methylpyrazolo[1,5-a]pyridin-3-yl)-9-(1-propionylpiperidin-3-yl)-7H-purin-8(9H)-one	Example 6r and propionic acid	3	1.85	406
10j	(S)-9-(1-(2-methoxyacetyl)piperidin-3-yl)-2-(5-methylpyrazolo[1,5-a]pyridin-3-yl)-7H-purin-8(9H)-one	Example 6r and 2-methoxyacetic acid	3	1.72	422

2014201789 26 Mar 2014

10k	(S)-7-(2-methoxyacetyl)-9-(1-(2-methoxyacetyl)piperidin-3-yl)-2-(5-methylpyrazolo[1,5-a]pyridin-3-yl)-7H-purin-8(9H)-one	Example 6r and 2-methoxyacetic acid	3	2.13	494
10l	(S)-9-(1-acetylpiperidin-3-yl)-2-(5-methylpyrazolo[1,5-a]pyridin-3-yl)-7H-purin-8(9H)-one	Example 6r and acetic acid	3	1.70	392
10m	(S)-9-(1-(2-hydroxyacetyl)piperidin-3-yl)-2-(5-methylpyrazolo[1,5-a]pyridin-3-yl)-7H-purin-8(9H)-one	Example 6r and 2-hydroxyacetic acid	3	1.60	408
10n	(S)-3-(9-(1-(cyclopropanecarbonyl)piperidin-3-yl)-8-oxo-8,9-dihydro-7H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	Example 6 and cyclopropanecarboxylic acid	3	1.88	429
10o	(S)-3-(1-(2-hydroxy-2-methylpropanoyl)piperidin-3-yl)-1-methyl-5-(pyrazolo[1,5-a]pyridin-3-yl)-1H-imidazo[4,5-b]pyridin-2(3H)-one	Example 6g and 2-hydroxy-2-methylpropanoic acid	4	1.76	435
10p	(S)-3-(1-(2-hydroxyacetyl)piperidin-3-yl)-1-methyl-5-(pyrazolo[1,5-a]pyridin-3-yl)-1H-imidazo[4,5-b]pyridin-2(3H)-one	Examle 6g and 2-hydroxyacetic acid	4	1.59	407
10q	(S)-3-(1-(2-(dimethylamino)acetyl)piperidin-3-yl)-1-methyl-5-(pyrazolo[1,5-a]pyridin-3-yl)-1H-imidazo[4,5-b]pyridin-2(3H)-one	Examle 6g and N,N-dimethylglicine	4	1.65	434
10r	1-methyl-5-(pyrazolo[1,5-a]pyridin-3-yl)-3-((S)-1-((S)-tetrahydrofuran-2-carbonyl)piperidin-3-yl)-1H-imidazo[4,5-b]pyridin-2(3H)-one	Examle 6g and (S)-tetrahydrofuran-2-carboxylic acid	4	1.76	447

26 Mar 2014
2014201789

10s	(S)-1-methyl-5-(pyrazolo[1,5-a]pyridin-3-yl)-3-(1-(3,3,3-trifluoropropanoyl)piperidin-3-yl)-1H-imidazo[4,5-b]pyridin-2(3H)-one	Example 6g and 3,3,3-trifluoropropanoic acid	4	1.99	459

EXAMPLE 11

(S)-3-(2-(5-Cyanopyrazolo[1,5-a]pyridin-3-yl)-8-oxo-7*H*-purin-9(8H)-yl)-N,N-dimethylpiperidine-1-sulfonamide

To a solution of the compound obtained in example 6 (110 mg, 0.22 mmol) in anhydrous DMF (3 mL), N,N-dimethylsulfamoyl chloride (0.03 mL, 0.27 mmol) and anhydrous TEA (0.13 mL, 0.90 mmol) were added. The reaction mixture was stirred at room temperature for 18 h, and the solvent was concentrated off. It was quenched with saturated $NaHCO_3$ aqueous solution (15 mL) and extracted with EtOAc (3x15 mL). The combined organic phases were dried over anhydrous Mg_2SO_4, filtered and concentrated. The crude residue was chromatographed on a silica gel flash system (ISCO Rf) using hexanes/acetone mixtures of increasing polarity as eluent to afford 39.2 mg of the titled compound (38% yield).

LC-MS (method 1): t_R = 1.95 min; *m/z* = 468 (MH^+).

Following a similar procedure to that described in example 11, but using the corresponding starting materials, the following compound was obtained:

Example	Name	Starting Materials	HPLC method	tR (min)	m/z (MH+)
11a	(S)-N,N-dimethyl-3-(1-methyl-2-oxo-5-(pyrazolo[1,5-a]pyridin-3-yl)-1H-imidazo[4,5-b]pyridin-3(2H)-yl)piperidine-1-sulfonamide	Example 6g	4	2.05	456

EXAMPLE 12

3-(9-(1-Acetylpyrrolidin-3-yl)-7-methyl-8-oxo-8,9-dihydro-7H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile

a) ***tert*-Butyl 3-(2-(5-cyanopyrazolo[1,5-a]pyridin-3-yl)-8-oxo-7H-purin-9(8*H*)-yl)pyrrolidine-1-carboxylate**

Following a similar procedure to that described in example 1, but using tert-butyl 3-aminopyrrolidine-1-carboxylate instead of tetrahydro-2*H*-pyran-4-amine, the desired compound was obtained.

b) ***tert*-Butyl 3-(2-(5-cyanopyrazolo[1,5-a]pyridin-3-yl)-7-methyl-8-oxo-7H-purin-9(8H)-yl)pyrrolidine-1-carboxylate**

Following a similar procedure to that described in example 5, but using the compound obtained in previous section as starting material, the desired compound was obtained (25% yield).

c) **3-(7-Methyl-8-oxo-9-(pyrrolidin-3-yl)-8,9-dihydro-7H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile hydrochloride**

Following a similar procedure to that described in example 6, but using the compound obtained in previous section as starting material, the desired compound was obtained (100% yield).

d) **Title compound**

Following a similar procedure to that described in example 8, but using the compound obtained in previous section as starting material, the desired compound was obtained (22% yield).

LC-MS (method 2): t_R = 1.67 min; m/z = 403 (MH^+).

EXAMPLE 13

3-(7-Methyl-9-(1-(methylsulfonyl)pyrrolidin-3-yl)-8-oxo-8,9-dihydro-7H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile

Following a similar procedure to that described in example 9, but using the compound obtained in example 12 section c as starting material, the desired compound was obtained (15% yield).

LC-MS (method 2): t_R = 1.83 min; m/z = 439 (MH^+).

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

Example	Name	Starting Material	HPLC method	t_R (min)	m/z (MH^+)
13a	(S)-3-(7-methyl-9-(1-(methylsulfonyl)pyrrolidin-3-yl)-8-oxo-8,9-dihydro-7H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	Example 6h	3	2.35	439
13b	(R)-3-(7-methyl-9-(1-(methylsulfonyl)pyrrolidin-3-yl)-8-oxo-8,9-dihydro-7H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	Example 6i	3	2.35	439

2014201789 26 Mar 2014

13c	(S)-9-(1-(methylsulfonyl)pyrrolidin-3-yl)-2-(pyrazolo[1,5-a]pyridin-3-yl)-7H-purin-8(9H)-one	Example 6j	3	1.53	400
13d	(S)-7-methyl-9-(1-(methylsulfonyl)pyrrolidin-3-yl)-2-(pyrazolo[1,5-a]pyridin-3-yl)-7H-purin-8(9H)-one	Example 6k	3	1.77	414
13e	(S)-3-(9-(1-(methylsulfonyl)pyrrolidin-3-yl)-8-oxo-8,9-dihydro-7H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	Example 6l	3	1.63	425
13f	(R)-1-methyl-3-(1-(methylsulfonyl)pyrrolidin-3-yl)-5-(pyrazolo[1,5-a]pyridin-3-yl)-1H-imidazo[4,5-b]pyridin-2(3H)-one	Example 6m	3	1.90	413
13g	(R)-3-(1-(methylsulfonyl)pyrrolidin-3-yl)-5-(pyrazolo[1,5-a]pyridin-3-yl)-1H-imidazo[4,5-b]pyridin-2(3H)-one	Example 6n	3	1.72	399
13h	(R)-3-(9-(1-(methylsulfonyl)pyrrolidin-3-yl)-8-oxo-8,9-dihydro-7H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	Example 6o	3	1.62	425
13i	(S)-3-(1-(methylsulfonyl)pyrrolidin-3-yl)-5-(pyrazolo[1,5-a]pyridin-3-yl)-1H-imidazo[4,5-b]pyridin-2(3H)-one	Example 6p	3	1.72	399
13j	(S)-1-methyl-3-(1-(methylsulfonyl)pyrrolidin-3-yl)-5-(pyrazolo[1,5-a]pyridin-3-yl)-1H-imidazo[4,5-b]pyridin-2(3H)-one	Example 6q	3	1.92	413
13k	(S)-7-methyl-9-(1-(methylsulfonyl)piperidin-3-yl)-2-(pyrazolo[1,5-a]pyridin-3-yl)-7H-purin-8(9H)-one	Example 6u	3	1.93	428

EXAMPLE 14

(2*R*)-2-[2-(5-Cyanopyrazolo[1,5-*a*]pyridin-3-yl)-8-oxo-7,8-dihydro-9*H*-purin-9-yl]propanoic acid

To a suspension of example 1a (65 mg, 018 mmol) in dioxane (1.6 mL) and H_2O (0.8 mL) at 0 °C, $LiOH·H_2O$ (15 mg, 0.36 mmol) was added. The reaction mixture was stirred at 0 °C for 1 h and room temperature for 26 h. The pH of the solution was adjusted to 5 by adding 10 % HCl aqueous solution. The solvent was removed under vacuum and the resulting solid was suspended in Et_2O (10 mL) and concentrated. The resulting solid was washed with water (2x5 mL), hexanes (3 mL) and Et_2O (2x5 mL) to afford 57 mg of the desired product (91%).

LC-MS (method 1): t_R = 13.59 min; m/z = 350 (MH^+).

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

Example	Name	Starting Material	HPLC method	t_R (min)	m/z (MH^+)
14a	(2*S*)-2-[2-(5-Cyanopyrazolo[1,5-*a*]pyridin-3-yl)-8-oxo-7,8-dihydro-9*H*-purin-9-yl]propanoic acid	Example 1i	1	13.59	350
14b	(S)-2-(8-oxo-2-(pyrazolo[1,5-a]pyridin-3-yl)-7H-purin-9(8H)-yl)propanoic acid	Example 3e	3	1.10	325

EXAMPLE 15

(2*R*)-2-[2-(5-Cyanopyrazolo[1,5-*a*]pyridin-3-yl)-8-oxo-7,8-dihydro-9*H*-purin-9-yl]-*N*-(2,2,2-trifluoroethyl)propanamide

To a solution of $HOBt.H_2O$ (31 mg, 0.20 mmol) and TEA (0.068 mL, 0.49 mmol) in THF (1 mL), example 14 (70 mg, 0.20 mmol) was added. After 15 min, EDC.HCl (40 mg, 0.21 mmol) and 2,2,2-trifluoroethylamine hydrochloride (14.6 mg, 0.11 mmol) were added and the resulting mixture was stirred at room temperature for 3.5 days. Then, it was quenched with H_2O (5 mL) and extracted with EtOAc (3x15 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product thus obtained was chromatographed over silica gel using $MeOH/CH_2Cl_2$ mixtures of increasing polarity as eluent, to afford 18 mg of the desired compound (50 % yield).

LC-MS (method 1): t_R = 15.34 min; m/z = 431 (MH^+).

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

Example	Name	Starting Material	HPLC method	t_R (min)	m/z (MH^+)
15a	(2R)-(2-(5-cyanopyrazolo[1,5-a]pyridin-3-yl)-8-oxo-7H-purin-9(8H)-yl)-N-methylpropanamide	Example 14 and N-methylamine	1	13.62	363
15b	(2S)-2-[2-(5-cyanopyrazolo[1,5-a]pyridin-3-yl)-8-oxo-7,8-dihydro-9H-purin-9-yl]-3-methyl-N-(2,2,2-trifluoroethyl)butanamide	(2S)-2-[2-(5-cyanopyrazolo[1,5-a]pyridin-3-yl)-8-oxo-7,8-dihydro-9H-purin-9-yl)-3-methylbutanoic acid (1) and 2,2,2-trifluoroethylamine	3	2.08	459
15c	(R)-2-(2-(5-cyanopyrazolo[1,5-a]pyridin-3-yl)-8-oxo-7H-purin-9(8H)-yl)-N-(2-hydroxyethyl)propanamide	Example 14 and 2-aminoethanol	3	1.35	393
15d	(R)-2-(2-(5-cyanopyrazolo[1,5-a]pyridin-3-yl)-8-oxo-7H-purin-9(8H)-yl)-N-(cyclopropylmethyl)propanamide	Example 14 and cyclopropylmethanamine	3	1.75	403
15e	(R)-2-(2-(5-cyanopyrazolo[1,5-a]pyridin-3-yl)-8-oxo-7H-purin-9(8H)-yl)-N-(2-(dimethylamino)ethyl)propanamide	Example 14 and N1,N1-dimethylethane-1,2-diamine	3	1.48	420
15f	(R)-2-(2-(5-cyanopyrazolo[1,5-a]pyridin-3-yl)-8-oxo-7H-purin-9(8H)-yl)-N-ethylpropanamide	Example 14 and N-ethylamine	3	1.57	377
15g	(R)-2-(2-(5-cyanopyrazolo[1,5-a]pyridin-3-yl)-8-oxo-7H-purin-9(8H)-yl)-N-isopropylpropanamide	Example 14 and N-isopropylamine	3	1.70	391
15h	(R)-2-(2-(5-cyanopyrazolo[1,5-a]pyridin-3-yl)-8-oxo-7H-purin-9(8H)-yl)-N,N-dimethylpropanamide	Example 14 and N,N-dimethylamine	3	1.53	377

15i	(S)-2-(2-(5-cyanopyrazolo[1,5-a]pyridin-3-yl)-8-oxo-7H-purin-9(8H)-yl)-N-(2,2,2-trifluoroethyl)propanamide	Example 14a and 2,2,2-trifluoroethylamine	3	1.72	431
15j	(S)-N-methyl-2-(8-oxo-2-(pyrazolo[1,5-a]pyridin-3-yl)-7H-purin-9(8H)-yl)propanamide	Example 14b and N-methylamine	3	1.35	338
15k	(S)-N,N-dimethyl-2-(8-oxo-2-(pyrazolo[1,5-a]pyridin-3-yl)-7H-purin-9(8H)-yl)propanamide	Example 14b and N,N-dimethylamine	5	1.90	352

(1) Obtained as example 14 but using HCl/Dioxane 4M/H_2O (1:1) instead of LiOH·H2O, and L-Valine methyl ester hydrochloride as starting material.

EXAMPLE 16

3-(7-(2-Methoxyethyl)-8-oxo-9-(tetrahydro-2*H*-pyran-4-yl)-8,9-dihydro-7*H*-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile

To a solution of example 1 (50 mg, 0.14 mmol) in DMF (8 mL), 55-65% NaH dispersion in mineral oil (6 mg, 0.15 mmol) was added and the resulting solution was stirred at room temperature for 10 min. Then 2-bromoethyl methyl ether (0.032 mL, 0.34 mmol) was added and the reaction mixture was stirred at 50 °C for 14.5 h. The reaction mixture was quenched with H_2O (10 mL) and extracted with EtOAc (3x10 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product thus obtained was chromatographed over silica gel using EtOAc/hexanes mixtures of increasing polarity as eluent, to afford 36 mg of the desired compound (62% yield).

LC-MS (method 1): t_R = 16.17 min; m/z = 420 (MH^+).

Following a similar procedure to that described in example 16, but using in each case the corresponding starting materials, the following compounds were obtained:

Example	Name	Starting Material	HPLC method	t_R (min)	m/z (MH^+)
16a	(*S*)-3-(9-(1-(2-cyanoacetyl)piperidin-3-yl)-7-(2-(dimethylamino)ethyl)-8-oxo-8,9-dihydro-7*H*-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	2-bromo-N,N-dimethylethanamine and example 1b (1)	.2	1.95	499

2014201789 26 Mar 2014

16b	(S)-3-(7-(2-(dimethylamino)ethyl)-8-oxo-9-(piperidin-3-yl)-8,9-dihydro-7H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	2-bromo-N,N-dimethylethanamine and example 1b (2)	2	1.83	432
16c	7-(2-(dimethylamino)ethyl)-2-(pyrazolo[1,5-a]pyridin-3-yl)-9-(tetrahydro-2H-pyran-4-yl)-7H-purin-8(9H)-one)	2-bromo-N,N-dimethylethanamine and example 3	2	1.921	408
16d	3-(7-(2-(dimethylamino)ethyl)-8-oxo-9-(tetrahydro-2H-pyran-4-yl)-8,9-dihydro-7H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	2-bromo-N,N-dimethylethanamine and example 1	1	14.79	433
16e	3-(7-(2-(dimethylamino)ethyl)-9-(8-fluorochroman-4-yl)-8-oxo-8,9-dihydro-7H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	2-bromo-N,N-dimethylethanamine and example 1p	4	2.12	499
16f	3-(9-(8-fluorochroman-4-yl)-7-(2-methoxyethyl)-8-oxo-8,9-dihydro-7H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	2-bromoethyl methyl ether and example 1p	4	2.20	486
16g	3-(9-(8-fluorochroman-4-yl)-7-(3-hydroxypropyl)-8-oxo-8,9-dihydro-7H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	3-bromopropan-1-ol and example 1p	4	1.96	486
16h	(S)-3-(3-(1-(2-(dimethylamino)ethyl)-2-oxo-5-(pyrazolo[1,5-a]pyridin-3-yl)-1H-imidazo[4,5-b]pyridin-3(2H)-yl)piperidin-1-yl)-3-oxopropanenitrile	2-bromo-N,N-dimethylethanamine and example 2a (1)	4	1.73	473
16i	(S)-3-(3-(1-(2-methoxyethyl)-2-oxo-5-(pyrazolo[1,5-a]pyridin-3-yl)-1H-imidazo[4,5-b]pyridin-3(2H)-yl)piperidin-1-yl)-3-oxopropanenitrile	2-bromoethyl methyl ether and example 2a (1)	4	1.82	460

26 Mar 2014
2014201789

16j	*(S)*-3-(3-(1-(cyclopropylmethyl)-2-oxo-5-(pyrazolo[1,5-a]pyridin-3-yl)-1H-imidazo[4,5-b]pyridin-3(2H)-yl)piperidin-1-yl)-3-oxopropanenitrile	(bromomethyl)cyclopropane and example 2a (1)	4	2.08	456

(1) followew by a similar procedure to that described in example 6 (tert-butoxtcarbonyl cleavage) and 7 (amide formation).

(2) followew by *tert*-butoxycarbonyl cleavage as example 6

.

EXAMPLE 17

3-(7-(2-Hydroxyethyl)-8-oxo-9-(tetrahydro-2H-pyran-4-yl)-8,9-dihydro-7*H*-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile

a) 3-(7-(2-(tert-Butyldimethylsilyloxy)ethyl)-8-oxo-9-(tetrahydro-2*H*-pyran-4-yl)-8,9-dihydro-7*H*-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile

To a solution of example 1 (50 mg, 0.14 mmol) in DMF (8 mL), 55-65% NaH dispersion in mineral oil (6 mg, 0.15 mmol) was added. The resulting solution was stirred at room temperature for 10 min. Then (2-bromoethoxy)-*tert*-butyldimethylsilane (0.074 mL, 0.34 mmol) was added and the reaction was stirred at 50 °C for 14.5 h. The reaction mixture was quenched with H_2O (10 mL) and extracted with EtOAc (3x10 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product thus obtained was chromatographed over silica gel using hexanes/EtOAc mixtures of increasing polarity as eluent, to afford 55 mg of the desired compound (76 % yield).

b) Title compound

To a solution of the compound obtained in the previous section (55 mg, 0.10 mmol) in THF (5 mL) 1 M TBAF solution in THF (0.14 mL, 0.14 mmol) was added and the resulting solution was stirred at room temperature for 1 h. The reaction mixture was quenched with H_2O (10 mL) and extracted with EtOAc (3x10 mL) and CH_2Cl_2 (2x10 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product thus obtained was chromatographed over silica gel using MeOH/EtOAc mixtures of increasing polarity as eluent, to afford 39 mg of the desired compound (91 % yield).

LC-MS (method 1): t_R = 14.13 min; m/z = 406 (MH^+).

Following a similar procedure to that described in example 17, but using in each case the corresponding starting materials, the following compounds were obtained:

2014201789 26 Mar 2014

Example	Name	Starting Material	HPLC method	t_R (min)	m/z (MH^+)
17a	(*S*)-3-(9-(1-(2-cyanoacetyl)piperidin-3-yl)-7-(2-hydroxyethyl)-8-oxo-8,9-dihydro-7*H*-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	Example 1b (1)	1	1.68	472
17b	(*S*)-3-(7-(2-hydroxyethyl)-8-oxo-9-(piperidin-3-yl)-8,9-dihydro-7*H*-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile hydrochloride	Example 1b (2)	1	1.55	405
17c	3-(9-(8-fluorochroman-4-yl)-7-(2-hydroxyethyl)-8-oxo-8,9-dihydro-7H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	Example 1p	1	15.99	472

(1) Followed by a similar procedure to that described in example 6 (tert-butoxtcarbonyl cleavage) and 7 (amide formation).

(2) Followed by *tert*-butoxycarbonyl cleavage as example 6

EXAMPLE 18

3-(9-Tetrahydro-2*H*-pyran-4-yl-9H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile

To a suspension of the compound obtained in exemple 1 section d (100 mg, 0.30 mmol) in EtOH (1 mL), PTSA monohydrate (5.7 mg, 0.03 mmol) and triethylorthoformate (1 mL) were added. The reaction mixture was heated in a CEM Explorer microwave oven at 123 °C and 270 W for 30 min. Then, it was evaporated to dryness. The crude product thus obtained was chromatographed over silica gel using MeOH/EtOAc mixtures of increasing polarity as eluent, to afford 81 mg of the desired compound (79 % yield).

LC-MS (method 1): t_R = 14.56 min; m/z = 346 (MH^+).

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

Example	Name	Starting Material	HPLC method	t_R (min)	m/z (MH^+)
18a	3-(8-methyl-9-tetrahydro-2*H*-pyran-4-yl-9H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	Example 1 section d and triethylorthoacetate	1	14.77	360
18b	3-(9-(4,4-difluorocyclohexyl)-8-methyl-9H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	triethylorthoacetate and 3-(5-amino-4-(4,4-difluorocyclohexylamino)pyrimidin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile (1)	2	2.17	394
18c	3-(9-(1,1-dioxotetrahydrothien-3-yl)-8-methyl-9H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	triethylorthoacetate and 3-(5-amino-4-(1,1-dioxotetrahydrothien-3-yl)aminopyrimidin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile (2)	2	1.65	394
18d	5-(pyrazolo[1,5-a]pyridin-3-yl)-3-(tetrahydro-2H-pyran-4-yl)-3H-imidazo[4,5-b]pyridine	Reference example 2g and triethylorthoformate	3	1.85	320
18e	(S)-tert-butyl 3-(5-(5-cyanopyrazolo[1,5-a]pyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)piperidine-1-carboxylate	Reference example 2h and triethylorthoformate	3	2.33	444
18f	(S)-tert-butyl 3-(5-(5-cyanopyrazolo[1,5-a]pyridin-3-yl)-2-methyl-3H-imidazo[4,5-b]pyridin-3-yl)piperidine-1-carboxylate	Reference example 2h and triethylorthoacetate	3	2.57	458
18g	2-methyl-5-(pyrazolo[1,5-a]pyridin-3-yl)-3-(tetrahydro-2H-pyran-4-yl)-3H-imidazo[4,5-b]pyridine	Reference example 2g and triethylorthoacetate	3	1.92	334
18h	3-(9-(*trans*-4-hydroxycyclohexyl)-8-methyl-9H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	Reference example 2j and triethylorthoacetate	3	1.70	374

18i	(S)-tert-butyl 3-(5-(pyrazolo[1,5-a]pyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)piperidine-1-carboxylate	Reference example 2d and triethylorthoformate	3	1.77	386

(1) obtained in example 1e section d

(2) obtained in example 1f section d

EXAMPLE 19

3-(3-(Tetrahydro-*2H*-pyran-4-yl)-*3H*-imidazo[4,5-b]pyridin-5-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile

To a suspension of the compound obtained in example 2 section d (33.6 mg, 0.1 mmol) in EtOH (1.5 mL), citric acid (2 mg, 0.1 mmol) and triethyl orthoformate (340 µL, 2 mmol) were added. The reaction mixture was heated in a CEM Explorer microwave oven at 145 °C and 270 W for 2.5 hours. The crude residue was cromatographed on a silica gel flash system (ISCO Rf) using hexanes/acetone mixtures of increasing polarity as eluent to afford 14.2 mg of the desired product (41% yield).

LC-MS (method 3): t_R = 1.76 min; m/z = 345 (MH^+).

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

Example	Name	Starting Material	HPLC method	t_R (min)	m/z (MH^+)
19a	(S)-3-(3-(1-acetylpiperidin-3-yl)-3H-imidazo[4,5-b]pyridin-5-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	Reference example 2f	5	2.22	386

EXAMPLE 20

3-(2-Methyl-3-(tetrahydro-2H-pyran-4-yl)-3H-imidazo[4,5-b]pyridin-5-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile

To a solution of the compound obtained in example 2 section d (56.4 mg, 0.169 mmol) in EtOH (1.5 mL), PTSA monohydrate (3.21 mg, 0.017 mmol) and triethyl orthoacetate (547 mg, 3.37 mmol) were added. The reaction mixture was heated in a CEM Explorer microwave oven at 145 °C and 270 W for 2.5 hours. The crude residue was cromatographed on a silica gel flash system (ISCO Rf) using CH_2Cl_2/MeOH mixtures of increasing polarity a eluent to afford the desired product (15% yield).

LC-MS (method 3): t_R = 1.79 min; m/z = 359.5 (MH^+).

EXAMPLE 21

3-(8-(1-Methyl-*1H*-imidazol-2-yl)-9-(tetrahydro-*2H*-pyran-4-yl)-9H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile

To a solution of the compound obtained in example 1 section d (100 mg, 0.30 mmol) in AcOH (0.025 mL) and DMA (2.5 mL), 1-methyl-1H-imidazole-2-carbaldehyde (46 mg, 0.42 mmol) was added. The reaction mixture was stirred in a sealed tube at 140 °C for 19 h. The crude mixture was quenched with H_2O (10 mL), extracted with EtOAc (3x10 mL) and the combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product thus obtained was chromatographed over silica gel using hexanes/EtOAc mixtures of increasing polarity as eluent, to afford 40 mg of the desired compound (31 % yield).

LC-MS (method 1): t_R = 16.436 min; m/z = 426 (MH^+).

Following a similar procedure to that described in example 21, but using the corresponding starting material, the following compound was obtained:

Example	Name	Starting Material	HPLC method	t_R (min)	m/z (MH^+)
21a	3-(8-(pyrimidin-5-yl)-9-(tetrahydro-2H-pyran-4-yl)-9H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	Example 1 section d and pyrimidine-5-carbaldehyde	4	1.67	424
21b	3-(9-(8-fluorochroman-4-yl)-8-(pyrimidin-5-yl)-9H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	Reference example 2e and pyrimidine-5-carbaldehyde	1	16.34	490
21c	3-(9-(8-fluorochroman-4-yl)-8-(1-methyl-1H-imidazol-2-yl)-9H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	Reference example 2e and 1-methyl-1H-imidazole-2-carbaldehyde	1	18.4	492
21d	2-(pyrazolo[1,5-a]pyridin-3-yl)-8-(1H-pyrrol-2-yl)-9-(tetrahydro-2H-pyran-4-yl)-9H-purine	Reference example 2c and 1H-pyrrole-2-carbaldehyde	3	2.15	386
21e	8-(5-methylthiophen-2-yl)-2-(pyrazolo[1,5-a]pyridin-3-yl)-9-(tetrahydro-2H-pyran-4-yl)-9H-purine	Reference example 2c and 5-methylthiophene-2-carbaldehyde	3	2.52	417

21f	8-(1-methyl-1H-imidazol-2-yl)-2-(pyrazolo[1,5-a]pyridin-3-yl)-9-(tetrahydro-2H-pyran-4-yl)-9H-purine	Reference example 2c and 1-methyl-1H-imidazole-2-carbaldehyde	3	2.05	401
21g	2-(pyrazolo[1,5-a]pyridin-3-yl)-9-(tetrahydro-2H-pyran-4-yl)-8-(2,2,2-trifluoroethyl)-9H-purine	Reference example 2c and 3,3,3-trifluoropropanal	3	2.22	403
21h	8-(1H-pyrazol-3-yl)-2-(pyrazolo[1,5-a]pyridin-3-yl)-9-(tetrahydro-2H-pyran-4-yl)-9H-purine	Reference example 2c and 1H-pyrazole-3-carbaldehyde	3	1.83	387
21i	8-(1-methyl-1H-pyrrol-2-yl)-2-(pyrazolo[1,5-a]pyridin-3-yl)-9-(tetrahydro-2H-pyran-4-yl)-9H-purine	Reference example 2c and 1-methyl-1H-pyrrole-2-carbaldehyde	3	2.33	400
21j	2-(2-(pyrazolo[1,5-a]pyridin-3-yl)-9-(tetrahydro-2H-pyran-4-yl)-9H-purin-8-yl)thiazole	Reference example 2c and thiazole-2-carbaldehyde	3	2.43	404
21k	2-(pyrazolo[1,5-a]pyridin-3-yl)-9-(tetrahydro-2H-pyran-4-yl)-8-(thiophen-2-yl)-9H-purine	Reference example 2c and thiophene-2-carbaldehyde	3	2.32	403
21l	(S)-3-(9-(1-acetylpiperidin-3-yl)-8-(pyrimidin-5-yl)-9H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	Reference example 2 and pyrimidine-5-carbaldehyde	3	1.8	465
21m	(S)-tert-butyl 3-(2-methyl-5-(pyrazolo[1,5-a]pyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)piperidine-1-carboxylate	Reference example 2d and acetaldehydee	3	2.60	433

EXAMPLE 22

3-[8-(Ethylamino)-9-tetrahydro-*2H*-pyran-4-yl-*9H*-purin-2-yl]pyrazolo[1,5-a]pyridine-5-carbonitrile

To a suspension of the compound obtained in example 1 section d (100 mg, 0.30 mmol) in CH_2Cl_2 (2 mL), ethyl isothiocyanate (0.042 mL, 0.48 mmol), EDC.HCl (171 mg, 0.89 mmol) and DIPEA (0.25 mL, 1.49 mmol) were added. The reaction mixture was heated in a CEM Explorer microwave oven at 80 °C and 150 W for 30 min. Then, it was evaporated to dryness. The crude product thus obtained was chromatographed over silica gel using MeOH/EtOAc mixtures of increasing polarity as eluent, to afford 42 mg of the desired compound (36 % yield).

LC-MS (method 1): t_R = 15.64 min; m/z = 389 (MH^+).

Following a similar procedure to that described in example 22, but using the corresponding starting material, the following compound was obtained:

Example	Name	Starting Material	HPLC method	t_R (min)	m/z (MH^+)
22a	3-(8-(pyridin-3-ylamino)-9-(tetrahydro-2H-pyran-4-yl)-9*H*-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	Example 1 section d, pyridine-3-isothiocyanate	1	16.20	438
22b	3-(8-(ethylamino)-9-(8-fluorochroman-4-yl)-9H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	Reference example 2e and ethyl isothiocyanate	1	17.07	455
22c	3-(9-(8-fluorochroman-4-yl)-8-(pyridin-3-ylamino)-9H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	Reference example 2e and pyridine-3-isothiocyanate	1	17.22	504

EXAMPLE 23

8-Cyclopentyl-2-(pyrazolo[1,5-*a*]pyridin-3-yl)-9-(tetrahydro-2*H*-pyran-4-yl)-9*H*-purine

To a solution of reference example 2c (0.05 g, 0.16 mmol) in DMF (1 mL), cyclopentanecarbaldehyde (0.018 mL, 0.17 mmol) and sodium bisulfite (0.030 g, 0.29 mmol) were added. The reaction mixture was stirred at 130 °C for 6h. The solvent was concentrated off and the crude residue was cromatographed on a silica gel flash system (ISCO Companion) using CH_2Cl_2/MeOH mixtures of increasing polarity as eluent to afford 37 mg of the desired product (60% yield).

LC-MS (method 3): t_R = 2.40 min; m/z = 389 (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:

2014201789 26 Mar 2014

Example	Name	Starting Material	HPLC method	t_R (min)	m/z (MH^+)
23a	(S)-3-(9-(1-acetylpiperidin-3-yl)-8-ethyl-9H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	Reference example 2 and propionaldehyde	5	2.42	415
23b	(S)-3-(9-(1-acetylpiperidin-3-yl)-8-isopropyl-9H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	Reference example 2 and isobutyraldehyde	5	2.57	429
23c	(S)-3-(9-(1-acetylpiperidin-3-yl)-8-methyl-9H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	Reference example 2 and acetaldehyde	3	1.78	401
23d	8-cyclopropyl-2-(pyrazolo[1,5-a]pyridin-3-yl)-9-(tetrahydro-2H-pyran-4-yl)-9H-purine	Reference example 2c and cyclopropanecarbaldehyde	3	2.05	361

EXAMPLE 24

(S)-3-(1-Acetylpiperidin-3-yl)-1-methyl-5-(pyrazolo[1,5-a]pyridin-3-yl)-1H-imidazo[4,5-b]pyridin-2(3H)-one

To a solution of example 6g (250 mg, 0.65 mmol) in pyridine (10 mL), acetyl chloride (0.92 mL, 1.3 mmol) was added. The reaction mixture was stirred at room temperature for 5h. The solvent was concentrated off and the crude residue was cromatographed on a silica gel flash system (SP1 Biotage) using EtOAc/MeOH mixtures of increasing polarity as eluent to afford 196 mg of the desired product (78% yield).

LC-MS (method 4): t_R = 1.66 min; m/z = 391 (MH^+).

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

Example	Name	Starting Material	HPLC method	t_R (min)	m/z (MH^+)
24a	(S)-1-methyl-3-(1-pivaloylpiperidin-3-yl)-5-(pyrazolo[1,5-a]pyridin-3-yl)-1H-imidazo[4,5-b]pyridin-2(3H)-one	Example 6g and pivaloyl chloride	4	2.10	433

2014201789 26 Mar 2014

24b	(S)-3-(1-(4-fluorobenzoyl)piperidin-3-yl)-1-methyl-5-(pyrazolo[1,5-a]pyridin-3-yl)-1H-imidazo[4,5-b]pyridin-2(3H)-one	Example 6g and 4-fluorobenzoyl chloride	4	2.11	472
24c	(S)-1-methyl-3-(1-propionylpiperidin-3-yl)-5-(pyrazolo[1,5-a]pyridin-3-yl)-1H-imidazo[4,5-b]pyridin-2(3H)-one	Example 6g and propionyl chloride	4	1.79	405

EXAMPLE 25

(S)-1-(3-(1-Methyl-2-oxo-5-(pyrazolo[1,5-a]pyridin-3-yl)-1H-imidazo[4,5-b]pyridin-3(2H)-yl)piperidine-1-carbonyl)cyclopropanecarbonitrile

To a solution of 1-cyano-1-cyclopropanecarboxylic acid (65 mg, 0.58 mmol), in DMF (7 mL), DIEA (0.31 mL, 1.7 mmol), example 6g (248 mg, 0.64 mmol) and HBTU (266 mg, 0.70 mmol) were added. The reaction mixture was stirred at room temperature overnight. The solvent was concentrated off and the crude residue was cromatographed on a silica gel flash system (SP1 Biotage) using EtOAc/MeOH mixtures of increasing polarity as eluent to afford the desired with quantitative yield.

LC-MS (method 4): t_R = 1.92 min; m/z = 442 (MH^+).

Following a similar procedure to that described in example 25, but using in each case the corresponding starting materials, the following compounds were obtained:

Example	Name	Starting Materials	HPLC method	t_R (min)	m/z (MH^+)
25a	9-(1-isobutyrylpiperidin-4-yl)-2-(pyrazolo[1,5-a]pyridin-3-yl)-7H-purin-8(9H)-one	Example 6d and isobutyric acid	4	1.59	406
25b	9-(1-(2-(dimethylamino)acetyl)piperidin-4-yl)-2-(pyrazolo[1,5-a]pyridin-3-yl)-7H-purin-8(9H)-one	Example 6d and 2-(dimethylamino)acetic acid	4	1.34	421

EXAMPLE 26

(S)-Methyl 3-(2-(5-cyanopyrazolo[1,5-a]pyridin-3-yl)-8-oxo-7H-purin-9(8H)-yl)piperidine-1-carboxylate

To a solution of example 6 (200 mg, 0.26 mmol) in DMF (2.6 mL), methyl chloroformate (27 mg, 0.28 mmol) and DIPEA (0.068 mL, 0.39 mmol) were added. The reaction mixture was stirred at room temperature overnight. The reaction mixture was evaporated under reduced pressure, dissolved in CH_2Cl_2, and washed thrice with saturated

$NaHCO_3$ aqueous solution. The combined organic phases were dried over MgSO4 and concentrated to dryness. The crude residue was cromatographed on a silica gel flash system (ISCO Combiflash) using CH_2Cl_2/MeOH mixtures of increasing polarity as eluent to afford 36 mg of the desired product (32% yield).

LC-MS (method 5): t_R = 2.37 min; m/z = 419 (MH^+).

Following a similar procedure to that described in example 26, but using in each case the corresponding starting materials, the following compounds were obtained:

Example	Name	Starting Materials	HPLC method	t_R (min)	m/z (MH^+)
26a	(S)-ethyl 3-(2-(5-cyanopyrazolo[1,5-a]pyridin-3-yl)-8-oxo-7H-purin-9(8H)-yl)piperidine-1-carboxylate	Example 6 and ethyl chloroformate	5	2.53	433
26b	(S)-isobutyl 3-(2-(5-cyanopyrazolo[1,5-a]pyridin-3-yl)-8-oxo-7H-purin-9(8H)-yl)piperidine-1-carboxylate	Example 6 and isobutyl chloroformate	5	2.82	461
26c	(S)-3-(2-(5-cyanopyrazolo[1,5-a]pyridin-3-yl)-8-oxo-7H-purin-9(8H)-yl)-N-isopropylpiperidine-1-carboxamide	Example 6 and isopropyl isocyanate	5	2.33	446
26d	(S)-N-tert-butyl-3-(2-(5-cyanopyrazolo[1,5-a]pyridin-3-yl)-8-oxo-7H-purin-9(8H)-yl)piperidine-1-carboxamide	Example 6 and *tert*-butyl isocyanate	5	2.52	460°
26e	(S)-ethyl 9-(1-(2-cyanoacetyl)piperidin-3-yl)-8-oxo-2-(pyrazolo[1,5-a]pyridin-3-yl)-8,9-dihydro-7H-purine-7-carboxylate	Example 7f and ethyl chloroformate	5	2.62	475
26f	(S)-3-(3-(7-acetyl-8-oxo-2-(pyrazolo[1,5-a]pyridin-3-yl)-7H-purin-9(8H)-yl)piperidin-1-yl)-3-oxopropanenitrile	Example 7f and acetyl chloride	5	2.60	445
26g	(S)-9-(1-acetylpiperidin-3-yl)-7-methyl-2-(pyrazolo[1,5-a]pyridin-3-yl)-7H-purin-8(9H)-one	Example 6u and acetyl chloride	3	1.80	392

2014201789 26 Mar 2014

26h	(S)-N-isopropyl-3-(1-methyl-2-oxo-5-(pyrazolo[1,5-a]pyridin-3-yl)-1H-imidazo[4,5-b]pyridin-3(2H)-yl)piperidine-1-carboxamide	Example 7p and isopropyl isocyanate	4	1.85	434
26i	(S)-3-(3-(1-acetyl-2-oxo-5-(pyrazolo[1,5-a]pyridin-3-yl)-1H-imidazo[4,5-b]pyridin-3(2H)-yl)piperidin-1-yl)-3-oxopropanenitrile	Example 7p and acetyl chloride	4	2.01	444
26j	(S)-ethyl 3-(1-(2-cyanoacetyl)piperidin-3-yl)-2-oxo-5-(pyrazolo[1,5-a]pyridin-3-yl)-2,3-dihydro-1H-imidazo[4,5-b]pyridine-1-carboxylate	Example 7p and ethyl chloroformate	4	1.97	474

EXAMPLE 27

(S)-3-(9-(1-(1-Cyanocyclopropanecarbonyl)piperidin-3-yl)-8-oxo-8,9-dihydro-7H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile

Following a similar procedure to that described in example 25, but using HATU instead of HBTU, and example 6 instead of example 6g, the desired compound was obtained (30% yield).

LC-MS (method 3): t_R = 1.87 min; m/z = 454 (MH^+).

Following a similar procedure to that described in example 27, but using the corresponding starting materials, the following compound was obtained:

Example	Name	Starting Materials	HPLC method	tR (min)	m/z (MH+)
27a	(S)-3-(9-(1-(1-hydroxycyclopropanecarbonyl)piperidin-3-yl)-8-oxo-8,9-dihydro-7H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile	Example 6 and 1-hydroxycyclopropanecarboxylic acid	3	1.7	455

EXAMPLE 28

(R)-3-(9-(1-Hydroxypropan-2-yl)-8-oxo-8,9-dihydro-7H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile

To a solution of example 14 (60 mg, 0.17 mmol) in THF (10 mL) at 0 °C, 1 M THF borane complex solution in THF (0.69 mL, 0.69 mmol) was added. The reaction mixture was stirred at room temperature overnight, quenched with MeOH (10 mL) and the reaction mixture was evaporated under reduced pressure. The crude residue was cromatographed on a silica gel flash system (ISCO Combiflash) using CH_2Cl_2/MeOH mixtures of increasing polarity as eluent to afford 4 mg of the desired product (7% yield).

LC-MS (method 3): t_R = 2.02 min; m/z = 336 (MH^+).

EXAMPLE 29

(S)-3-(3-(2-(5-Methylpyrazolo[1,5-a]pyridin-3-yl)-9H-purin-9-yl)piperidin-1-yl)-3-oxopropanenitrile

a) (S)-tert-Butyl 3-(2-(5-methylpyrazolo[1,5-a]pyridin-3-yl)-9H-purin-9-yl)piperidine-1-carboxylate

Following a similar procedure to that described in example 18, but using reference example 2a instead of the compound obtained in example 1 section d, the desired compound was obtained (10% yield).

LC-MS (method 3): t_R = 2.53 min; m/z = 434 (MH^+).

b) (S)-2-(5-Methylpyrazolo[1,5-a]pyridin-3-yl)-9-(piperidin-3-yl)-9H-purine hydrochloride

Following a similar procedure to that described in example 6, but using the compound obtained in the previous section, the desired compound was obtained (quantitative yield).

LC-MS (method 3): t_R = 1.7 min; m/z = 334 (MH^+).

c) Title compound

Following a similar procedure to that described in example 7, but using the compound obtained in the previous section, the desired compound was obtained (57 % yield).

LC-MS (method 3): t_R = 1.78 min; m/z = 401 (MH^+).

EXAMPLE 30

1-(4-(2-(Pyrazolo[1,5-a]pyridin-3-yl)-9H-purin-9-yl)piperidin-1-yl)ethanone

a) 9-(Piperidin-4-yl)-2-(pyrazolo[1,5-a]pyridin-3-yl)-9H-purine hydrochloride

Following a similar procedure to that described in example 29 section a and b, but using the compound obtained in reference example 2b instead of reference examlpe 2a, the desired compound was obtained (10% yield).

b) Title compound

Following a similar procedure to that described in example 24, but using the compound obtained in the previous section, the desired compound was obtained (quantitative yield).

LC-MS (method 4): t_R = 1.35 min; m/z = 362 (MH^+).

EXAMPLE 31

(S)-(9-(1-(2-Cyanoacetyl)piperidin-3-yl)-8-oxo-2-(pyrazolo[1,5-a]pyridin-3-yl)-8,9-dihydro-7H-purin-7-yl)methyl acetate

a) (S)-tert-Butyl 3-(7-(acetoxymethyl)-8-oxo-2-(pyrazolo[1,5-a]pyridin-3-yl)-7H-purin-9(8H)-yl)piperidine-1-carboxylate

Following a similar procedure to that described in example 4, but using the compound obtained in example 3b instead of example 1 and bromomethyl acetate instead of methyl iodide, the desired compound was obtained (83% yield).

LC-MS (method 3): t_R = 2.72 min; m/z = 508 (MH^+).

b) (S)-(8-Oxo-9-(piperidin-3-yl)-2-(pyrazolo[1,5-a]pyridin-3-yl)-8,9-dihydro-7H-purin-7-yl)methyl acetate hydrochloride

Following a similar procedure to that described in example 6, but using the compound obtained in the previous section, the desired compound was obtained (quantitative yield).

LC-MS (method 3): t_R = 1.80 min; m/z = 408 (MH^+).

c) Title compound

Following a similar procedure to that described in example 7, but using the compound obtained in the previous section, the desired compound was obtained (36 % yield).

LC-MS (method 3): t_R = 1.82 min; m/z = 475 (MH^+).

Following a similar procedure to that described in example 31, but using the corresponding starting materials, the following compound was obtained:

Example	Name	Starting Materials	HPLC method	tR (min)	m/z (MH+)
31a	(S)-(3-(1-(2-cyanoacetyl)piperidin-3-yl)-2-oxo-5-(pyrazolo[1,5-a]pyridin-3-yl)-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)methyl acetate	Example 7p	4	1.84	474

EXAMPLE 32

(R)-3-(9-(1-Hydroxypropan-2-yl)-7-methyl-8-oxo-8,9-dihydro-7H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile

To a solution of example 28 (20 mg, 0.06 mmol) in AcN (2 mL) and DMF (0.5 mL) silver (I) oxide (28 mg, 0.12 mmol) and methyl iodide (0.006 mL, 0.09 mmol) were added. The reaction mixture was stirred at room temperature overnight. The reaction mixture was filtered through a plug of Celite® and the solvent was evaporated under reduced pressure. The crude residue was cromatographed on a silica gel flash system (ISCO Combiflash) using CH_2Cl_2/MeOH mixtures of increasing polarity as eluent to afford 6 mg of the desired product (29% yield).

LC-MS (method 3): t_R = 1.75 min; m/z = 350 (MH^+).

EXAMPLE 33

2-(Pyrazolo[1,5-a]pyridin-3-yl)-9-(tetrahydro-2H-pyran-4-yl)-9H-purin-8-amine

To a solution of reference example 2c (144 mg, 0.46 mmol) in EtOH (4 mL), cyanogen bromide (147 mg, 1.39 mmol) was added. The reaction mixture was stirred at 70 °C overnight. The reaction mixture was evaporated under reduced pressure, dissolved in EtOAc, and washed thrice with saturated $NaHCO_3$ aqueous solution. The combined organic phases were dried over $MgSO_4$ and concentrated to dryness. The reaction crude was used in next step without further purification.

LC-MS (Method 3) : t_R = 1.53 min; m/z = 336 (MH^+)

EXAMPLE 34

1-(2-(Pyrazolo[1,5-a]pyridin-3-yl)-9-(tetrahydro-2H-pyran-4-yl)-9H-purin-8-yl)pyrrolidin-2-one

To a suspension of example 33 (25 mg, 0.075 mmol) in DMF (1.5 mL), DIPEA (0.04 mL, 0.22 mmol) and 4-bromobutyryl chloride (0.01 mL, 0.082 mmol) were added. The reaction mixture was stirred at room temperature overnight. The solvent was evaporated to dryness and 1.7 mg of the title compound were obtained (yield 6%) after HPLC preparative purification.

LC-MS (method 3): t_R = 1.82 min; m/z = 404 (MH^+)

Following a similar procedure to that described in example 34, but using in each case the corresponding starting materials, the following compounds were obtained:

Example	Name	Starting Materials	HPLC method	t_R (min)	m/z (MH^+)
34a	N-(2-(pyrazolo[1,5-a]pyridin-3-yl)-9-(tetrahydro-2H-pyran-4-yl)-9H-purin-8-yl)isobutyramide	Example 33 and isobutyryl chloride	3	1.97	406

2014201789 26 Mar 2014

34b	N-(2-(pyrazolo[1,5-a]pyridin-3-yl)-9-(tetrahydro-2H-pyran-4-yl)-9H-purin-8-yl)propionamide	Example 33 and propionyl chloride	3	1.77	392
34c	N-(2-(pyrazolo[1,5-a]pyridin-3-yl)-9-(tetrahydro-2H-pyran-4-yl)-9H-purin-8-yl)acetamide	Example 33 and acetyl chloride	3	1.60	378

EXAMPLE 35

3-(9-(*trans*-4-Hydroxycyclohexyl)-7-methyl-8-oxo-8,9-dihydro-7H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile

a) 3-(9-(*trans*-4-(tert-butyldimethylsilyloxy)cyclohexyl)-8-oxo-8,9-dihydro-7H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile

To a suspension of example 1o (584 mg, 1.55 mmol) in DMF (15 mL), imidazole (265 mg, 3.89 mmol) and tert-butylchlorodimethylsilane (281 mg, 1.86 mmol) were added. The reaction mixture was stirred at room temperature overnight. The solvent was evaporated to dryness, dissolved in CH_2Cl_2 and washed thrice with water. The combined organic phases were dried over MgSO4 and concentrated to dryness. The reaction crude was used in next step without further purification

LC-MS (method 3): t_R = 3.38 min; m/z = 490 (MH^+)

b) 3-(9-(*trans*-4-(tert-butyldimethylsilyloxy)cyclohexyl)-7-methyl-8-oxo-8,9-dihydro-7H-purin-2-yl)pyrazolo[1,5-a]pyridine-5-carbonitrile

Following a similar procedure to that described in example 5, but using the compound obtained in the previous section, the desired compound was obtained (72 % yield).

LC-MS (method 2): t_R = 3.67 min; m/z = 504 (MH^+).

c) Title compound

To a suspension of the compound obtained in the previous section (246 mg, 0.488 mmol) in AcN (10 mL), at 0 °C, 1 M TBAF solution in THF (0.73 mL, 0.73 mmol) was added. The reaction mixture was stirred at room temperature overnight. The solvent was evaporated to dryness, dissolved in EtOAc and washed thrice with water. The combined organic phases were dried over MgSO4 and concentrated to dryness. The crude residue was cromatographed on a silica gel flash system (ISCO Combiflash) using CH_2Cl_2/MeOH mixtures of increasing polarity as eluent to afford 77 mg of the desired product (40% yield).

LC-MS (method 3): t_R = 1.82 min; m/z = 390 (MH^+).

EXAMPLE 36

2-(2-(5-Cyanopyrazolo[1,5-a]pyridin-3-yl)-8-oxo-7H-purin-9(8H)-yl)-N-(2,2,2-trifluoroethyl)acetamide

a) 2-(2-(5-cyanopyrazolo[1,5-a]pyridin-3-yl)-8-oxo-7H-purin-9(8H)-yl)acetic acid

Following a similar procedure to that described in example 14, but using the compound obtained in example 1n instead of example 1a,, the desired compound was obtained

LC-MS (method 3): t_R = 1.05 min; m/z = 336 (MH^+).

b) Title compound

Following a similar procedure to that described in example 15, but using the compound obtained in the previous section and 2,2,2-trifluoroethylamine, the desired compound was obtained.

LC-MS (method 3): t_R = 1.065min; m/z = 417 (MH^+).

Following a similar procedure to that described in example 36, but using the corresponding starting materials, the following compound was obtained:

Example	Name	Starting Materials	HPLC method	tR (min)	m/z (MH+)
36a	2-(2-(5-cyanopyrazolo[1,5-a]pyridin-3-yl)-8-oxo-7H-purin-9(8H)-yl)-N-ethylacetamide	N-ethylamine	3	1.40	363

EXAMPLE 37

2-(Imidazo[1,2-a]pyridin-3-yl)-7-methyl-9-(tetrahydro-2H-pyran-4-yl)-7H-purin-8(9H)-one

a) 2-Chloro-N4-(tetrahydro-2H-pyran-4-yl)pyrimidine-4,5-diamine

Following a similar procedure to that described in example 1 section d, but using the compound obtained in example 1 section a instead of the compound obtained in example 1 section c,, the desired compound was obtained (quantitative yield).

LC-MS (method 1): t_R = 6.73 min; m/z = 229 (MH^+).

b) 2-Chloro-9-(tetrahydro-2H-pyran-4-yl)-7H-purin-8(9H)-one

Following a similar procedure to that described in example 1 section e, but using the compound obtained in the previous section instead of the compound obtained in example 1 section d, the desired compound was obtained (83 % yield).

LC-MS (method 1): t_R = 7.16 min; m/z = 254 (MH^+).

26 Mar 2014
2014201789

c) 2-chloro-7-methyl-9-(tetrahydro-2H-pyran-4-yl)-7H-purin-8(9H)-one

Following a similar procedure to that described in example 5, but using the compound obtained in the previous section instead of the compound obtained in example 3b, the desired compound was obtained (58 % yield).

LC-MS (method 1): t_R = 7.51 min; m/z = 268 (MH^+).

d) Title compound

To a suspension of the compound obtained the previous section (30 mg, 0.11 mmol) in EtOH (0.5 mL) and dioxane (1 mL), imidazo[1,2-a]pyridine (16 mg, 0.13 mmol), triphenylphosphine (5.8 mg, 0.02 mmol), potassium carbonate (3.1 mg, 0.22 mmol) and palladium (II) acetate (2.5 mg, 0.01 mmol) were added. The reaction mixture was heated in a CEM Explorer microwave oven at 110 °C for 10 min and at 90 °C for 3 h. The reaction mixture was filtered through a plug of Celite® and the solvent was concentrated off. A sample was purified by preparative HPLC.

LC-MS (method 4): t_R = 1.55 min; m/z = 351 (MH^+).

EXAMPLE 38

Inhibition of JAK3 activity

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

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

The compounds 1 to 1b, 1d to 1j, 1n to 1p, 1s, 2, 2e, 3 to 3e, 3h to 3i, 4, 4b to 5i, 5s, 6 to 6b, 6d to 6f, 6x, 7 to 7d, 7f to 16a, and 16c to 17a, 17c to 19, 20 to 29, 31 to 37 showed more than 50% inhibition of JAK3 activity at 1µM in this assay.

EXAMPLE 39

Inhibition of JAK2 activity

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

In a final volume of 10 µL per well, 2.5 µL of the product to be tested dissolved in 4% DMSO (final concentration of the product to be tested, 0.1-10000 nM) was incubated with 0.5 µg/well of the catalytic domain of human JAK2, 2 µM of the substrate peptide Z'-Lyte® Tyr 6 and 16 µM of ATP; all components were dissolved in 50 mM pH 7.5 Hepes buffer, 10 mM Magnesium chloride (II), 1 mM EGTA and 0.01% Brij® 35. The reaction was started by the addition of said 16 µM ATP; after incubation for 1 hour at 25°C, 5 µL of A Z'-Lyte® Tyr 6 development reagent was

added and the mixture was incubated for 1 hour at 25°C. Phosphorylation was then quantified in each well using a Safire2® fluorescence microplate reader from Tecan.

The compounds 1 to 1b, 1e to 1g, 1n to 1p, 1s, 2, 2e, 3, 3b, 3d, 3e, 4, 4c, 5, 5a, 5b, 5e, 5f, 5h, 5i, 5s, 7 to 7c, 7f to 7n, 7p, 7r to 7u, 8 to 8c, 8d, 8f to 8h, 9a, 9b, 9c, 9f, 9g, 9i to 9k, 9m to 9s, 10a, 10b, 10e, 10h, 10i, 10k, 10l, 10m, 10n, 13b to 13k, 15 to 15b, 15 f, 15 h, 15i, 15k, 16, 16a, 16d to16f, 17 to 17c, 18a, 18b, 18d to 18i, 19, 20, 21a to 21d, 21g to 21i, 21k, 22 to 23, 23d, 24, 24a, 24b, 24c, 25, 26, 26a, 26c, 26d, 26e, 26f, 26g, 27, 27a, 29, 31, 33, 34, 34b, and 35 to 36a showed more than 50% inhibition of JAK2 activity at 1μM in this assay.

EXAMPLE 40

Determination of clearance in human liver microsomes

A single concentration (1 μM in pH7.4 buffer) of a compound to be tested was incubated with human liver microsomes for 0, 10, 30 and 60 minutes at 37° C (0.4 mg protein/mL). The degree of hepatic metabolism was measured by LC-MS/MS as the decrease in the peak area of the parent compound and expressed as the intrinsic clearance.

Several compounds of the invention were tested in this assay.

EXAMPLE 41

Cytotoxicity in Hep G2 cells assay

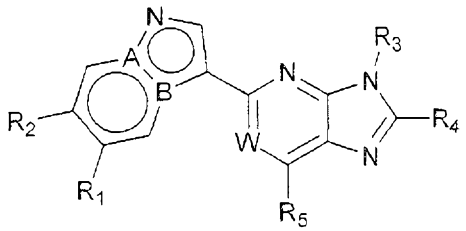
Alamar blue (AB) was used to evaluate the possible toxicity of a compound to be tested on Human hepatocyte carcinoma cells (HepG2). The cells (20000 cells/well) were cultured in 96-well plates in the presence of the compound at different concentrations (1 to 20 μM) containing 0.2% DMSO for 72 h at 37°C. After addition of AB, fluorescence was measured. EC_{50} value, defined as the concentration of the compound that results in a decrease in AB fluorescence equivalent to 50% of the control, was calculated.

Several compounds of the invention were tested in this assay.

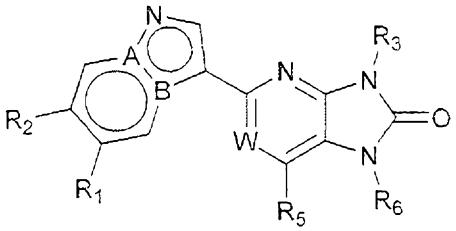
2014201789 26 Mar 2014

CLAIMS

1.- A compound of formula I or II:



I



II

wherein

A is carbon and B is nitrogen, or A is nitrogen and B is carbon;

W is CH or N;

R_1 and R_2 independently are hydrogen, C_{1-4}alkyl, haloC_{1-4}alkyl, hydroxyC_{1-4}alkyl, cyanoC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, halogen, –CN, $–OR_8$ or $–SR_8$;

R_3 is C_{1-4}alkyl, R_9-C_{1-4}alkyl, Cy_1 or Cy_2-C_{1-4}alkyl, wherein Cy_1 and Cy_2 are optionally substituted with one or more R_{10};

R_4 is hydrogen, C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl, cyanoC_{1-4}alkyl, $R_{12}R_7N$-C_{0-4}alkyl, $R_{13}CONR_7$-C_{0-4}alkyl, $R_{13}R_7NCO$-C_{0-4}alkyl, $R_{12}R_7NCONR_7$-C_{0-4}alkyl, $R_{13}CO_2NR_7$-C_{0-4}alkyl, $R_{13}SO_2NR_7$-C_{0-4}alkyl, $–OR_{12}$ or Cy_2-C_{0-4}alkyl; wherein Cy_2 is optionally substituted with one or more R_{11};

R_5 is hydrogen, C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl, cyanoC_{1-4}alkyl, halogen, –CN, $–OR_{12}$, $–NR_7R_{12}$, or Cy_2-C_{0-4}alkyl, wherein Cy_2 is optionally substituted with one or more R_{11};

R_6 is hydrogen, C_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl, $R_{12}R_7N$-C_{1-4}alkyl, $R_{16}CO$-C_{0-4}alkyl, $R_{16}CO_2$-C_{0-4}alkyl, $R_{16}CO$-O-C_{1-4}alkyl, cyanoC_{1-4}alkyl, Cy_1 or Cy_2-C_{1-4}alkyl, wherein Cy_1 and Cy_2 are optionally substituted with one or more R_{11};

R_7 is hydrogen or C_{1-4}alkyl;

R_8 is hydrogen, C_{1-4}alkyl, haloC_{1-4}alkyl, hydroxyC_{1-4}alkyl, or C_{1-4}alkoxyC_{1-4}alkyl;

R_9 is halogen, –CN, $–CONR_7R_{12}$, $–COR_{13}$, $–CO_2R_{12}$, $–OR_{12}$, $–OCONR_7R_{12}$, $–SO_2R_{13}$, $–SO_2NR_7R_{12}$, $–NR_7R_{12}$, $–NR_7COR_{12}$, $–NR_7CONR_7R_{12}$, $–NR_7CO_2R_{13}$ or $–NR_7SO_2R_{13}$;

R_{10} is C_{1-4}alkyl or R_9-C_{0-4}alkyl;

R_{11} is C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl, cyanoC_{1-4}alkyl, halogen, –CN, $–CONR_7R_{14}$, $–COR_{14}$, $–CO_2R_{15}$, $–OR_{14}$, $–OCONR_7R_{14}$, $–SO_2R_{15}$, $–SO_2NR_7R_{14}$, $–NR_7R_{14}$, $–NR_7COR_{14}$, $–NR_7CONR_7R_{14}$, $–NR_7CO_2R_{15}$ or $–NR_7SO_2R_{15}$;

R_{12} is hydrogen or R_{13};

R_{13} is C_{1-5}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl, cyanoC_{1-4}alkyl, Cy_2-C_{0-4}alkyl, or $R_{14}R_7N$-C_{1-4}alkyl; wherein Cy_2 is optionally substituted with one or more R_{11};

R_{14} is hydrogen or R_{15};

R_{15} is C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl or cyanoC_{1-4}alkyl;

2014201789 28 May 2015

R_{16} is C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl or cyanoC_{1-4}alkyl;

Cy_1 is a 3- to 7-membered monocyclic or 6- to 11-membered bicyclic ring, which is saturated, partially unsaturated or aromatic, and which is carbocyclic or heterocyclic containing from 1 to 4 heteroatoms independently selected from N, S and O, wherein said ring is bonded to the rest of the molecule through any available C atom, and wherein one or more C or S ring atoms are optionally oxidized forming CO, SO or SO_2; and

Cy_2 is a 3- to 7-membered monocyclic or 6- to 11-membered bicyclic ring, which is saturated, partially unsaturated or aromatic, and which is carbocyclic or heterocyclic containing from 1 to 4 heteroatoms independently selected from N, S and O, wherein said ring is bonded to the rest of the molecule through any available C or N atom, and wherein one or more C or S ring atoms are optionally oxidized forming CO, SO or SO_2;

or a salt thereof.

2. A compound according to claim 1 of formula **II**.

3. A compound according to claim 1 or 2 wherein A is nitrogen and B is carbon.

4. A compound according to any one of claims 1 to 3 wherein R_1 is hydrogen or -CN.

5. A compound according to claim 4 wherein R_1 is hydrogen.

6. A compound according to any of claims 1 to 5 wherein R_2 is hydrogen.

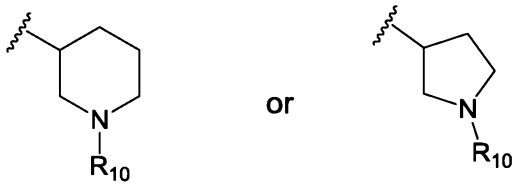
7. A compound according to any one of claims 1 to 6 wherein Cy_1 in R_3 is a 3- to 7-membered, preferably 5- to 6-membered, saturated monocyclic ring, which is carbocyclic or heterocyclic containing from 1 to 3 heteroatoms independently selected from N, S and O, wherein said ring is bonded to the rest of the molecule through any available C atom, and wherein one or more C or S ring atoms are optionally oxidized forming CO, SO or SO_2; and wherein said Cy_1 is optionally substituted with one or more R_{10}.

8. A compound according to claim 1 wherein R_3 is piperidinyl or pyrrolidinyl, which are optionally substituted with one or more R_{10}.

9. A compound according to claim 8 wherein R_3 is piperidin-3-yl or pyrrolidin-3-yl, which are optionally substituted with one or more R_{10}.

2014201789 28 May 2015

10. A compound according to claim 8 wherein R_3 is a cycle of formula



Cy_{1a} Cy_{1b}

11. A compound according to claim 10 wherein R_3 is a cycle of formula Cy_{1a}.

12. A compound according to claim 11 wherein Cy_{1a} has the (S)-stereochemistry.

13. A compound according to claim 10 wherein R_3 is a cycle of formula Cy_{1b}.

14. A compound according to any one of claims 10 to 13 wherein R_{10} is R_9-C_{0-4}alkyl, i.e., wherein R_{10} is R_9.

15. A compound according to any one of claims 10 to 13 wherein R_{10} is R_9 and R_9 is -COR_{13} or –SO_2R_{13}.

16. A compound according to claim 1 or 2 wherein R_{13} is C_{1-4}alkyl or cyanoC_{1-4}alkyl.

17. A compound according to claim 16 wherein R_{13} is methyl, isopropyl or cyanomethyl.

18. A compound according to any one of claims 1 to 17 wherein R_5 is hydrogen.

19. A compound according to any one of claims 1 to 18 wherein R_6 is hydrogen, C_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl, $R_{12}R_7N$-C_{1-4}alkyl, $R_{16}CO$-C_{0-4}alkyl, $R_{16}CO_2$-C_{0-4}alkyl, Cy_1 or Cy_2-C_{1-4}alkyl, wherein Cy_1 and Cy_2 are optionally substituted with one or more R_{11}.

20. A compound according to claim 19 wherein R_6 is hydrogen or C_{1-4}alkyl.

21. A compound according to claim 19 wherein R_6 is C_{1-4}alkyl.

2014201789 28 May 2015

22. A compound according to claim 20 wherein R_6 is methyl or ethyl.

23. A compound according to claim 1 which is (S)-3-(3-(1-methyl-2-oxo-5-(pyrazolo[1,5-a]pyridine-3-yl)-1H-imidazo[4,5-b]pyridine-3(2H)-yl)piperidin-1-yl)-3-oxopropanenitrile

24. A pharmaceutical composition which comprises a compound according to any one of claims 1 to 23 or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable excipients.

25. A compound according to any one of claims 1 to 23 or a pharmaceutically acceptable salt thereof for use in therapy.

26. Use of a compound according to any one of claims 1 to 23 or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment or prevention of at least one disease selected from transplant rejection, immune, autoimmune or inflammatory diseases, neurodegenerative diseases, or proliferative disorders.

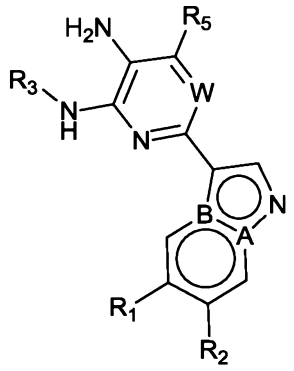
27. Use of a compound according to any one of claims 1 to 23 or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment or prevention of a disease selected from transplant rejection, rheumatoid arthritis, psoriatic arthritis, psoriasis, type I diabetes, complications from diabetes, multiple sclerosis, systemic lupus erythematosus, atopic dermatitis, mast cell-mediated allergic reactions, inflammatory or autoimmune ocular diseases, leukemias, lymphomas, and thromboembolic and allergic complications associated with leukemias and lymphomas.

28. A method of treating or preventing at least one disease selected from transplant rejection, immune, autoimmune or inflammatory diseases, neurodegenerative diseases, or proliferative disorders, in a subject in need thereof which comprises administering to said subject an amount of a compound according to any one of claims 1 to 23 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim 24 effective to treat said disease.

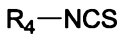
2014201789 28 May 2015

29. A process for the preparation of a compound of formula **I** or **II** according to claim 1, which comprises:

(a) for a compound of formula **I**, reacting a compound of formula **VI** with a compound of formula **III**



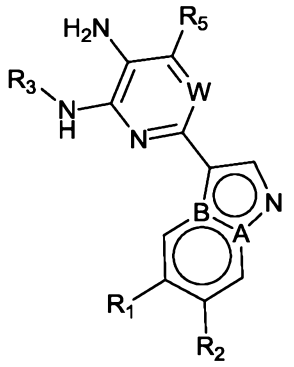
VI



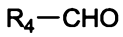
III

wherein A, B, W, R_1, R_2, R_3, R_4 and R_5 have the meaning described in claim 1; or

(b) for a compound of formula **I**, reacting a compound of formula **VI** with a compound of formula **IV**



VI

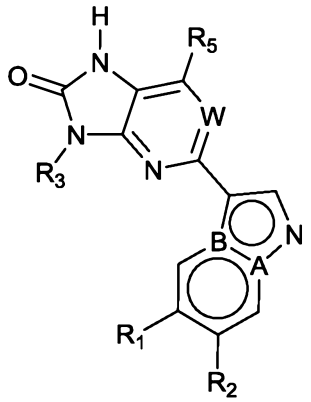


IV

wherein A, B, W, R_1, R_2, R_3, R_4 and R_5 have the meaning described in claim 1; or

2014201789 28 May 2015

(c) when in a compound of formula **II** R_6 is hydrogen (a compound of formula **IIa**), reacting a compound of formula **VI**, as defined above, with a synthetic equivalent for the CO synthon



IIa

wherein A, B, W, R_1, R_2, R_3 and R_5 have the meaning described in claim 1; or

(d) when in a compound of formula **II** R_6 is other than hydrogen, reacting a compound of formula **IIa** with a compound of formula **V** (R_6-X) in the presence of a base, wherein X is a leaving group; or

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

Vectura Limited

Patent Attorneys for the Applicant/Nominated Person
SPRUSON & FERGUSON