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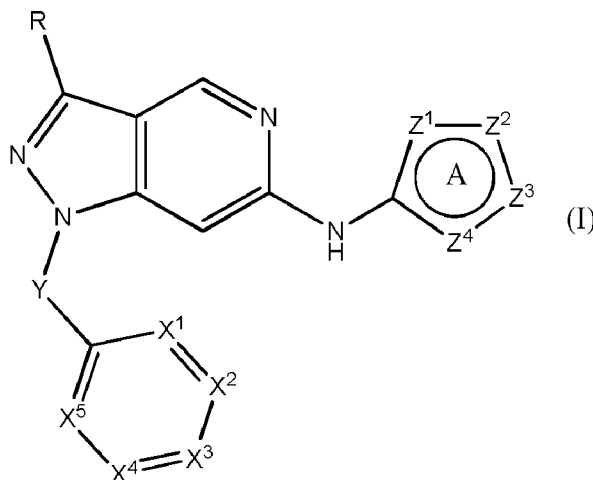
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(54) Title: PYRAZOLO[4,3-C]PYRIDINE DERIVATIVES AS JAK INHIBITORS



(57) Abstract: The present invention relates to compounds of formula (I) wherein X^1 to X^5 , Y, Z^1 to Z^4 , and R have the meaning as cited in the description and the claims. Said compounds are useful as JAK inhibitors for the treatment or prophylaxis of immunological, inflammatory, autoimmune, allergic disorders, and immunologically-mediated diseases. The invention also relates to pharmaceutical compositions including said compounds, the preparation of such compounds as well as the use as medicaments.



Pyrazolo[4,3-c]pyridine derivatives as JAK inhibitors

5 The present invention relates to a novel class of kinase inhibitors, including pharmaceutically acceptable salts, prodrugs and metabolites thereof, which are useful for modulating protein kinase activity for modulating cellular activities such as signal transduction, proliferation, and cytokine secretion. More specifically the invention provides compounds which inhibit, regulate and/or modulate kinase activity, in particular JAK3 activity, and signal transduction
10 pathways relating to cellular activities as mentioned above. Furthermore, the present invention relates to pharmaceutical compositions comprising said compounds, for example for the treatment or prevention of an immunological, inflammatory, autoimmune, or allergic disorder or disease or a transplant rejection or a Graft-versus host disease and processes for preparing said compounds.

15 Kinases catalyze the phosphorylation of proteins, lipids, sugars, nucleosides and other cellular metabolites and play key roles in all aspects of eukaryotic cell physiology. Especially, protein kinases and lipid kinases participate in the signaling events which control the activation, growth, differentiation and survival of cells in response to extracellular mediators or stimuli
20 such as growth factors, cytokines or chemokines. In general, protein kinases are classified in two groups, those that preferentially phosphorylate tyrosine residues and those that preferentially phosphorylate serine and/or threonine residues. The tyrosine kinases include membrane-spanning growth factor receptors such as the epidermal growth factor receptor (EGFR) and cytosolic non-receptor kinases such as Janus kinases (JAK).

25 Inappropriately high protein kinase activity is involved in many diseases including cancer, metabolic diseases, autoimmune or inflammatory disorders. This effect can be caused either directly or indirectly by the failure of control mechanisms due to mutation, overexpression or inappropriate activation of the enzyme. In all of these instances, selective inhibition of the
30 kinase is expected to have a beneficial effect.

One group of kinases that has become a recent focus of drug discovery is the Janus kinase (JAK) family of non-receptor tyrosine kinases. In mammals, the family has four members, JAK1, JAK2, JAK3 and Tyrosine kinase 2 (TYK2). Each protein has a kinase domain and a

catalytically inactive pseudo-kinase domain. The JAK proteins bind to cytokine receptors through their amino-terminal FERM (Band-4.1, ezrin, radixin, moesin) domains. After the binding of cytokines to their receptors, JAKs are activated and phosphorylate the receptors, thereby creating docking sites for signalling molecules, especially for members of the signal transducer and activator of transcription (Stat) family (Yamaoka et al., 2004. The Janus kinases (Jaks). Genome Biology 5(12): 253).

In mammals, JAK1, JAK2 and TYK2 are ubiquitously expressed. By contrast, the expression of JAK3 is predominantly in hematopoietic cells and it is highly regulated with cell development and activation (Musso et al., 1995. 181(4):1425-31).

The study of JAK-deficient cell lines and gene-targeted mice has revealed the essential, nonredundant functions of JAKs in cytokine signalling. JAK1 knockout mice display a perinatal lethal phenotype, probably related to the neurological effects that prevent them from sucking (Rodig et al., 1998. Cell 93(3):373-83). Deletion of the JAK2 gene results in embryonic lethality at embryonic day 12.5 as a result of a defect in erythropoiesis (Neubauer et al., 1998. Cell 93(3):397-409). Interestingly, JAK3 deficiency was first identified in humans with autosomal recessive severe combined immunodeficiency (SCID) (Macchi et al., 1995. Nature 377(6544):65-68). JAK3 knockout mice too exhibit SCID but do not display non-immune defects, suggesting that an inhibitor of JAK3 as an immunosuppressant would have restricted effects *in vivo* and therefore presents a promising drug for immunosuppression (Papageorgiou and Wikman 2004, Trends in Pharmacological Sciences 25(11):558-62).

Activating mutations for JAK3 have been observed in acute megakaryoblastic leukemia (AMKL) patients (Walters et al., 2006. Cancer Cell 10(1):65-75). These mutated forms of JAK3 can transform Ba/F3 cells to factor-independent growth and induce features of megakaryoblastic leukemia in a mouse model.

Diseases and disorders associated with JAK3 inhibition are further described, for example in WO 01/42246 and WO 2008/060301.

Several JAK3 inhibitors have been reported in the literature which may be useful in the medical field (O'Shea et al., 2004. Nat. Rev. Drug Discov. 3(7):555-64). A potent JAK3 inhibitor (CP-690,550) was reported to show efficacy in an animal model of organ

transplantation (Changelian et al., 2003, Science 302(5646):875-888) and clinical trials (reviewed in: Pesu et al., 2008. Immunol. Rev. 223, 132-142). The CP-690,550 inhibitor is not selective for the JAK3 kinase and inhibits JAK2 kinase with almost equipotency (Jiang et al., 2008, J. Med. Chem. 51(24):8012-8018). It is expected that a selective JAK3 inhibitor that
5 inhibits JAK3 with greater potency than JAK2 may have advantageous therapeutic properties, because inhibition of JAK2 can cause anemia (Ghoreschi et al., 2009. Nature Immunol. 4, 356-360).

Pyrimidine derivatives exhibiting JAK3 and JAK2 kinase inhibiting activities are described in
10 WO-A 2008/009458. Pyrimidine compounds in the treatment of conditions in which modulation of the JAK pathway or inhibition of JAK kinases, particularly JAK3 are described in WO-A 2008/118822 and WO-A 2008/118823.

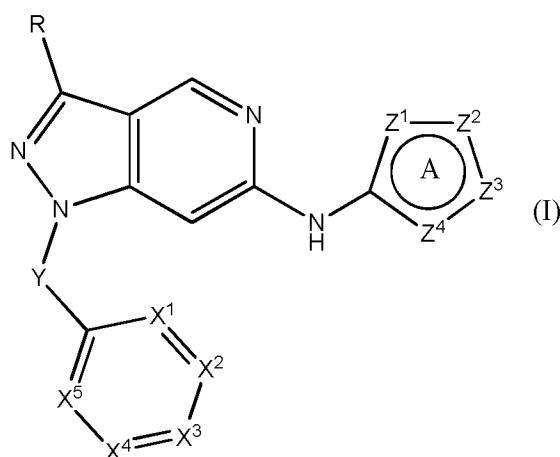
Fluoro substituted pyrimidine compounds as JAK3 inhibitors are described in WO-A
15 2010/118986. Heterocyclyl pyrazolopyrimidine analogues as JAK inhibitors WO-A 2011/048082.

Pyrazolopyridines and their preparation are known from WO 2006/063820 A1, WO2011/019780 A1 and R.V. Fucini et al., Bioorg. & Med. Chem. Lett. 18 (2008), 5648-
20 5652.

Even though JAK inhibitors are known in the art there is a need for providing additional JAK inhibitors having at least partially more effective pharmaceutically relevant properties, like activity, selectivity especially over JAK2 kinase, and ADME properties.

25 Thus, an object of the present invention is to provide a new class of compounds as JAK inhibitors which preferably show selectivity over JAK2 and may be effective in the treatment or prophylaxis of disorders associated with JAK.

30 Accordingly, the present invention provides compounds of formula (I)



or a pharmaceutically acceptable salt thereof, wherein

5 R is H or F;

Ring A is a 5 membered aromatic heterocycle in which Z^1 , Z^2 , Z^3 and Z^4 are independently selected from the group consisting of $C(R^1)$, N, $N(R^1)$, O and S, provided that at least one of Z^1 , Z^2 , Z^3 , Z^4 is N or $N(R^1)$;

10

Each R^1 is independently H, halogen; CN; $C(O)OR^2$; OR^2 ; $C(O)R^2$; $C(O)N(R^{2a}R^{2b})$; $S(O)_2N(R^{2a}R^{2b})$; $S(O)N(R^{2a}R^{2b})$; $S(O)_2R^2$; $S(O)R^2$; $N(R^2)S(O)_2N(R^{2a}R^{2b})$; $N(R^2)S(O)N(R^{2a}R^{2b})$; SR^2 ; $N(R^{2a}R^{2b})$; NO_2 ; $OC(O)R^2$; $N(R^2)C(O)R^{2a}$; $N(R^2)S(O)_2R^{2a}$; $N(R^2)S(O)R^{2a}$; $N(R^2)C(O)N(R^{2a}R^{2b})$; $N(R^2)C(O)OR^{2a}$; $OC(O)N(R^{2a}R^{2b})$; T^1 ; or C_{1-6} alkyl, wherein C_{1-6} alkyl

15 is optionally substituted with one or more R^3 , which are the same or different;

R^2 , R^{2a} , R^{2b} are independently selected from the group consisting of H; T^1 ; and C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more R^3 , which are the same or different;

20

R^3 is halogen; CN; $C(O)OR^4$; OR^4 ; $C(O)R^4$; $C(O)N(R^{4a}R^{4b})$; $S(O)_2N(R^{4a}R^{4b})$; $S(O)N(R^{4a}R^{4b})$; $S(O)_2R^4$; $S(O)R^4$; $N(R^4)S(O)_2N(R^{4a}R^{4b})$; $N(R^4)S(O)N(R^{4a}R^{4b})$; SR^4 ; $N(R^{4a}R^{4b})$; NO_2 ; $OC(O)R^4$; $N(R^4)C(O)R^{4a}$; $N(R^4)S(O)_2R^{4a}$; $N(R^4)S(O)R^{4a}$; $N(R^4)C(O)N(R^{4a}R^{4b})$; $N(R^4)C(O)OR^{4a}$; $OC(O)N(R^{4a}R^{4b})$; or T^1 ;

25

R^4 , R^{4a} , R^{4b} are independently selected from the group consisting of H; T^1 ; and C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different;

- 5 T^1 is C_{3-7} cycloalkyl; saturated 4 to 7 membered heterocyclyl; or saturated 7 to 11 membered heterobicyclyl, wherein T^1 is optionally substituted with one or more R^{10} , which are the same or different;

Y is $(C(R^5R^{5a}))_n$;

10

n is 0, 1, 2, 3 or 4;

R^5 , R^{5a} are independently selected from the group consisting of H; and unsubstituted C_{1-6} alkyl; or jointly form oxo (=O);

15

Optionally, R^5 , R^{5a} are joined to form an unsubstituted C_{3-7} cycloalkyl;

X^1 is $C(R^6)$ or N; X^2 is $C(R^{6a})$ or N; X^3 is $C(R^{6b})$ or N; X^4 is $C(R^{6c})$ or N; X^5 is $C(R^{6d})$ or N, provided that at most two of X^1 , X^2 , X^3 , X^4 , X^5 are N;

20

R^6 , R^{6a} , R^{6b} , R^{6c} , R^{6d} are independently selected from the group consisting of H; halogen; CN; $C(O)OR^7$; OR^7 ; $C(O)R^7$; $C(O)N(R^7R^{7a})$; $S(O)_2N(R^7R^{7a})$; $S(O)N(R^7R^{7a})$; $S(O)_2R^7$; $S(O)R^7$; $N(R^7)S(O)_2N(R^{7a}R^{7b})$; $N(R^7)S(O)N(R^{7a}R^{7b})$; SR^7 ; $N(R^7R^{7a})$; NO_2 ; $OC(O)R^7$; $N(R^7)C(O)R^{7a}$; $N(R^7)S(O)_2R^{7a}$; $N(R^7)S(O)R^{7a}$; $N(R^7)C(O)N(R^{7a}R^{7b})$; $N(R^7)C(O)OR^{7a}$; $OC(O)N(R^7R^{7a})$; T^2 ; and C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more R^{11} , which are the same or different;

25

Optionally one of the pairs R^6/R^{6a} , R^{6a}/R^{6b} is joined to form a ring T^3 ;

30

R^7 , R^{7a} , R^{7b} are independently selected from the group consisting of H; T^2 ; and C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more R^8 , which are the same or different;

R^8 is halogen; CN; $C(O)OR^9$; OR^9 ; $C(O)R^9$; $C(O)N(R^9R^{9a})$; $S(O)_2N(R^9R^{9a})$; $S(O)N(R^9R^{9a})$; $S(O)_2R^9$; $S(O)R^9$; $N(R^9)S(O)_2N(R^{9a}R^{9b})$; $N(R^9)S(O)N(R^{9a}R^{9b})$; SR^9 ; $N(R^9R^{9a})$; NO_2 ; $OC(O)R^9$; $N(R^9)C(O)R^{9a}$; $N(R^9)S(O)_2R^{9a}$; $N(R^9)S(O)R^{9a}$; $N(R^9)C(O)N(R^{9a}R^{9b})$; $N(R^9)C(O)OR^{9a}$; $OC(O)N(R^9R^{9a})$; or T^2 ;

5

R^9 , R^{9a} , R^{9b} are independently selected from the group consisting of H; T^2 ; and C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more R^{12} , which are the same or different;

- 10 R^{10} is halogen; CN; $C(O)OR^{13}$; OR^{13} ; oxo ($=O$), where the ring is at least partially saturated; $C(O)R^{13}$; $C(O)N(R^{13}R^{13a})$; $S(O)_2N(R^{13}R^{13a})$; $S(O)N(R^{13}R^{13a})$; $S(O)_2R^{13}$; $S(O)R^{13}$; $N(R^{13})S(O)_2N(R^{13a}R^{13b})$; $N(R^{13})S(O)N(R^{13a}R^{13b})$; SR^{13} ; $N(R^{13}R^{13a})$; NO_2 ; $OC(O)R^{13}$; $N(R^{13})C(O)R^{13a}$; $N(R^{13})S(O)_2R^{13a}$; $N(R^{13})S(O)R^{13a}$; $N(R^{13})C(O)N(R^{13a}R^{13b})$; $N(R^{13})C(O)OR^{13a}$; $OC(O)N(R^{13}R^{13a})$; or C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted
- 15 with one or more R^{14} , which are the same or different;

R^{13} , R^{13a} , R^{13b} are independently selected from the group consisting of H; and C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more R^{14} , which are the same or different;

20

R^{11} , R^{12} are independently selected from the group consisting of halogen; CN; $C(O)OR^{15}$; OR^{15} ; $C(O)R^{15}$; $C(O)N(R^{15}R^{15a})$; $S(O)_2N(R^{15}R^{15a})$; $S(O)N(R^{15}R^{15a})$; $S(O)_2R^{15}$; $S(O)R^{15}$; $N(R^{15})S(O)_2N(R^{15a}R^{15b})$; $N(R^{15})S(O)N(R^{15a}R^{15b})$; SR^{15} ; $N(R^{15}R^{15a})$; NO_2 ; $OC(O)R^{15}$; $N(R^{15})C(O)R^{15a}$; $N(R^{15})S(O)_2R^{15a}$; $N(R^{15})S(O)R^{15a}$; $N(R^{15})C(O)N(R^{15a}R^{15b})$;

25 $N(R^{15})C(O)OR^{15a}$; $OC(O)N(R^{15}R^{15a})$; and T^2 ;

R^{15} , R^{15a} , R^{15b} are independently selected from the group consisting of H; T^2 ; and C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different;

30

R^{14} is halogen; CN; $C(O)OR^{16}$; OR^{16} ; $C(O)R^{16}$; $C(O)N(R^{16}R^{16a})$; $S(O)_2N(R^{16}R^{16a})$; $S(O)N(R^{16}R^{16a})$; $S(O)_2R^{16}$; $S(O)R^{16}$; $N(R^{16})S(O)_2N(R^{16a}R^{16b})$; $N(R^{16})S(O)N(R^{16a}R^{16b})$; SR^{16} ; $N(R^{16}R^{16a})$; NO_2 ; $OC(O)R^{16}$; $N(R^{16})C(O)R^{16a}$; $N(R^{16})S(O)_2R^{16a}$; $N(R^{16})S(O)R^{16a}$; $N(R^{16})C(O)N(R^{16a}R^{16b})$; $N(R^{16})C(O)OR^{16a}$; or $OC(O)N(R^{16}R^{16a})$;

R^{16} , R^{16a} , R^{16b} are independently selected from the group consisting of H; and C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different;

5

T^2 is phenyl; naphthyl; indenyl; indanyl; C_{3-7} cycloalkyl; 4 to 7 membered heterocyclyl; or 7 to 11 membered heterobicyclyl, wherein T^2 is optionally substituted with one or more R^{17} , which are the same or different;

10 T^3 is phenyl; C_{3-7} cycloalkyl; or 4 to 7 membered heterocyclyl, wherein T^3 is optionally substituted with one or more R^{18} , which are the same or different;

R^{17} , R^{18} are independently selected from the group consisting of halogen; CN; $C(O)OR^{19}$; OR^{19} ; oxo (=O), where the ring is at least partially saturated; $C(O)R^{19}$; $C(O)N(R^{19}R^{19a})$;
 15 $S(O)_2N(R^{19}R^{19a})$; $S(O)N(R^{19}R^{19a})$; $S(O)_2R^{19}$; $S(O)R^{19}$; $N(R^{19})S(O)_2N(R^{19a}R^{19b})$; $N(R^{19})S(O)N(R^{19a}R^{19b})$; SR^{19} ; $N(R^{19}R^{19a})$; NO_2 ; $OC(O)R^{19}$; $N(R^{19})C(O)R^{19a}$; $N(R^{19})S(O)_2R^{19a}$; $N(R^{19})S(O)R^{19a}$; $N(R^{19})C(O)N(R^{19a}R^{19b})$; $N(R^{19})C(O)OR^{19a}$; $OC(O)N(R^{19}R^{19a})$; and C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more R^{20} , which are the same or different;

20

R^{19} , R^{19a} , R^{19b} are independently selected from the group consisting of H; and C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more R^{20} , which are the same or different;

25 R^{20} is halogen; CN; $C(O)OR^{21}$; OR^{21} ; $C(O)R^{21}$; $C(O)N(R^{21}R^{21a})$; $S(O)_2N(R^{21}R^{21a})$; $S(O)N(R^{21}R^{21a})$; $S(O)_2R^{21}$; $S(O)R^{21}$; $N(R^{21})S(O)_2N(R^{21a}R^{21b})$; $N(R^{21})S(O)N(R^{21a}R^{21b})$; SR^{21} ; $N(R^{21}R^{21a})$; NO_2 ; $OC(O)R^{21}$; $N(R^{21})C(O)R^{21a}$; $N(R^{21})S(O)_2R^{21a}$; $N(R^{21})S(O)R^{21a}$; $N(R^{21})C(O)N(R^{21a}R^{21b})$; $N(R^{21})C(O)OR^{21a}$; or $OC(O)N(R^{21}R^{21a})$;

30 R^{21} , R^{21a} , R^{21b} are independently selected from the group consisting of H; and C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different.

In case a variable or substituent can be selected from a group of different variants and such variable or substituent occurs more than once the respective variants can be the same or different.

5 Within the meaning of the present invention the terms are used as follows:

The term “optionally substituted” means unsubstituted or substituted. Generally -but not limited to-, “one or more substituents” means one, two or three, preferably one or two and more preferably one substituents. Generally these substituents can be the same or different.

10

“Alkyl” means a straight-chain or branched hydrocarbon chain. Each hydrogen of an alkyl carbon may be replaced by a substituent as further specified herein.

15 “C₁₋₄ alkyl” means an alkyl chain having 1 - 4 carbon atoms, e.g. if present at the end of a molecule: methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, or e.g. -CH₂-, -CH₂-CH₂-, -CH(CH₃)-, -CH₂-CH₂-CH₂-, -CH(C₂H₅)-, -C(CH₃)₂-, when two moieties of a molecule are linked by the alkyl group. Each hydrogen of a C₁₋₄ alkyl carbon may be replaced by a substituent as further specified herein.

20 “C₁₋₆ alkyl” means an alkyl chain having 1 - 6 carbon atoms, e.g. if present at the end of a molecule: C₁₋₄ alkyl, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl; tert-butyl, n-pentyl, n-hexyl, or e.g. -CH₂-, -CH₂-CH₂-, -CH(CH₃)-, -CH₂-CH₂-CH₂-, -CH(C₂H₅)-, -C(CH₃)₂-, when two moieties of a molecule are linked by the alkyl group. Each hydrogen of a C₁₋₆ alkyl carbon may be replaced by a substituent as further specified herein.

25

“C₃₋₇ cycloalkyl” or “C₃₋₇ cycloalkyl ring” means a cyclic alkyl chain having 3 - 7 carbon atoms, e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, cycloheptyl. Preferably, cycloalkyl refers to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl. Each hydrogen of a cycloalkyl carbon may be replaced by a substituent as further
30 specified herein. The term “C₃₋₅ cycloalkyl” or “C₃₋₅ cycloalkyl ring” is defined accordingly.

“Halogen” means fluoro, chloro, bromo or iodo. It is generally preferred that halogen is fluoro or chloro.

“4 to 7 membered heterocyclyl” or “4 to 7 membered heterocycle” means a ring with 4, 5, 6 or 7 ring atoms that may contain up to the maximum number of double bonds (aromatic or non-aromatic ring which is fully, partially or un-saturated) wherein at least one ring atom up to 4 ring atoms are replaced by a heteroatom selected from the group consisting of sulfur (including -S(O)-, -S(O)₂-), oxygen and nitrogen (including =N(O)-) and wherein the ring is linked to the rest of the molecule via a carbon or nitrogen atom. Examples for a 4 to 7 membered heterocycles are azetidine, oxetane, thietane, furan, thiophene, pyrrole, pyrroline, imidazole, imidazoline, pyrazole, pyrazoline, oxazole, oxazoline, isoxazole, isoxazoline, thiazole, thiazoline, isothiazole, isothiazoline, thiadiazole, thiadiazoline, tetrahydrofuran, tetrahydrothiophene, pyrrolidine, imidazolidine, pyrazolidine, oxazolidine, isoxazolidine, thiazolidine, isothiazolidine, thiadiazolidine, sulfolane, pyran, dihydropyran, tetrahydropyran, imidazolidine, pyridine, pyridazine, pyrazine, pyrimidine, piperazine, piperidine, morpholine, tetrazole, triazole, triazolidine, tetrazolidine, diazepane, azepine or homopiperazine. The term “5 to 6 membered heterocyclyl” or “5 to 6 membered heterocycle” is defined accordingly.

“Saturated 4 to 7 membered heterocyclyl” or “saturated 4 to 7 membered heterocycle” means fully saturated “4 to 7 membered heterocyclyl” or “4 to 7 membered heterocycle”.

“5 membered aromatic heterocyclyl” or “5 membered aromatic heterocycle” means a heterocycle derived from cyclopentadienyl, where at least one carbon atom is replaced by a heteroatom selected from the group consisting of sulfur (including -S(O)-, -S(O)₂-), oxygen and nitrogen (including =N(O)-). Examples for such heterocycles are furan, thiophene, pyrrole, imidazole, pyrazole, oxazole, isoxazole, thiazole, isothiazole, thiadiazole, triazole, tetrazole.

“7 to 11 membered heterobicyclyl” or “7 to 11 membered heterobicycle” means a heterocyclic system of two rings with 7 to 11 ring atoms, where at least one ring atom is shared by both rings and that may contain up to the maximum number of double bonds (aromatic or non-aromatic ring which is fully, partially or un-saturated) wherein at least one ring atom up to 6 ring atoms are replaced by a heteroatom selected from the group consisting of sulfur (including -S(O)-, -S(O)₂-), oxygen and nitrogen (including =N(O)-) and wherein the ring is linked to the rest of the molecule via a carbon or nitrogen atom. Examples for a 7 to 11 membered heterobicycle are indole, indoline, benzofuran, benzothiophene, benzoxazole, benzisoxazole, benzothiazole, benzisothiazole, benzimidazole, benzimidazoline, quinoline,

quinazoline, dihydroquinazoline, quinoline, dihydroquinoline, tetrahydroquinoline, decahydroquinoline, isoquinoline, decahydroisoquinoline, tetrahydroisoquinoline, dihydroisoquinoline, benzazepine, purine or pteridine. The term 7 to 11 membered heterobicycle also includes spiro structures of two rings like 6-oxa-2-azaspiro[3,4]octane, 2-oxa-6-azaspiro[3.3]heptan-6-yl or 2,6-diazaspiro[3.3]heptan-6-yl or bridged heterocycles like 8-aza-bicyclo[3.2.1]octane or 2,5-diazabicyclo[2.2.2]octan-2-yl or 3,8-diazabicyclo[3.2.1]octane.

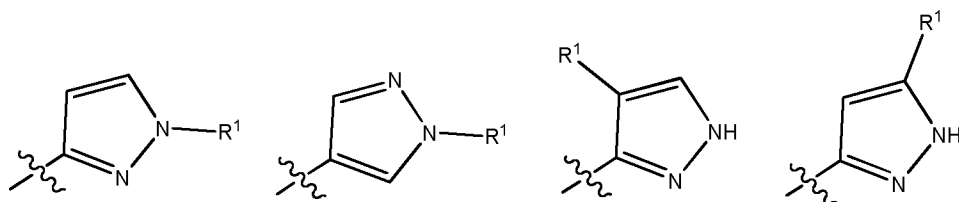
“Saturated 7 to 11 membered heterobicyclicyl” or “saturated 7 to 11 membered heterobicycle” means fully saturated “7 to 11 membered heterobicyclicyl” or “7 to 11 membered heterobicycle”.

Preferred compounds of formula (I) are those compounds in which one or more of the residues contained therein have the meanings given below, with all combinations of preferred substituent definitions being a subject of the present invention. With respect to all preferred compounds of the formula (I) the present invention also includes all tautomeric and stereoisomeric forms and mixtures thereof in all ratios, and their pharmaceutically acceptable salts.

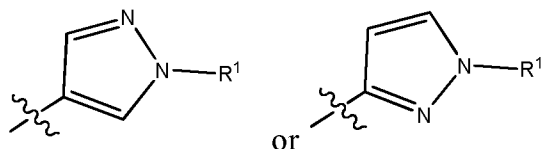
In preferred embodiments of the present invention, the substituents mentioned below independently have the following meaning. Hence, one or more of these substituents can have the preferred or more preferred meanings given below.

Preferably, R is H.

Preferably, ring A is a pyrazole, an oxazole, an isoxazole or a triazole. More preferably, ring A is a pyrazolyl ring; even more preferred a ring selected from the group consisting of:



Even more preferred is



Preferably, 0, 1, or 2 R^1 , which are the same or different, are other than H. More preferably, 1 or 2 R^1 are other than H. Even more preferably, 1 R^1 is other than H. Accordingly, ring A is preferably unsubstituted or substituted with one or two (more preferably one) R^1 , which are different from H and the same or different.

Preferably, R^1 is C_{1-4} alkyl, which is optionally substituted with 1 or 2 R^3 , which are the same or different. Accordingly, R^1 is preferably unsubstituted C_{1-4} alkyl; or C_{1-4} alkyl, substituted with one or two R^3 . More preferably, R^1 is CH_3 ; CH_2CH_2OH ; $CH_2C(O)N(R^4R^{4a})$; CH_2CH_2CN ; CH_2CHF_2 or $CH_2C(O)T^1$.

Preferably, R^3 is halogen; CN; OR^4 ; $C(O)N(R^4R^{4a})$; $S(O)_2R^4$; or $C(O)T^1$. More preferably, R^3 is halogen; CN; OR^4 ; $C(O)N(R^4R^{4a})$; or $C(O)T^1$.

Preferably, R^{4a} is H; or unsubstituted C_{1-4} alkyl.

Preferably, R^4 is H; or unsubstituted C_{1-4} alkyl.

Preferably, T^1 is morpholin-4-yl; piperazin-1-yl; pyrrolidin-1-yl; tetrahydro-1H-furo[3,4-c]pyrrol-5(3H)-yl; 2,5-diazabicyclo[2.2.2]octan-2-yl; 2-tert.-butoxycarbonyl-2,5-diazabicyclo[2.2.2]octan-5-yl; 1-tert.butyloxy-piperazin-4-yl; 2-oxa-6-azaspiro[3.3]heptan-6-yl; or 2,6-diazaspiro[3.3]heptan-6-yl.

Preferably, n is 0, 1 or 2. More preferably, n is 1.

Preferably, R^5 , R^{5a} are H.

Preferably, none or one of X^1 , X^2 , X^3 , X^4 , X^5 is N. More preferably, none of X^1 , X^2 , X^3 , X^4 , X^5 is N.

Preferably, R^6 , R^{6a} , R^{6b} , R^{6c} , R^{6d} are H. Also preferably, at least one (more preferably one, two or three; even more preferably one or two) of R^6 , R^{6a} , R^{6b} , R^{6c} , R^{6d} is other than H.

- 5 Preferably, R^6 , R^{6a} , R^{6b} , R^{6c} , R^{6d} are independently selected from the group consisting of H; halogen; CN; C(O)N(R^7R^{7a}); N(R^7R^{7a}); T^2 , provided that 1 or 2 or 3 (more preferably 1 or 2) of R^6 , R^{6a} , R^{6b} , R^{6c} , R^{6d} are other than H. More preferably, R^6 , R^{6a} , R^{6b} , R^{6c} , R^{6d} are independently selected from the group consisting of H; halogen; CN; C(O)N(R^7R^{7a}); T^2 , provided that 1 or 2 of R^6 , R^{6a} , R^{6b} , R^{6c} , R^{6d} are other than H. More preferably, R^6 , R^{6a} , R^{6b} , R^{6c} , R^{6d} are independently selected from the group consisting of H; F; CN; C(O)NH₂; or morpholin-3-on-4-yl.

- Preferably, T^2 is unsubstituted morpholine; substituted morpholine; unsubstituted pyrazole; or substituted pyrazole, wherein substituted morpholine and substituted pyrazole are independently substituted with one or more R^{17} , which are the same or different.

- More preferably, T^2 is unsubstituted morpholine; or morpholine, substituted with one or more (preferably, one) R^{17} , which are the same or different. Even more preferably, T^2 is morpholin-3-on-4-yl.

- More preferably, T^2 is unsubstituted pyrazole; or morpholine, substituted with one or more (preferably, one) R^{17} , which are the same or different. Even more preferably, T^2 is 1-methyl-1H-pyrazol-4-yl.

- 25 Compounds of formula (I) in which some or all of the above-mentioned groups have the preferred meanings are also an object of the present invention.

- Further preferred compounds of the present invention are selected from the group consisting of

- 30 N-(1,3-Dimethyl-1H-pyrazol-4-yl)-1-(2-fluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-amine;
1-(2-Fluorobenzyl)-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-c]pyridin-6-amine;

1-(2-Fluorobenzyl)-N-(1-methyl-1H-pyrazol-3-yl)-1H-pyrazolo[4,3-c]pyridin-6-amine;

2-(4-((1-(2-Fluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)ethanol;

5 1-(2,5-Difluorobenzyl)-N-(1-methyl-1H-pyrazol-3-yl)-1H-pyrazolo[4,3-c]pyridin-6-amine;

3-(3-((1-(2,5-Difluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)propanenitrile;

10 1-(2,5-Difluorobenzyl)-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-c]pyridin-6-amine;

2-(3-((1-(2-Fluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)ethanol;

1-(2-Fluorobenzyl)-N-(1-methyl-1H-1,2,4-triazol-3-yl)-1H-pyrazolo[4,3-c]pyridin-6-amine;

15

3-(3-((1-(2-Fluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)propanenitrile;

1-(2,5-Difluorobenzyl)-N-(1-methyl-1H-1,2,4-triazol-3-yl)-1H-pyrazolo[4,3-c]pyridin-6-amine;

20

4-(3-Fluoro-5-((6-((1-methyl-1H-pyrazol-4-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)phenyl)morpholin-3-one;

25 4-(3-Fluoro-5-((6-((1-(2-hydroxyethyl)-1H-pyrazol-4-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)phenyl)morpholin-3-one;

4-Fluoro-2-((6-((1-methyl-1H-pyrazol-3-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)benzonitrile;

30

4-Fluoro-2-((6-((1-methyl-1H-pyrazol-4-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)benzonitrile;

2-(4-((1-(2,5-Difluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)ethanol;

2-(3-((1-(2,5-Difluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-5-methyl-1H-pyrazol-1-yl)ethanol;

5-((1-(2,5-Difluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-N-methyl-1H-pyrazole-3-carboxamide;

N-(1,5-Dimethyl-1H-pyrazol-4-yl)-1-(2-fluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-amine;

N-(1,5-Dimethyl-1H-pyrazol-3-yl)-1-(2-fluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-amine;

1-(3,5-Dimethylpiperazin-1-yl)-2-(3-((1-(2-fluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)ethanone;

4-(3-Fluoro-5-((6-((1-(2-hydroxyethyl)-1H-pyrazol-3-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)phenyl)morpholin-3-one;

3-(3-((1-(3-Fluoro-5-(3-oxomorpholino)benzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)propanenitrile;

4-(3-Fluoro-5-((6-((1-methyl-1H-pyrazol-3-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)phenyl)morpholin-3-one;

tert-Butyl 5-(2-(3-((1-(2-fluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)acetyl)-2,5-diazabicyclo[2.2.2]octane-2-carboxylate;

3-(4-((1-(2,5-Difluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)propanenitrile;

2-(3-((1-(2,5-Difluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)ethanol;

3-(4-((1-(3-Fluoro-5-(3-oxomorpholino)benzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)propanenitrile;

2-(4-((1-(2,5-Difluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)-N-methylacetamide;

2-(4-((1-(2,5-Difluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)-N,N-dimethylacetamide;

10 3-(4-((1-(2-Fluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)propanenitrile;

N-(1-(2,5-Difluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-methylisothiazol-5-amine;

15 N-(1-(2-Fluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)oxazol-2-amine;

1-(2-Fluorobenzyl)-N-(5-methyl-1H-pyrazol-3-yl)-1H-pyrazolo[4,3-c]pyridin-6-amine;

1-(2,5-Diazabicyclo[2.2.2]octan-2-yl)-2-(3-((1-(2-fluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)ethanone;

2-(3-((1-(2-Fluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)-N-methylacetamide;

25 2-(3-((1-(2-Fluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)-N,N-dimethylacetamide;

N-(1-(2-Fluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)thiazol-2-amine;

30 N-(1-(2-Fluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)-5-methylthiazol-2-amine;

4-(2,5-Difluoro-3-((6-((1-methyl-1H-pyrazol-4-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)phenyl)morpholin-3-one;

4-(2,5-Difluoro-3-((6-((1-(2-hydroxyethyl)-1H-pyrazol-4-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)phenyl)morpholin-3-one;

N-(1-(2-Fluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)-4-methylthiazol-2-amine;

5

1-Benzyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-c]pyridin-6-amine;

2-(3-((1-Benzyl-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)ethanol;

10 2-(4-((1-Benzyl-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)ethanol;

2-(3-((1-Benzyl-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)-N-methylacetamide;

15 2-(3-((1-Benzyl-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)-N,N-dimethylacetamide;

2-(((6-((1-(2-Hydroxyethyl)-1H-pyrazol-3-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)benzonitrile;

20

1-Benzyl-N-(1-(2,2-difluoroethyl)-1H-pyrazol-3-yl)-1H-pyrazolo[4,3-c]pyridin-6-amine;

2-(((6-((1-(2,2-Difluoroethyl)-1H-pyrazol-3-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)benzonitrile;

25

2-(((6-((1-(2-Hydroxyethyl)-1H-pyrazol-4-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)benzonitrile;

N-(1-(2,2-Difluoroethyl)-1H-pyrazol-3-yl)-1-(pyridin-2-ylmethyl)-1H-pyrazolo[4,3-c]pyridin-6-amine;

30

1-(2,3-Difluorobenzyl)-N-(1-methyl-1H-pyrazol-3-yl)-1H-pyrazolo[4,3-c]pyridin-6-amine;

2-(3-((1-(2,3-Difluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)ethanol;

1-(2,3-Difluorobenzyl)-N-(1-(2,2-difluoroethyl)-1H-pyrazol-3-yl)-1H-pyrazolo[4,3-c]pyridin-6-amine; and

3-(((6-((1-(2-Hydroxyethyl)-1H-pyrazol-3-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)benzonitrile.

10 Further preferred compounds of the present invention are selected from the group consisting of

2-(((6-((1-(2,2-Difluoroethyl)-1H-pyrazol-3-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)-6-fluorobenzonitrile;

3-(((6-((1-(2,2-Difluoroethyl)-1H-pyrazol-3-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)-2-fluorobenzonitrile;

2-(3-((1-(2-Fluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)-1-(piperazin-1-yl)ethanone;

2-(((6-((1-(2,2-Difluoroethyl)-1H-pyrazol-3-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)-4-fluorobenzonitrile;

2-Fluoro-6-(((6-((1-(2-hydroxyethyl)-1H-pyrazol-3-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)benzonitrile;

2-Fluoro-3-(((6-((1-(2-hydroxyethyl)-1H-pyrazol-3-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)benzonitrile;

2-Fluoro-6-(((6-((1-(2-hydroxyethyl)-1H-pyrazol-3-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)benzamide;

2-Fluoro-3-((6-((1-(2-hydroxyethyl)-1H-pyrazol-3-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)benzamide;

5 2-Fluoro-6-((6-((1-(2-hydroxypropyl)-1H-pyrazol-3-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)benzonitrile;

2-((6-((1-(2-Hydroxypropyl)-1H-pyrazol-3-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)benzonitrile;

10 2-Fluoro-3-((6-((1-(2-hydroxypropyl)-1H-pyrazol-3-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)benzonitrile;

2-((6-((1-Methyl-1H-pyrazol-3-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)benzonitrile;

15 1-(2,6-Difluorobenzyl)-N-(1-methyl-1H-pyrazol-3-yl)-1H-pyrazolo[4,3-c]pyridin-6-amine;

2-(3-((1-(2,6-Difluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)ethanol;

20 1-(3-((1-(2,6-Difluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)propan-2-ol;

25 2-(3-((1-(3-(1-Methyl-1H-pyrazol-4-yl)benzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)ethanol;

2-(3-((1-(2-Fluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)acetamide;

30 2-Fluoro-6-((6-((1-(3-hydroxypropyl)-1H-pyrazol-3-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)benzonitrile;

2-((6-((1-(3-Hydroxypropyl)-1H-pyrazol-3-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)benzonitrile;

3-(3-((1-(2-Fluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)propan-1-ol;

5 4-Fluoro-2-((6-((1-(2-hydroxyethyl)-1H-pyrazol-3-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)benzonitrile;

1-(2-Fluorobenzyl)-N-(1H-pyrazol-3-yl)-1H-pyrazolo[4,3-c]pyridin-6-amine;

10 3-Fluoro-2-((6-((1-(2-hydroxyethyl)-1H-pyrazol-3-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)benzonitrile;

4-Fluoro-3-((6-((1-(2-hydroxyethyl)-1H-pyrazol-3-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)benzonitrile;

15

2-(3-((1-(2-Cyanobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)acetamide;

1-(2-Fluorobenzyl)-N-(1-(2-(methylsulfonyl)ethyl)-1H-pyrazol-3-yl)-1H-pyrazolo[4,3-c]pyridin-6-amine;

20

1-(2,6-Difluorobenzyl)-N-(1-(2-(methylsulfonyl)ethyl)-1H-pyrazol-3-yl)-1H-pyrazolo[4,3-c]pyridin-6-amine;

25 2-(3-((1-(2-Fluoro-3-(1-methyl-1H-pyrazol-4-yl)benzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)ethanol;

2-(3-((1-(3-Fluoro-5-(1-methyl-1H-pyrazol-4-yl)benzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)ethanol;

30

2-(3-((1-(2,5-Difluoro-3-(1-methyl-1H-pyrazol-4-yl)benzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)ethanol;

(*R*)-1-(3-((1-(2,6-Difluorobenzyl)-1H-pyrazolo[4,3-*c*]pyridin-6-yl)amino)-1H-pyrazol-1-yl)propan-2-ol;

(*R*)-1-(3-((1-(2-Fluorobenzyl)-1H-pyrazolo[4,3-*c*]pyridin-6-yl)amino)-1H-pyrazol-1-yl)propan-2-ol;

2-(2-((1-(2-Fluorobenzyl)-1H-pyrazolo[4,3-*c*]pyridin-6-yl)amino)thiazol-4-yl)-*N*-methylacetamide;

(*S*)-1-(3-((1-(2,6-Difluorobenzyl)-1H-pyrazolo[4,3-*c*]pyridin-6-yl)amino)-1H-pyrazol-1-yl)propan-2-ol;

(*S*)-1-(3-((1-(2-Fluorobenzyl)-1H-pyrazolo[4,3-*c*]pyridin-6-yl)amino)-1H-pyrazol-1-yl)propan-2-ol;

1-(3-((1-(2-Fluorobenzyl)-1H-pyrazolo[4,3-*c*]pyridin-6-yl)amino)-1H-pyrazol-1-yl)propan-2-ol;

1-(3-Aminobenzyl)-*N*-(1-methyl-1H-pyrazol-3-yl)-1H-pyrazolo[4,3-*c*]pyridin-6-amine; and

1-(3-Amino-5-fluorobenzyl)-*N*-(1-methyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-*c*]pyridin-6-amine.

Where tautomerism, e.g. keto-enol tautomerism, of compounds of general formula (I) may occur, the individual forms, e.g. the keto and enol form, are comprised separately and together as mixtures in any ratio. The same applies for stereoisomers, e.g. enantiomers, *cis/trans* isomers, conformers and the like.

Isotopic labeled compounds ("isotopic derivatives") of formula (I) are also within the scope of the present invention. Methods for isotope labeling are known in the art. Preferred isotopes are those of the elements H, C, N, O and S.

If desired, isomers can be separated by methods well known in the art, e.g. by liquid chromatography. The same applies for enantiomers by using e.g. chiral stationary phases.

Additionally, enantiomers may be isolated by converting them into diastereomers, i.e. coupling with an enantiomerically pure auxiliary compound, subsequent separation of the resulting diastereomers and cleavage of the auxiliary residue. Alternatively, any enantiomer of a compound of formula (I) may be obtained from stereoselective synthesis using optically
5 pure starting materials.

The compounds of formula (I) may exist in crystalline or amorphous form. Furthermore, some of the crystalline forms of the compounds of formula (I) may exist as polymorphs, which are included within the scope of the present invention. Polymorphic forms of
10 compounds of formula (I) may be characterized and differentiated using a number of conventional analytical techniques, including, but not limited to, X-ray powder diffraction (XRPD) patterns, infrared (IR) spectra, Raman spectra, differential scanning calorimetry (DSC), thermogravimetric analysis (TGA) and solid state nuclear magnetic resonance (ssNMR).

In case the compounds according to formula (I) contain one or more acidic or basic groups, the invention also comprises their corresponding pharmaceutically or toxicologically acceptable salts, in particular their pharmaceutically utilizable salts. Thus, the compounds of the formula (I) which contain acidic groups can be used according to the invention, for
20 example, as alkali metal salts, alkaline earth metal salts or as ammonium salts. More precise examples of such salts include sodium salts, potassium salts, calcium salts, magnesium salts or salts with ammonia or organic amines such as, for example, ethylamine, ethanolamine, triethanolamine or amino acids. Compounds of the formula (I) which contain one or more basic groups, i.e. groups which can be protonated, can be present and can be used according
25 to the invention in the form of their addition salts with inorganic or organic acids. Examples for suitable acids include hydrogen chloride, hydrogen bromide, phosphoric acid, sulfuric acid, nitric acid, methanesulfonic acid, p-toluenesulfonic acid, naphthalenedisulfonic acids, oxalic acid, acetic acid, tartaric acid, lactic acid, salicylic acid, benzoic acid, formic acid, propionic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid,
30 fumaric acid, maleic acid, malic acid, sulfaminic acid, phenylpropionic acid, gluconic acid, ascorbic acid, isonicotinic acid, citric acid, adipic acid, and other acids known to the person skilled in the art. If the compounds of the formula (I) simultaneously contain acidic and basic groups in the molecule, the invention also includes, in addition to the salt forms mentioned, inner salts or betaines (zwitterions). The respective salts according to the formula (I) can be

obtained by customary methods which are known to the person skilled in the art like, for example by contacting these with an organic or inorganic acid or base in a solvent or dispersant, or by anion exchange or cation exchange with other salts. The present invention also includes all salts of the compounds of the formula (I) which, owing to low physiological compatibility, are not directly suitable for use in pharmaceuticals but which can be used, for example, as intermediates for chemical reactions or for the preparation of pharmaceutically acceptable salts.

Throughout the invention, the term “pharmaceutically acceptable” means that the corresponding compound, carrier or molecule is suitable for administration to humans. Preferably, this term means approved by a regulatory agency such as the EMEA (Europe) and/or the FDA (US) and/or any other national regulatory agency for use in animals, preferably in humans.

The present invention furthermore includes all solvates of the compounds according to the invention.

According to the present invention “JAK” comprises all members of the JAK family (e.g. JAK1, JAK2, JAK3, and TYK2).

According to the present invention, the expression “JAK1” or “JAK1 kinase” means “Janus kinase 1”. The human gene encoding JAK1 is located on chromosome 1p31.3.

According to the present invention, the expression “JAK2” or “JAK2 kinase” means “Janus kinase 2”. The human gene encoding JAK2 is located on chromosome 9p24.

According to the present invention, the expression “JAK3” or “JAK3 kinase” means “Janus kinase 3”. The gene encoding JAK3 is located on human chromosome 19p13.1 and it is predominantly in hematopoietic cells. JAK3 is a cytoplasmic protein tyrosine kinase that associates with the gamma-chain of the interleukin 2 (IL-2) receptor. This chain also serves as a component for the receptors of several lymphotropic cytokines, including interleukins IL-4, IL-7, IL-9, IL-15 and IL-21 (Schindler et al., 2007. J. Biol. Chem. 282(28):20059-63). JAK3 plays a key role in the response of immune cells to cytokines, especially in mast cells, lymphocytes and macrophages. Inhibition of JAK3 has shown beneficial effects in the prevention of transplant rejection (Changelian et al., 2003, Science 302(5646):875-888).

Moreover, according to the present invention, the expression “JAK3” or “JAK3 kinase” includes mutant forms of JAK3, preferably JAK3 mutants found in acute megakaryoblastic leukemia (AMKL) patients. More preferred, these mutants are single amino acid mutations.

5 Activating JAK3 mutations were observed in acute megakaryoblastic leukemia (AMKL) patients (Walters et al., 2006. Cancer Cell 10(1):65-75). Therefore, in a preferred embodiment, the expression “JAK” also includes a JAK3 protein having a V722I or P132T mutation.

10 According to the present invention, the expression “TYK2” or “TYK2 kinase” means “Protein-Tyrosine kinase 2”. The JAK3 and TYK2 genes are clustered on chromosome 19p13.1 and 19p13.2, respectively.

As shown in the examples, compounds of the invention were tested for their selectivity for

15 JAK3 over JAK2 kinases. As shown, all tested compounds bind JAK3 more selectively than, JAK2 (see table 7 below).

Consequently, the compounds of the present invention are considered to be useful for the prevention or treatment of diseases and disorders associated with JAK, for example

20 immunological, inflammatory, autoimmune, or allergic disorders, transplant rejection, Graft-versus-Host-Disease or proliferative diseases such as cancer.

In a preferred embodiment, the compounds of the present invention are selective JAK3 inhibitors.

25 Equally preferred are dual JAK1/JAK3 inhibitors.

The compounds of the present invention may be further characterized by determining whether they have an effect on JAK3, for example on its kinase activity (Changelian et al., 2003, Science 302(5646):875-888 and online supplement; Yang et al., 2007. Bioorg. Med. Chem. Letters 17(2): 326-331).

30

Briefly, JAK3 kinase activity can be measured using a recombinant GST-JAK3 fusion protein comprising the catalytic domain (JH1 catalytic domain). JAK3 kinase activity is measured by

ELISA as follows: Plates are coated overnight with a random L-glutamic acid and tyrosine co-polymer (4:1; 100 µg/ml) as a substrate. The plates are washed and recombinant JAK3 JH1:GST protein (100 ng/well) with or without inhibitors is incubated at room temperature for 30 minutes. The a HPR-conjugated PY20 anti-phosphotyrosine antibody (ICN) is added and developed by TMB (3,3',5,5'-tetramethylbenzidine) (Changelian et al., 2003, Science 302(5646):875-888 and online supplement).

A cell-based assays (TF-1 cell proliferation) was described to assess the inhibitory activity of small molecule drugs toward JAK2 or JAK3-dependent signal transduction (Chen et al., 2006. Bioorg. Med. Chem. Letters 16(21): 5633-5638).

The present invention provides pharmaceutical compositions comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof as active ingredient together with a pharmaceutically acceptable carrier, optionally in combination with one or more other pharmaceutical compositions.

“Pharmaceutical composition” means one or more active ingredients, and one or more inert ingredients that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing a compound of the present invention and a pharmaceutically acceptable carrier.

The term “carrier” refers to a diluent, adjuvant, excipient, or vehicle with which the therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, including but not limited to peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred carrier when the pharmaceutical composition is administered orally. Saline and aqueous dextrose are preferred carriers when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions are preferably employed as liquid carriers for injectable solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene,

glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. These compositions can take the form of solutions, suspensions, emulsions, tablets, pills, capsules, powders, sustained-release formulations and the like. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin. Such compositions will contain a therapeutically effective amount of the therapeutic, preferably in purified form, together with a suitable amount of carrier so as to provide the form for proper administration to the patient. The formulation should suit the mode of administration.

A pharmaceutical composition of the present invention may comprise one or more additional compounds as active ingredients like one or more compounds of formula (I) not being the first compound in the composition or other JAK inhibitors. Further bioactive compounds may be steroids, leukotriene antagonists, cyclosporine or rapamycin.

The compounds of the present invention or pharmaceutically acceptable salt(s) thereof and the other pharmaceutically active agent(s) may be administered together or separately and, when administered separately, this may occur separately or sequentially in any order. When combined in the same formulation it will be appreciated that the two compounds must be stable and compatible with each other and the other components of the formulation. When formulated separately they may be provided in any convenient formulation, conveniently in such manner as are known for such compounds in the art.

It is further included within the present invention that the compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of formula (I) is administered in combination with another drug or pharmaceutically active agent and/or that the pharmaceutical composition of the invention further comprises such a drug or pharmaceutically active agent.

In this context, the term "drug or pharmaceutically active agent" includes a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought, for instance, by a researcher or clinician.

“Combined” or “in combination” or “combination” should be understood as a functional coadministration, wherein some or all compounds may be administered separately, in different formulations, different modes of administration (for example subcutaneous, intravenous or oral) and different times of administration. The individual compounds of such combinations may be administered either sequentially in separate pharmaceutical compositions as well as simultaneously in combined pharmaceutical compositions.

For example, in rheumatoid arthritis therapy, combination with other chemotherapeutic or antibody agents is envisaged. Suitable examples of pharmaceutically active agents which may be employed in combination with the compounds of the present invention and their salts for rheumatoid arthritis therapy include: immunosuppressants such as amtolmetin guacil, mizoribine and rimexolone; anti-TNF α agents such as etanercept, infliximab, Adalimumab, Anakinra, Abatacept, Rituximab; tyrosine kinase inhibitors such as leflunomide; kallikrein antagonists such as subreum; interleukin 11 agonists such as oprelvekin; interferon beta 1 agonists; hyaluronic acid agonists such as NRD-101 (Aventis); interleukin 1 receptor antagonists such as anakinra; CD8 antagonists such as amiprilose hydrochloride; beta amyloid precursor protein antagonists such as reumacon; matrix metalloprotease inhibitors such as cipemastat and other disease modifying anti-rheumatic drugs (DMARDs) such as methotrexate, sulphasalazine, cyclosporin A, hydroxychloroquine, auranofin, aurothioglucose, gold sodium thiomalate and penicillamine.

In particular, the treatment defined herein may be applied as a sole therapy or may involve, in addition to the compounds of the invention, conventional surgery or radiotherapy or chemotherapy. Accordingly, the compounds of the invention can also be used in combination with existing therapeutic agents for the treatment proliferative diseases such as cancer. Suitable agents to be used in combination include:

(i) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology such as alkylating agents (for example cis-platin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan and nitrosoureas); antimetabolites (for example antifolates such as fluoropyrimidines like 5-fluorouracil and tegafur, raltitrexed, methotrexate, cytosine arabinoside, hydroxyurea and gemcitabine); antitumour antibiotics (for example anthracyclines like adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin,

idarubicin, mitomycin-C, dactinomycin and mithramycin); antimitotic agents (for example vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine and taxoids like paclitaxel and taxotere); and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan and camptothecins);

5

(ii) cytostatic agents such as antioestrogens (for example tamoxifen, toremifene, raloxifene, droloxifene and idoxifene), oestrogen receptor down regulators (for example fulvestrant), antiandrogens (for example bicalutamide, flutamide, nilutamide and cyproterone acetate), LHRH antagonists or LHRH agonists (for example goserelin, leuprorelin and buserelin),
 10 progestogens (for example megestrol acetate), aromatase inhibitors (for example as anastrozole, letrozole, vorazole and exemestane) and inhibitors of 5 α -reductase such as finasteride;

(iii) anti-invasion agents (for example c-Src kinase family inhibitors like 4-(6-chloro- 2,3 -
 15 methylenedioxyanilino)-7- [2-(4-methylpiperazin- 1 -yl)ethoxy] -5 -tetrahydropyran- 4-yloxy-
 quinazoline (AZD0530) and N-(2-chloro-6-methylphenyl)-2-{6-[4-(2-
 hydroxyethyl)piperazin-1-yl]-2-methylpyrimidin- 4-ylamino}thiazole-5-carboxamide
 (dasatinib, BMS-354825), and metalloproteinase inhibitors like marimastat and inhibitors of
 urokinase plasminogen activator receptor function);

20

(iv) inhibitors of growth factor function: for example such inhibitors include growth factor
 antibodies and growth factor receptor antibodies (for example the anti-erbB2 antibody
 trastuzumab [Herceptin™] and the anti-erbB1 antibody cetuximab [C225]); such inhibitors
 also include, for example, tyrosine kinase inhibitors, for example inhibitors of the epidermal
 25 growth factor family (for example EGFR family tyrosine kinase inhibitors such as N-(3-
 chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib,
 ZD 1839), Λ -(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib,
 OSI-774) and 6-acrylamido- Λ -(3-chloro-4-fluorophenyl)-7-(3- morpholinopropoxy)-
 quinazolin-4-amine (CI 1033) and erbB2 tyrosine kinase inhibitors such as lapatinib),
 30 inhibitors of the hepatocyte growth factor family, inhibitors of the platelet-derived growth
 factor family such as imatinib, inhibitors of serine/threonine kinases (for example Ras/Raf
 signalling inhibitors such as farnesyl transferase inhibitors, for example sorafenib (BAY 43-
 9006)) and inhibitors of cell signalling through MEK and/or Akt kinases;

(v) antiangiogenic agents such as those which inhibit the effects of vascular endothelial growth factor, for example the anti-vascular endothelial cell growth factor antibody bevacizumab (Avastin™) and VEGF receptor tyrosine kinase inhibitors such as 4-(4-bromo-2-fluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline (ZD6474; Example 2 within WO 01/32651), 4-(4-fluoro-2-methylindol-5-ylloxy)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline (AZD2171; Example 240 within WO 00/47212), vatalanib (PTK787; WO 98/35985) and SU11248 (sunitinib; WO 01/60814), and compounds that work by other mechanisms (for example linomide, inhibitors of integrin $\alpha v \beta 3$ function and angiostatin);

(vi) vascular damaging agents such as combretastatin A4 and compounds disclosed in International Patent Application WO 99/02166;

(vii) antisense therapies, for example those which are directed to the targets listed above, such as ISIS 2503, an anti-ras antisense agent;

(viii) gene therapy approaches, including approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy; and (ix) immunotherapeutic approaches, including ex-vivo and in-vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies.

Further combination treatments are described in WO-A 2009/008992 and WO-A 2007/107318), incorporated herein by reference.

Accordingly, the individual compounds of such combinations may be administered either sequentially in separate pharmaceutical compositions as well as simultaneously in combined pharmaceutical compositions.

The pharmaceutical compositions of the present invention include compositions suitable for oral, rectal, topical, parenteral (including subcutaneous, intramuscular, and intravenous), ocular (ophthalmic), pulmonary (nasal or buccal inhalation), or nasal administration, although
5 the most suitable route in any given case will depend on the nature and severity of the conditions being treated and on the nature of the active ingredient. They may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

10 In practical use, the compounds of formula (I) can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, *e.g.*, oral or parenteral (including intravenous). In preparing the compositions for oral dosage form, any of the usual pharmaceutical media may
15 be employed, such as water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like in the case of oral liquid preparations, such as, for example, suspensions, elixirs and solutions; or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents and the like in the case of oral solid preparations such as powders, hard and soft capsules and tablets, with the solid oral
20 preparations being preferred over the liquid preparations.

Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be coated by standard aqueous or non-aqueous techniques. Such
25 compositions and preparations should contain at least 0.1 percent of active compound. The percentage of active compound in these compositions may, of course, be varied and may conveniently be between about 2 percent to about 60 percent of the weight of the unit. The amount of active compound in such therapeutically useful compositions is such that an effective dosage will be obtained. The active compounds can also be administered
30 intranasally, for example, as liquid drops or spray.

The tablets, pills, capsules, and the like may also contain a binder such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid; a lubricant such as magnesium stearate; and a

sweetening agent such as sucrose, lactose or saccharin. When a dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as fatty oil.

Various other materials may be present as coatings or to modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain, in addition to the active ingredient, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and a flavoring such as cherry or orange flavor.

Compounds of formula (I) may also be administered parenterally. Solutions or suspensions of these active compounds can be prepared in water suitably mixed with a surfactant such as hydroxypropyl-cellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (*e.g.*, glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

Any suitable route of administration may be employed for providing a mammal, especially a human, with an effective dose of a compound of the present invention. For example, oral, rectal, topical, parenteral, ocular, pulmonary, nasal, and the like may be employed. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, creams, ointments, aerosols, and the like. Preferably compounds of formula (I) are administered orally.

The effective dosage of active ingredient employed may vary depending on the particular compound employed, the mode of administration, the condition being treated and the severity of the condition being treated. Such dosage may be ascertained readily by a person skilled in the art.

A therapeutically effective amount of a compound of the present invention will normally depend upon a number of factors including, for example, the age and weight of the animal, the precise condition requiring treatment and its severity, the nature of the formulation, and the route of administration. However, an effective amount of a compound of formula (I) for the treatment of an inflammatory disease, for example rheumatoid arthritis (RA), will generally be in the range of 0.1 to 100 mg/kg body weight of recipient (mammal) per day and more usually in the range of 1 to 10 mg/kg body weight per day. Thus, for a 70 kg adult mammal, the actual amount per day would usually be from 70 to 700 mg and this amount may be given in a single dose per day or more usually in a number (such as two, three, four, five or six) of sub-doses per day such that the total daily dose is the same. An effective amount of a pharmaceutically acceptable salt, prodrug or metabolite thereof, may be determined as a proportion of the effective amount of the compound of formula (I) per se. It is envisaged that similar dosages would be appropriate for treatment of the other conditions referred to above.

As used herein, the term "effective amount" means that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought, for instance, by a researcher or clinician.

Furthermore, the term "therapeutically effective amount" means any amount which, as compared to a corresponding subject who has not received such amount, results in improved treatment, healing, prevention, or amelioration of a disease, disorder, or side effect, or a decrease in the rate of advancement of a disease or disorder. The term also includes within its scope amounts effective to enhance normal physiological function.

Another aspect of the present invention is a compound of the present invention or a pharmaceutically acceptable salt thereof for use as a medicament.

Another aspect of the present invention is a compound of the present invention or a pharmaceutically acceptable salt thereof for use in a method of treating or preventing a disease or disorder associated with JAK.

In the context of the present invention, a disease or disorder associated with JAK is defined as a disease or disorder where JAK is involved.

In a preferred embodiment, wherein the diseases or disorder is associated with JAK is an immunological, inflammatory, autoimmune, or allergic disorder or disease of a transplant rejection or a Graft-versus host disease.

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Consequently, another aspect of the present invention is a compound or a pharmaceutically acceptable salt thereof of the present invention for use in a method of treating or preventing an immunological, inflammatory, autoimmune, or allergic disorder or disease of a transplant rejection or a Graft-versus host disease.

10

Inflammation of tissues and organs occurs in a wide range of disorders and diseases and in certain variations, results from activation of the cytokine family of receptors. Exemplary inflammatory disorders associated with activation of JAK include, in a non-limiting manner, skin inflammation due radiation exposure, asthma, allergic inflammation and chronic inflammation.

15

According to the present invention, an autoimmune disease is a disease which is at least partially provoked by an immune reaction of the body against own components, for example proteins, lipids or DNA. Examples of organ-specific autoimmune disorders are insulin-dependent diabetes (Type I) which affects the pancreas, Hashimoto's thyroiditis and Graves' disease which affect the thyroid gland, pernicious anemia which affects the stomach, Cushing's disease and Addison's disease which affect the adrenal glands, chronic active hepatitis which affects the liver; polycystic ovary syndrome (PCOS), celiac disease, psoriasis, inflammatory bowel disease (IBD) and ankylosing spondylitis. Examples of non-organ-specific autoimmune disorders are rheumatoid arthritis, multiple sclerosis, systemic lupus and myasthenia gravis.

20

25

Type I diabetes ensues from the selective aggression of autoreactive T-cells against insulin secreting beta-cells of the islets of Langerhans. Targeting JAK3 in this disease is based on the observation that multiple cytokines that signal through the JAK pathway are known to participate in the T-cell mediated autoimmune destruction of beta-cells. Indeed, a JAK3 inhibitor, JANEX-1 was shown to prevent spontaneous autoimmune diabetes development in the NOD mouse model of type I diabetes.

30

In a preferred embodiment, the autoimmune disease is selected from the group consisting of rheumatoid arthritis (RA), inflammatory bowel disease (IBD; Crohn's disease and ulcerative colitis), psoriasis, systemic lupus erythematosus (SLE), and multiple sclerosis (MS).

5 Rheumatoid arthritis (RA) is a chronic progressive, debilitating inflammatory disease that affects approximately 1% of the world's population. RA is a symmetric polyarticular arthritis that primarily affects the small joints of the hands and feet. In addition to inflammation in the synovium, the joint lining, the aggressive front of tissue called pannus invades and destroys local articular structures (Firestein 2003, Nature 423:356-361).

10

Inflammatory bowel disease (IBD) is characterized by a chronic relapsing intestinal inflammation. IBD is subdivided into Crohn's disease and ulcerative colitis phenotypes. Crohn disease involves most frequently the terminal ileum and colon, is transmural and discontinuous. In contrast, in ulcerative colitis, the inflammation is continuous and limited to
15 rectal and colonic mucosal layers. In approximately 10% of cases confined to the rectum and colon, definitive classification of Crohn's disease or ulcerative colitis cannot be made and are designated 'indeterminate colitis.' Both diseases include extraintestinal inflammation of the skin, eyes, or joints. Neutrophil-induced injuries may be prevented by the use of neutrophils migration inhibitors (Asakura et al., 2007, World J Gastroenterol. 13(15):2145-9).

20

Psoriasis is a chronic inflammatory dermatosis that affects approximately 2% of the population. It is characterized by red, scaly skin patches that are usually found on the scalp, elbows, and knees, and may be associated with severe arthritis. The lesions are caused by abnormal keratinocyte proliferation and infiltration of inflammatory cells into the dermis and
25 epidermis (Schön et al., 2005, New Engl. J. Med. 352:1899-1912).

Systemic lupus erythematosus (SLE) is a chronic inflammatory disease generated by T cell-mediated B-cell activation, which results in glomerulonephritis and renal failure. Human SLE is characterized at early stages by the expansion of long-lasting autoreactive CD4⁺ memory
30 cells (D'Cruz et al., 2007, Lancet 369(9561):587-596).

Multiple sclerosis (MS) is an inflammatory and demyelating neurological disease. It has been considered as an autoimmune disorder mediated by CD4⁺ type 1 T helper cells, but recent

studies indicated a role of other immune cells (Hemmer et al., 2002, Nat. Rev. Neuroscience 3, 291-301).

5 Mast cells express JAK3 and JAK3 is a key regulator of the IgE mediated mast cell responses including the release of inflammatory mediators. JAK3 was shown to be a valid target in the treatment of mast cell mediated allergic reaction. Allergic disorders associated with mast cell activation include Type I immediate hypersensitivity reactions such as allergic rhinitis (hay fever), allergic urticaria (hives), angioedema, allergic asthma and anaphylaxis, for example anaphylactic shock. These disorders may be treated or prevented by inhibition of JAK3
10 activity, for example, by administration of a JAK3 inhibitor according to the present invention.

Transplant rejection (allograft transplant rejection) includes, without limitation, acute and chronic allograft rejection following for example transplantation of kidney, heart, liver, lung,
15 bone marrow, skin and cornea. It is known that T cells play a central role in the specific immune response of allograft rejection. Hyperacute, acute and chronic organ transplant rejection may be treated. Hyperacute rejection occurs within minutes of transplantation. Acute rejection generally occurs within six to twelve months of the transplant. Hyperacute and acute rejections are typically reversible where treated with immunosuppressant agents. Chronic
20 rejection, characterized by gradual loss of organ function, is an ongoing concern for transplant recipients because it can occur anytime after transplantation.

Graft-versus-host disease (GVHD) is a major complication in allogeneic bone marrow transplantation (BMT). GVHD is caused by donor T cells that recognize and react to recipient
25 differences in the histocompatibility complex system, resulting in significant morbidity and mortality. JAK3 plays a key role in the induction of GVHD and treatment with a JAK3 inhibitor, JANEX-1, was shown to attenuate the severity of GVHD (reviewed in Cetkovic-Cvrlje and Ucken, 2004).

30 In a preferred embodiment, the inflammatory disease is an eye disease.

Dry eye syndrome (DES, also known as keratoconjunctivitis sicca) is one of the most common problems treated by eye physicians. Sometimes DES is referred to as dysfunctional tear syndrome (Jackson, 2009. Canadian Journal Ophthalmology 44(4), 385-394). DES

affects up to 10% of the population between the ages of 20 to 45 years, with this percentage increasing with age. Although a wide variety of artificial tear products are available, these products provide only transitory relief of symptoms. As such, there is a need for agents, compositions and therapeutic methods to treat dry eye.

5

As used herein, "dry eye disorder" is intended to encompass the disease states summarized in a recent official report of the Dry Eye Workshop (DEWS), which defined dry eye as "a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolality of the tear film and inflammation of the ocular surface." (Lemp, 2007. "The Definition and Classification of Dry Eye Disease: Report of the Definition and Classification Subcommittee of the International Dry Eye Workshop", *The Ocular Surface*, 5(2), 75-92). Dry eye is also sometimes referred to as keratoconjunctivitis sicca. In some embodiments, the treatment of the dry eye disorder involves ameliorating a particular symptom of dry eye disorder, such as eye discomfort, visual disturbance, tear film instability, tear hyperosmolality, and inflammation of the ocular surface.

Uveitis is the most common form of intraocular inflammation and remains a significant cause of visual loss. Current treatments for uveitis employs systemic medications that have severe side effects and are globally immunosuppressive. Clinically, chronic progressive or relapsing forms of non-infectious uveitis are treated with topical and/or systemic corticosteroids. In addition, macrolides such as cyclosporine and rapamycin are used, and in some cases cytotoxic agents such as cyclophosphamide and chlorambucil, and antimetabolites such as azathioprine, methotrexate, and leflunomide (Srivastava et al., 2010. Uveitis: Mechanisms and recent advances in therapy. *Clinica Chimica Acta*, doi:10.1016/j.cca.2010.04.017).

Further eye diseases, combination treatments and route of administration are described for example in WO-A 2010/039939, which is hereby incorporated herein by reference.

In a further preferred embodiment, the disease or disorder associated with JAK is a proliferative disease, especially cancer.

Diseases and disorders associated especially with JAK are proliferative disorders or diseases, especially cancer.

Therefore, another aspect of the present invention is a compound or a pharmaceutically acceptable salt thereof of the present invention for use in a method of treating or preventing a proliferative disease, especially cancer.

5

Cancer comprises a group of diseases characterized by uncontrolled growth and spread of abnormal cells. All types of cancers generally involve some abnormality in the control of cell growth, division and survival, resulting in the malignant growth of cells. Key factors contributing to said malignant growth of cells are independence from growth signals, insensitivity to anti-growth signals, evasion of apoptosis, limitless replicative potential, sustained angiogenesis, tissue invasion and metastasis, and genome instability (Hanahan and Weinberg, 2000. The Hallmarks of Cancer. Cell 100, 57-70).

10

Typically, cancers are classified as hematological cancers (for example leukemias and lymphomas) and solid cancers such as sarcomas and carcinomas (for example cancers of the brain, breast, lung, colon, stomach, liver, pancreas, prostate, ovary).

15

The JAK inhibitors of the present invention may also useful in treating certain malignancies, including skin cancer and hematological malignancy such as lymphomas and leukemias.

20

Especially cancers in which the JAK-STAT signal transduction pathway is activated, for example due to activation of JAK3 are expected to respond to treatment with JAK3 inhibitors. Examples of cancers harboring JAK3 mutations are acute megakaryoblastic leukemia (AMKL) (Walters et al., 2006. Cancer Cell 10(1):65-75) and breast cancer (Jeong et al., 2008. Clin. Cancer Res. 14, 3716-3721).

25

Proliferative diseases or disorders comprise a group of diseases characterized by increased cell multiplication as observed in myeloproliferative disorders (MPD) such as polycythemia vera (PV).

30

Yet another aspect of the present invention is the use of a compound of the present invention or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment or prophylaxis of diseases and disorders associated with JAK.

Yet another aspect of the present invention is the use of a compound of the present invention or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for treating or preventing an immunological, inflammatory, autoimmune, or allergic disorder or disease or a transplant rejection or a Graft-versus host disease.

5

Yet another aspect of the present invention is the use of a compound of the present invention or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for treating or preventing a proliferative disease, especially cancer.

10 In the context of these uses of the invention, diseases and disorders associated with JAK are as defined above.

Yet another aspect of the present invention is a method for treating, controlling, delaying or preventing in a mammalian patient in need thereof one or more conditions selected from the
15 group consisting of diseases and disorders associated with JAK, wherein the method comprises the administration to said patient a therapeutically effective amount of a compound according to present invention or a pharmaceutically acceptable salt thereof.

Yet another aspect of the present invention is a method for treating, controlling, delaying or
20 preventing in a mammalian patient in need thereof one or more conditions selected from the group consisting of an immunological, inflammatory, autoimmune, or allergic disorder or disease or a transplant rejection or a Graft-versus host disease, wherein the method comprises the administration to said patient a therapeutically effective amount of a compound according to present invention or a pharmaceutically acceptable salt thereof.

25

Yet another aspect of the present invention is a method for treating, controlling, delaying or preventing in a mammalian patient in need thereof a proliferative disease, especially cancer, wherein the method comprises the administration to said patient a therapeutically effective amount of a compound according to present invention or a pharmaceutically acceptable salt
30 thereof.

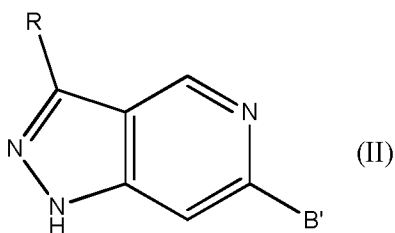
In the context of these methods of the invention, diseases and disorders associated with JAK are as defined above.

As used herein, the term "treating" or "treatment" is intended to refer to all processes, wherein there may be a slowing, interrupting, arresting, or stopping of the progression of a disease, but does not necessarily indicate a total elimination of all symptoms.

- 5 All embodiments discussed above with respect to the pharmaceutical composition of the invention also apply to the above mentioned first or second medical uses or methods of the invention.

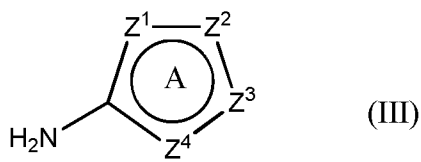
10 In general, compounds of the present invention may be prepared according to a method comprising the steps of

- reacting a compound of formula (II)



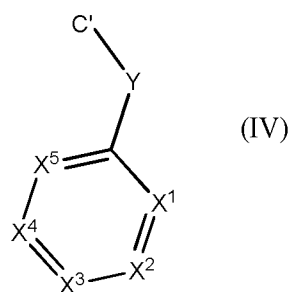
15

wherein B' is a suitable leaving group (like chloro) and R has the meaning as indicated above with a compound of formula (III)



20

wherein A, Z¹ to Z⁴ have the meaning as indicated above and subsequently with a compound of formula (IV)

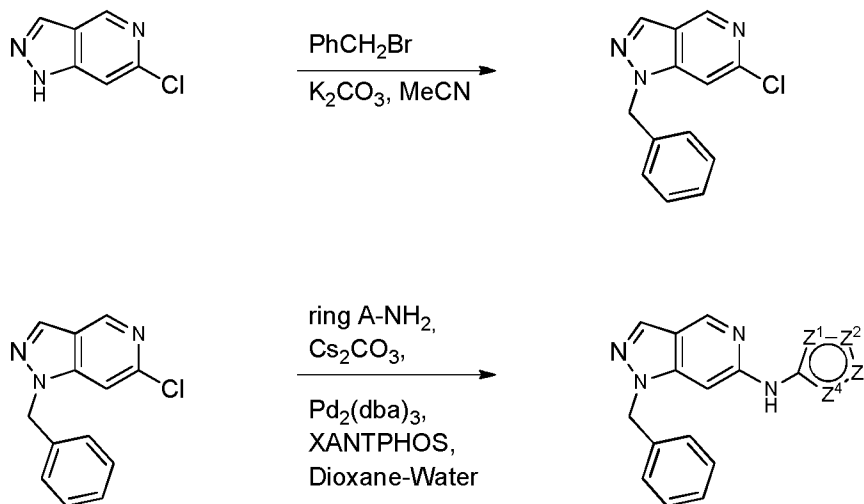


wherein X^1 to X^5 and Y have the meaning as indicated above and C' is suitable reactive group (like bromo), or first with a compound of formula (IV) followed by reaction with compound
5 (III) to yield a compound of formula (I).

Exemplary routes for the preparation of compounds of the present invention are described below. It is clear to a practitioner in the art to combine or adjust such routes especially in combination with the introduction of activating or protective chemical groups.

10

Exemplary general routes for the preparation of compounds according to the present invention are outlined in Schemes 1.



15

Scheme 1

Examples

Analytical Methods

NMR spectra were obtained on a Bruker dpx400. LCMS was carried out on an Agilent 1100 using a Gemini C18, 3 x 30 mm, 3micron. Column flow was 1.2mL/min and solvents used were water and acetonitrile (0.1% formic acid- high pH, 0.1% ammonia- low pH) with an injection volume of 3µL. Wavelengths were 254 and 210nm.

Method A

Column: Phenomenex Gemini-C18, 3 x 30mm, 3microns. Flow rate: 1.2mL/min

Table 1

Time (min)	Water (%)	ACN (%)
0	95	5
3	5	95
4.5	5	95
4.6	95	5
5	STOP	

Method B

Column: Phenomenex Gemini-C18, 4.6 x 150mm, 5microns. Flow rate: 1.0mL/min

Table 2

Time (min)	Water (%)	ACN (%)
0.00	95.0	5.0
11.00	5.0	95.0
13.00	5.0	95.0
13.01	95.0	5.0
14.00	STOP	

Method C

Column: Phenomenex Gemini-NX C18, 4.6 x 150 mm, 5 microns. Flow: 1 mL/min. Gradient:

Table 3

Time (min)	Water	Acetonitrile
0	95	5

11	5	95
13	5	95
13.01	95	5
16.00	95	5
16.01	STOP	

Table 4: Abbreviations

5

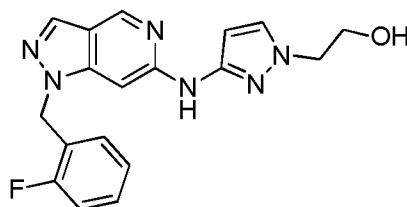
ACN	Acetonitrile
Ar	Aryl
aq	Aqueous
br	Broad
Boc	<i>Tert</i> -Butoxycarbonyl
BuLi	Butyllithium
Cs ₂ CO ₃	Cesium carbonate
d	Doublet
DCM	Dichloromethane
dd	Double doublet
ddd	Double doublet of doublets
DEAD	Diethyl azodicarboxylate
DIAD	Diisopropyl azodicarboxylate
DIPEA	Diisopropylethylamine
DME	1,2-Dimethoxyethane
DMF	<i>N,N'</i> -Dimethylformamide
DMF-DMA	<i>N,N</i> -dimethylformamide dimethylacetal
DMSO	<i>N,N'</i> -dimethylsulfoxide
DP	Drug pulldown
dt	Doublet of triplets
DTT	Dithiothreitol
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
EDTA	Ethylenediaminetetraacetic acid

EtOAc	Ethyl acetate
EtOH	Ethanol
eq	Equivalents
g	Grams
h	Hours
HATU	<i>O</i> -(7-Azabenzotriazol-1-yl)- <i>N,N,N',N'</i> -tetramethyluronium hexafluorophosphate
HCl	Hydrochloric acid
H ₂ O	Water
H ₂ S	Hydrogen sulfide
HOBt	1-Hydroxybenzotriazole
HPLC	High performance liquid chromatography
IC ₅₀	50% inhibition concentration
iPr	Isopropyl
L	Litres
LC-MS	Liquid chromatography mass spectroscopy
m	Multiplet
M	Molar
MeOH	Methanol
Mesyl	Methanesulfonyl chloride
mg	Milligrams
MgSO ₄	Magnesium Sulphate
min	Minutes
mL	Millilitres
mm	Millimetres
mmol	Millimoles
mol%	Molar percent
μL	Microlitres
nm	Nanometres
NMR	Nuclear magnetic resonance
PBS	Phosphate buffered saline
Pd ₂ (dba) ₃	Tris(dibenzylideneacetone)dipalladium(0)
q	Quartet

rpm	Revolutions per minute
rt	Room temperature
RT	Retention time
s	Singlet
sat.	Saturated
t	Triplet
td	Triplet of doublets
tdd	Triple doublet of doublets
THF	Tetrahydrofuran
tt	Triplet of triplets
tert	Tertiary
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

Experimental

Example 1: 2-(3-((1-(2-Fluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-ylamino)-1H-pyrazol-1-yl)ethanol



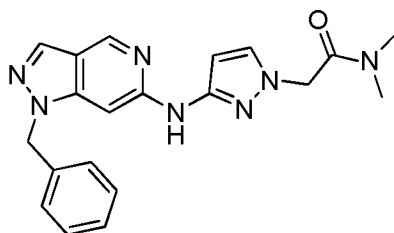
A suspension of 6-chloro-1H-pyrazolo[4,3-c]pyridine (1g, 6.54mmol), 1-(bromomethyl)-2-fluorobenzene (1.1eq) and potassium carbonate (2eq) in acetonitrile (20mL) was heated at 60°C for 18h. The resultant mixture was diluted with DCM and washed with H₂O. The organic phase was collected, dried (hydrophobic frit) and concentrated *in vacuo*. The resultant residue was purified by column chromatography (DCM:EtOAc) to give 6-chloro-1-(2-fluorobenzyl)-1H-pyrazolo[4,3-c]pyridine.

A solution of 3-nitropyrazole (300mg, 2.65mmol), potassium carbonate (2eq) and 2-bromoethanol (1.1eq) in acetonitrile (10mL) was heated at 60°C for 18h. After cooling to rt the mixture was diluted with EtOAc and washed with H₂O. The organic phase was collected, dried (hydrophobic frit) and concentrated *in vacuo*. The crude residue was dissolved in methanol (10mL), palladium on carbon (50mg) was added and the reaction was stirred under

a balloon of hydrogen for 18h. The resulting mixture was filtered through Celite and the filtrate concentrated *in vacuo* to give 2-(3-amino-1*H*-pyrazol-1-yl)ethanol.

A suspension of 6-chloro-1-(2-fluorobenzyl)-1*H*-pyrazolo[4,3-*c*]pyridine (150mg, 0.57mmol), 2-(3-amino-1*H*-pyrazol-1-yl)ethanol (1.1eq), Xantphos (0.1eq), Pd₂(dba)₃ (0.1eq) and cesium carbonate (2eq) in dioxane:H₂O (5:1) (5mL) was heated at 150°C for 30min under microwave irradiation. The resultant mixture was diluted with DCM and washed with H₂O. The organic phase was collected, dried (hydrophobic frit) and concentrated *in vacuo*. The resultant mixture was purified by prep. HPLC to give the title compound. ¹H NMR (d₆-DMSO) δ 9.19 (s, 1H), 8.68 (d, 1H), 8.08 (d, 1H), 7.64 (d, 1H), 7.53 (d, 1H), 7.33-7.39 (m, 1H), 7.20-7.25 (m, 2H), 7.14-7.18 (m, 1H), 5.99 (d, 1H), 5.53 (s, 2H), 4.86 (t, 1H), 4.05-4.08 (m, 2H), 3.76-3.80 (m, 2H); LC-MS method C, (ES⁺) 353, RT = 5.46 min.

Example 2: 2-(3-((1-Benzyl-1*H*-pyrazolo[4,3-*c*]pyridin-6-ylamino)-1*H*-pyrazol-1-yl)-*N,N*-dimethylacetamide



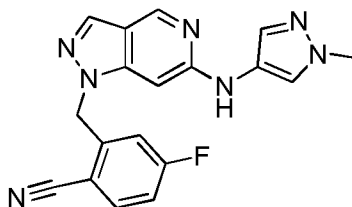
A solution of 3-nitropyrazole (300mg, 2.65mmol), potassium carbonate (2eq) and 2-chloro-*N,N*-dimethylacetamide (1.1eq) in acetonitrile (10mL) was heated at 60°C for 48h. After cooling to rt the mixture was filtered and the filtrate diluted with DCM then washed with H₂O. The organic phase was collected, dried (hydrophobic frit) and concentrated *in vacuo*. The crude residue was dissolved in methanol (10mL), palladium on carbon (50mg) was added and the reaction was stirred under a balloon of hydrogen for 18h. The resulting mixture was filtered through Celite and the filtrate concentrated *in vacuo* to give 2-(3-amino-1*H*-pyrazol-1-yl)-*N,N*-dimethylacetamide.

A suspension of 6-chloro-1*H*-pyrazolo[4,3-*c*]pyridine (750mg, 4.87mmol), benzyl bromide (1.1eq) and potassium carbonate (2eq) in acetonitrile (20mL) was heated at 60°C for 18h. The resultant mixture was filtered, the filtrate diluted with DCM and washed with H₂O. The organic phase was collected, dried (hydrophobic frit) and concentrated *in vacuo*. The

resultant residue was purified by column chromatography (hexane:EtOAc) to give 1-benzyl-6-chloro-1*H*-pyrazolo[4,3-*c*]pyridine.

A suspension of 1-benzyl-6-chloro-1*H*-pyrazolo[4,3-*c*]pyridine (50mg, 0.21mmol), 2-(3-amino-1*H*-pyrazol-1-yl)-*N,N*-dimethylacetamide (1.1eq), Xantphos (0.1eq), Pd₂(dba)₃ (0.1eq) and cesium carbonate (2eq) in dioxane:H₂O (5:1) (5mL) was heated at 150°C for 30min under microwave irradiation. The resultant mixture was diluted with DCM and washed with H₂O. The organic phase was collected, dried (hydrophobic frit) and concentrated *in vacuo*. The resultant mixture was purified by prep. HPLC to give the title compound. ¹H NMR (d₆-DMSO) δ 9.18 (s, 1H), 8.69 (d, 1H), 8.08 (d, 1H), 7.60 (s, 1H), 7.51 (d, 1H), 7.21-7.33 (m, 5H), 6.03 (d, 1H), 5.47 (s, 2H), 4.98 (s, 2H), 3.06 (s, 3H), 2.85 (s, 3H); LC-MS method C, (ES⁺) 376, RT = 5.45 min.

Example 3: 4-Fluoro-2-((6-((1-methyl-1*H*-pyrazol-4-yl)amino)-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)methyl)benzonitrile



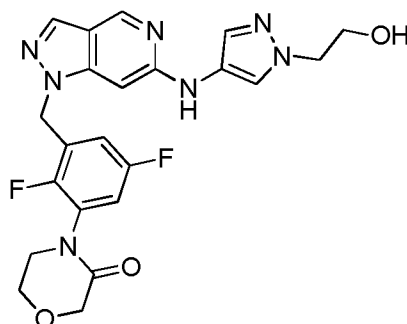
A suspension of 6-chloro-1*H*-pyrazolo[4,3-*c*]pyridine (712mg, 4.6mmol), 2-cyano-5-fluorobenzyl bromide (1.1eq) and potassium carbonate (2.2eq) in acetonitrile (60mL) was heated at 80°C for 72h. The resultant mixture was diluted with DCM and washed with H₂O. The organic phase was collected, dried (hydrophobic frit) and concentrated *in vacuo*. The resultant residue was purified by column chromatography (petrol:EtOAc) to give 2-((6-chloro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)methyl)-4-fluorobenzonitrile.

A solution of 4-nitro-1*H*-pyrazole (1g, 8.84mmol), potassium carbonate (2.2eq) and iodomethane (1.1eq) in acetonitrile (60mL) was heated at 60°C for 18h. After cooling to rt the mixture was diluted with EtOAc and washed with H₂O and then brine. The organic phase was collected, dried (MgSO₄) and concentrated *in vacuo*. The crude residue was dissolved in ethanol (60mL), palladium on carbon (50mg) was added and the reaction was stirred under a

balloon of hydrogen for 18h. The resulting mixture was filtered through Celite and the filtrate concentrated *in vacuo* to give 1-methyl-1H-pyrazol-4-amine.

5 A suspension of 2-((6-chloro-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)-4-fluorobenzonitrile (100mg, 0.35mmol), 1-methyl-1H-pyrazol-4-amine (1.2eq), Xantphos (0.1eq), Pd₂(dba)₃ (0.1eq) and cesium carbonate (2eq) in dioxane:H₂O (5:1) (5mL) was heated at 150°C for 30min under microwave irradiation. The resultant mixture was diluted with DCM and washed with H₂O. The organic phase was collected, dried (hydrophobic frit) and concentrated *in vacuo*. The resultant mixture was purified by prep. HPLC to give the title compound. ¹H
10 NMR (d₆-DMSO) δ 8.70 (d, 1H), 8.60 (s, 1H), 8.13-8.12 (m, 1H), 8.01 (dd, 1H), 7.82 (m, 1H), 7.44-7.39 (m, 2H), 7.00 (dd, 1H), 6.57-6.59 (m, 1H), 5.68 (s, 2H), 3.81 (s, 3H); LC-MS method C, (ES⁺) 348, RT = 5.65 min.

15 **Example 4:** 4-(2,5-Difluoro-3-(((6-((1-(2-hydroxyethyl)-1H-pyrazol-4-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)phenyl)morpholin-3-one



To a solution of 4-amino-3-bromo-2,5-difluorobenzonitrile (10g, 43.1mmol) in THF (150mL)
20 at -78°C was added diisobutylaluminium hydride (1 eq of a 1M solution in toluene) and the reaction was allowed to warm to rt over 16h. The mixture was then recooled to -78°C and further diisobutylaluminium hydride (0.5 eq of a 1M solution in toluene) was added and the reaction allowed to warm to rt over 4h. The mixture was then recooled to -78°C, quenched with aqueous Rochelle salt solution and allowed to warm to rt. The product was then
25 extracted into EtOAc and the organic phase was dried (MgSO₄), reduced *in vacuo* and purified by column chromatography (petrol:EtOAc) to give 4-amino-3-bromo-2,5-difluorobenzaldehyde.

To a solution of 4-amino-3-bromo-2,5-difluorobenzaldehyde (6.2g, 26.4mmol) in acetic acid (140mL) at 0°C was added hypophosphorus acid (80mL of a 50% solution in water). Sodium nitrite (1.4eq dissolved in 8mL of water) was then added dropwise and the reaction was stirred at rt for 2h. The mixture was then poured onto ice-H₂O and extracted into DCM. The organics were dried (MgSO₄) and reduced *in vacuo* to give 3-bromo-2,5-difluorobenzaldehyde.

To a solution of 3-bromo-2,5-difluorobenzaldehyde (3.8g, 17.3mmol) in methanol (100mL) was added sodium borohydride (1eq) and the reaction was stirred at rt for 10 min. The mixture was then quenched with aqueous 0.1M HCl solution. The solvent was then reduced *in vacuo* and the residue partitioned between EtOAc and H₂O. The organics were dried (MgSO₄) and reduced *in vacuo* to give (3-bromo-2,5-difluorophenyl)methanol.

To a solution of (3-bromo-2,5-difluorophenyl)methanol (0.4g, 1.79mmol) in dioxane (10mL) was added morpholinone (1.5eq), potassium carbonate (2eq) copper iodide (0.2eq) and then N,N'-diethylethylenediamine (0.4eq) and the reaction was stirred at 100°C for 16h. After cooling to rt the reaction was partitioned between EtOAc and H₂O. The organics were washed with aqueous 0.5M aq EDTA solution, dried (MgSO₄), reduced *in vacuo* and purified by column chromatography (petrol:EtOAc) to give 4-(2,5-difluoro-3-(hydroxymethyl)phenyl)morpholin-3-one.

To a solution of 4-(2,5-difluoro-3-(hydroxymethyl)phenyl)morpholin-3-one (0.2g, 0.82mmol) in DCM (10mL) was added phosphorus tribromide (2.5eq) and the reaction stirred at rt for 16h. The mixture was then quenched with saturated aqueous sodium hydrogen carbonate solution and the product extracted into DCM. The organics were dried (MgSO₄) and reduced *in vacuo* to give 4-(3-(bromomethyl)-2,5-difluorophenyl)morpholin-3-one.

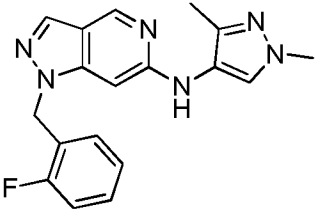
A suspension of 6-chloro-1H-pyrazolo[4,3-c]pyridine (0.1g, 0.65mmol), 4-(3-(bromomethyl)-2,5-difluorophenyl)morpholin-3-one (1.1eq) and potassium carbonate (2eq) in acetonitrile (20mL) was heated at 60°C for 18h. The resultant mixture was diluted with DCM and washed with H₂O. The organic phase was collected, dried (hydrophobic frit) and concentrated *in vacuo*. The resultant residue was purified by column chromatography (petrol:EtOAc) to give 4-(3-((6-chloro-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)-2,5-difluorophenyl)morpholin-3-one.

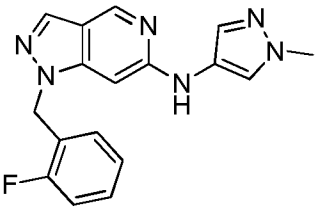
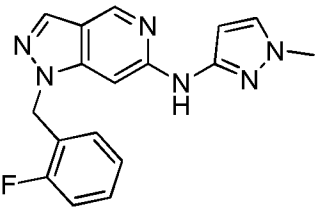
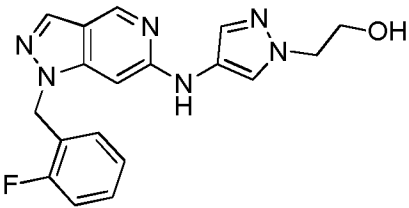
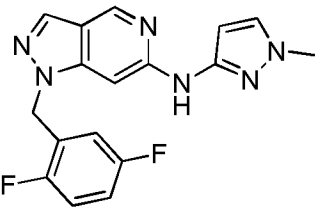
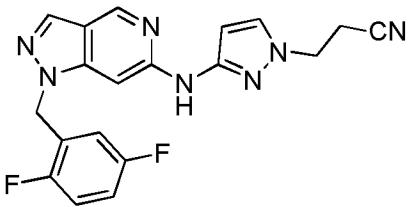
A solution of 4-nitro-1H-pyrazole (1.0g, 8.85mmol), potassium carbonate (2eq) and 2-bromoethanol (1.1eq) in acetonitrile (30mL) was heated at 60°C for 18h. After cooling to rt the mixture was diluted with EtOAc and washed with H₂O. The organic phase was collected, dried (hydrophobic frit) and concentrated *in vacuo*. The crude residue was dissolved in ethanol (30mL), palladium on carbon (50mg) was added and the reaction was stirred under a balloon of hydrogen for 18h. The resulting mixture was filtered through Celite and the filtrate concentrated *in vacuo* to give 2-(4-amino-1H-pyrazol-1-yl)ethanol.

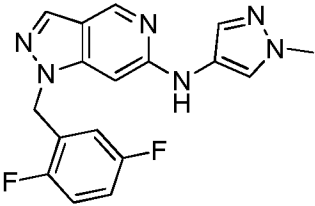
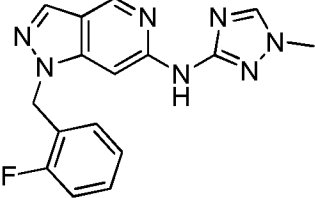
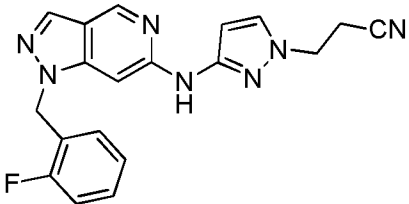
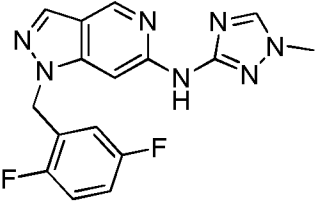
A suspension of 4-(3-((6-chloro-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)-2,5-difluorophenyl)morpholin-3-one (50mg, 0.13mmol), 2-(4-amino-1H-pyrazol-1-yl)ethanol (1.1eq), Xantphos (0.1eq), Pd₂(dba)₃ (0.1eq) and cesium carbonate (2eq) in dioxane:H₂O (5:1) (5mL) was heated at 150°C for 30min under microwave irradiation. The resultant mixture was diluted with DCM and washed with H₂O. The organic phase was collected, dried (hydrophobic frit) and concentrated *in vacuo*. The resultant mixture was purified by column chromatography (petrol:EtOAc) to give the title compound. ¹H NMR (d₆-DMSO) δ 8.69 (s, 1H), 8.62 (s, 1H), 8.09 (s, 1H), 7.86 (s, 1H), 7.46 (s, 1H), 7.43-7.46 (m, 1H), 6.95-6.97 (m, 1H), 6.61 (s, 1H), 5.56 (s, 2H), 4.88 (t, 1H), 4.23 (s, 2H), 4.09-4.12 (m, 2H), 3.95-3.98 (m, 2H), 3.72-3.76 (m, 2H), 3.65-3.68 (m, 2H); LC-MS method C, (ES+) 470, RT = 54.62 min.

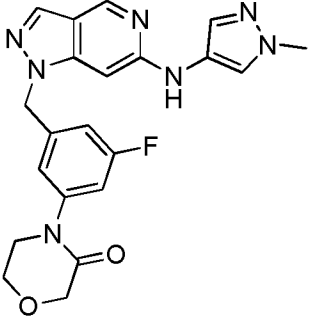
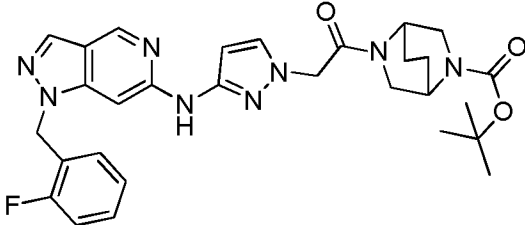
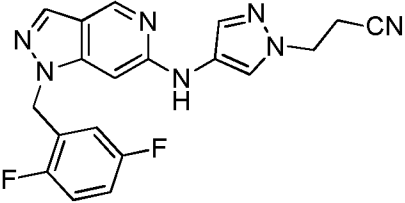
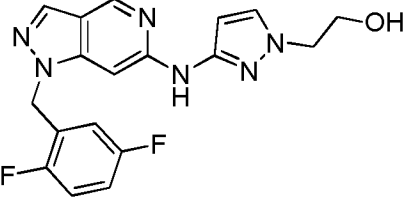
The following compounds were synthesized by procedures analogous to those described above:

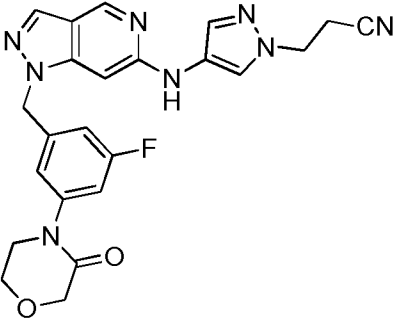
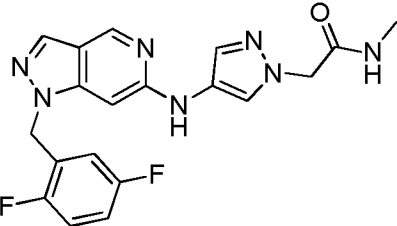
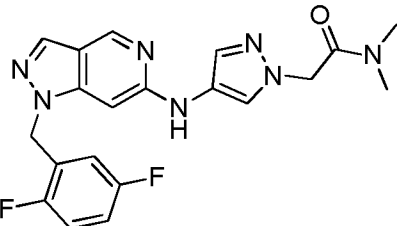
Table 5

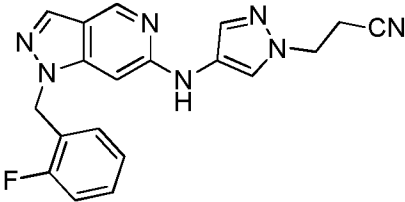
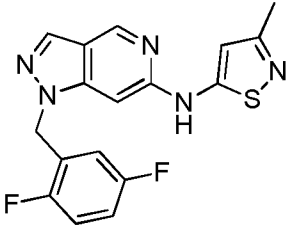
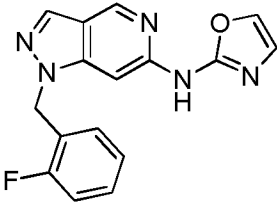
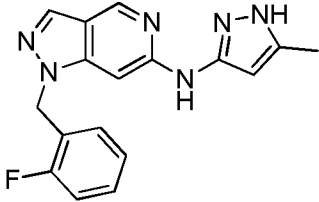
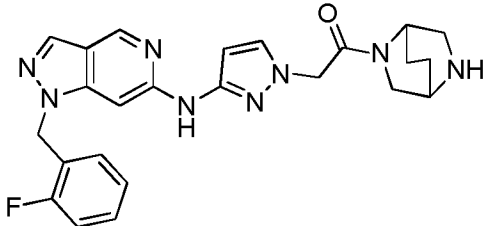
Structure	Name	N°	LCMS Method	ES+	RT (min)	Purity (%)
	N-(1,3-dimethyl-1H-pyrazol-4-yl)-1-(2-fluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-amine	5	C	337	5.68	>90%

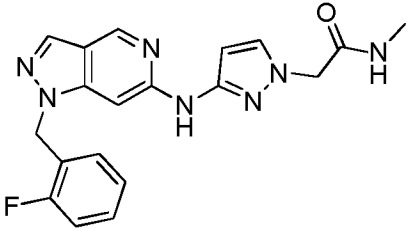
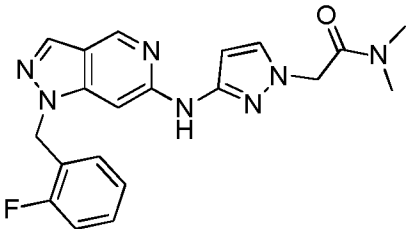
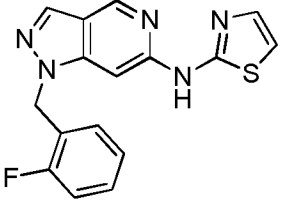
	1-(2-fluorobenzyl)- N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-c]pyridin-6-amine	6	C	323	5.49	>80%
	1-(2-fluorobenzyl)- N-(1-methyl-1H-pyrazol-3-yl)-1H-pyrazolo[4,3-c]pyridin-6-amine	7	C	323	5.77	>80%
	2-(4-((1-(2-fluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)ethanol	8	C	353	5.30	>90%
	1-(2,5-difluorobenzyl)- N-(1-methyl-1H-pyrazol-3-yl)-1H-pyrazolo[4,3-c]pyridin-6-amine	9	C	341	6.09	>95%
	3-(3-((1-(2,5-difluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)propanenitrile	10	C	380	6.21	>95%

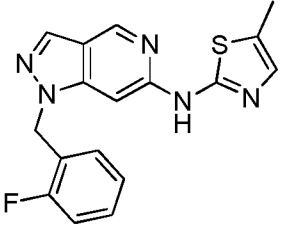
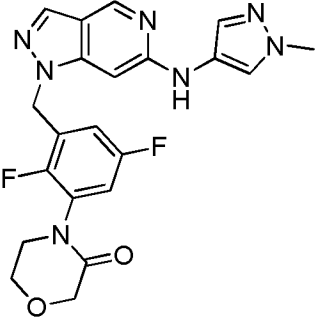
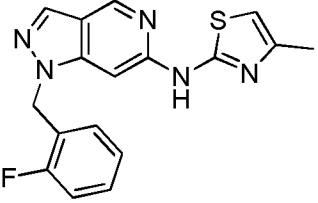
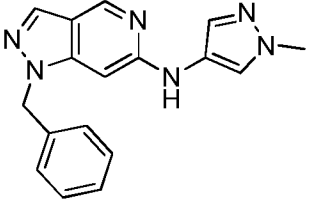
	yl)amino)-1H-pyrazol-1-yl)propanenitrile					
	1-(2,5-difluorobenzyl)-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-c]pyridin-6-amine	11	C	341	5.85	>95%
	1-(2-fluorobenzyl)-N-(1-methyl-1H-1,2,4-triazol-3-yl)-1H-pyrazolo[4,3-c]pyridin-6-amine	12	C	324	6.03	>95%
	3-(3-((1-(2-fluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)propanenitrile	13	C	362	6.08	>95%
	1-(2,5-difluorobenzyl)-N-(1-methyl-1H-1,2,4-triazol-3-yl)-1H-pyrazolo[4,3-c]pyridin-6-amine	14	C	342	6.4	>95%

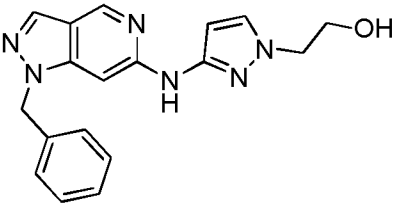
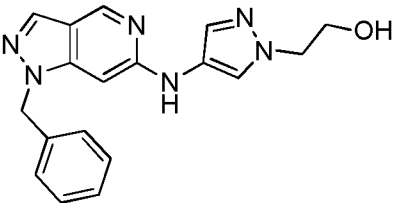
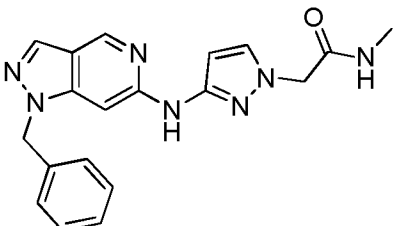
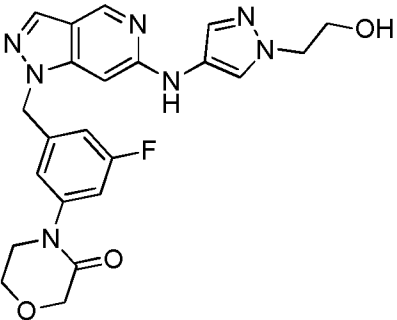
	c]pyridin-6-amine					
	4-(3-fluoro-5-(((6-((1-methyl-1H-pyrazol-4-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)phenyl)morpholin-3-one	15	C	422	5.05	>95%
	tert-butyl 5-(2-(3-((1-(2-fluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)acetyl)-2,5-diazabicyclo[2.2.2]octane-2-carboxylate	16	C	561	7.13	>95%
	3-(4-((1-(2,5-difluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)propanenitrile	17	C	380	6.17	>95%
	2-(3-((1-(2,5-difluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)ethanol	18	C	371	5.47	>95%

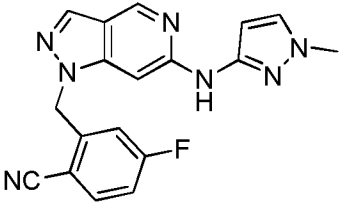
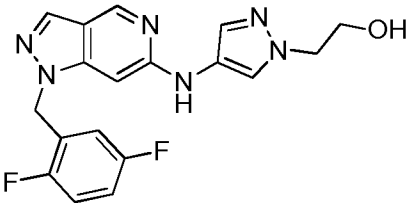
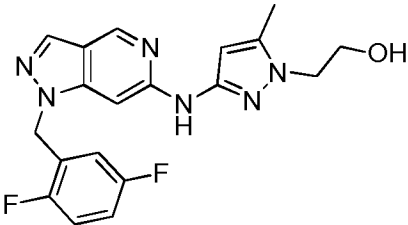
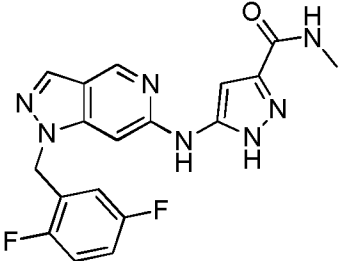
	yl)amino)-1H-pyrazol-1-yl)ethanol					
	3-(4-((1-(3-fluoro-5-(3-oxomorpholino)benzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)propanenitrile	19	C	461	5.3	>95%
	2-(4-((1-(2,5-difluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)-N-methylacetamide	20	C	398	5.46	>95%
	2-(4-((1-(2,5-difluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)-N,N-dimethylacetamide	21	C	412	5.56	>95%

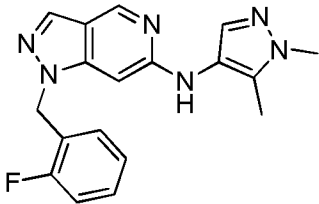
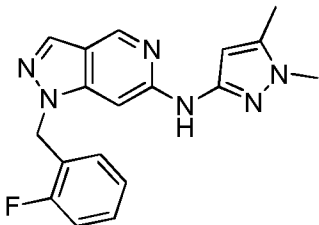
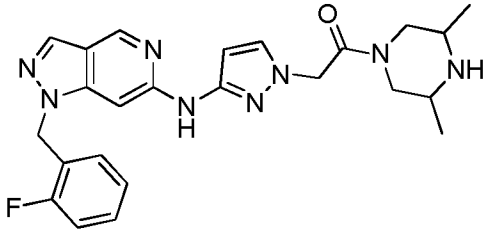
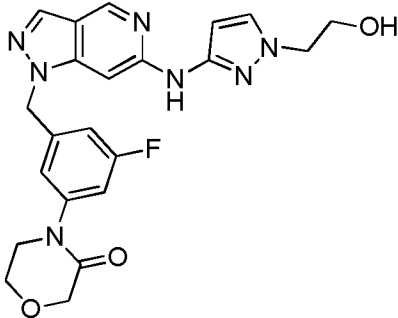
	3-(4-((1-(2-fluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)propanenitrile	22	C	362	5.92	>95%
	N-(1-(2,5-difluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-methylisothiazol-5-amine	23	C	358	6.57	>95%
	N-(1-(2-fluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)oxazol-2-amine	24	C	310	7.22	>95%
	1-(2-fluorobenzyl)-N-(5-methyl-1H-pyrazol-3-yl)-1H-pyrazolo[4,3-c]pyridin-6-amine	25	C	323	5.83	>95%
	1-(2,5-diazabicyclo[2.2.2]octan-2-yl)-2-(3-((1-(2-fluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)ethanone	26	C	461	4.36	>90%

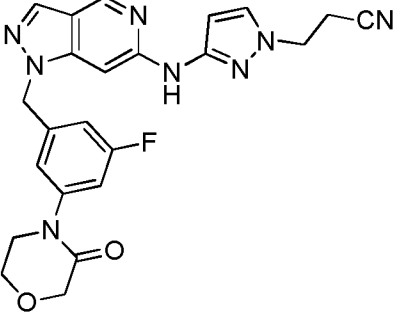
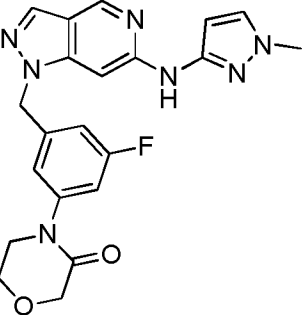
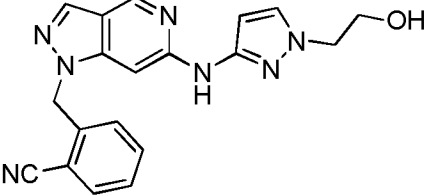
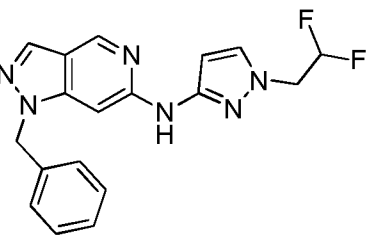
	1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)ethanone					
	2-(3-((1-(2-fluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)-N-methylacetamide	27	C	380	5.26	>95%
	2-(3-((1-(2-fluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)-N,N-dimethylacetamide	28	C	394	5.41	>95%
	N-(1-(2-fluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)thiazol-2-amine	29	C	326	5.26	>95%

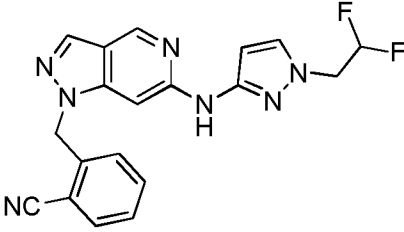
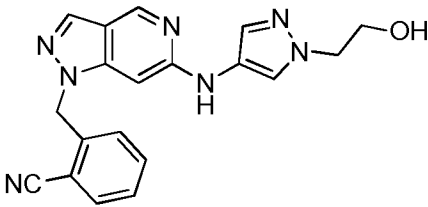
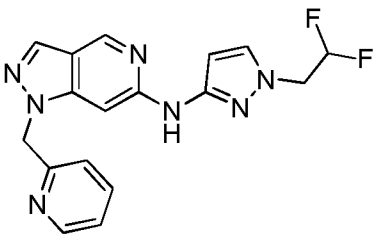
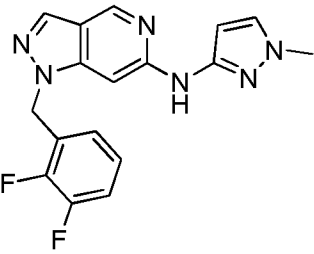
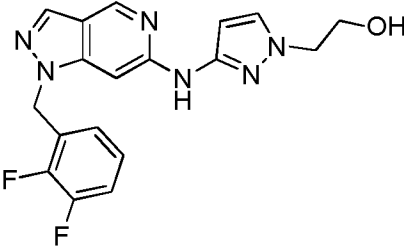
	N-(1-(2-fluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)-5-methylthiazol-2-amine	30	C	340	5.41	>95%
	4-(2,5-difluoro-3-((6-((1-methyl-1H-pyrazol-4-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)phenyl)morpholin-3-one	31	C	440	5.06	>95%
	N-(1-(2-fluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)-4-methylthiazol-2-amine	32	C	340	7.42	>80%
	1-benzyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-c]pyridin-6-amine	33	C	305	5.5	>95%

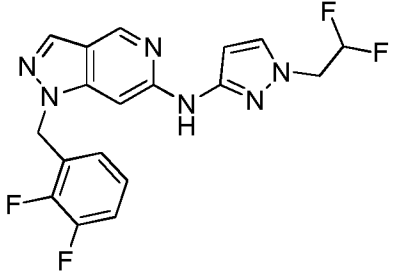
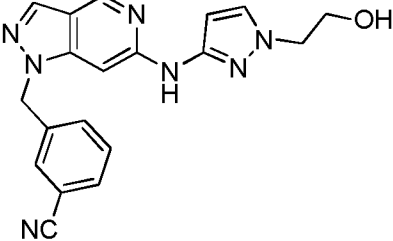
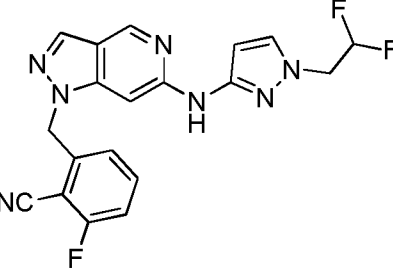
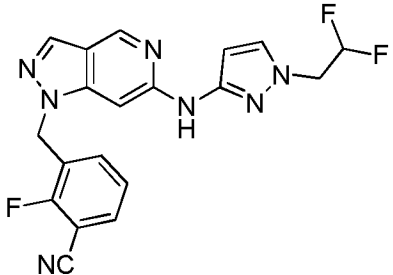
	2-(3-((1-benzyl-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)ethanol	34	C	335	5.3	>95%
	2-(4-((1-benzyl-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)ethanol	35	C	335	5.08	>95%
	2-(3-((1-benzyl-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)-N-methylacetamide	36	C	362	5.28	>95%
	4-(3-fluoro-5-(((6-((1-(2-hydroxyethyl)-1H-pyrazol-4-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)phenyl)morpholin-3-one	37	C	452	4.7	>95%

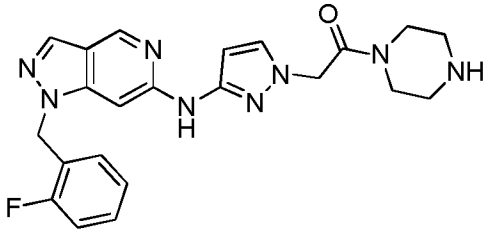
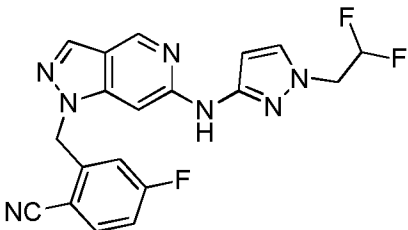
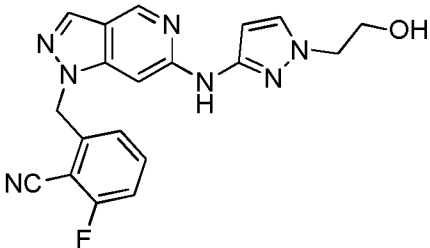
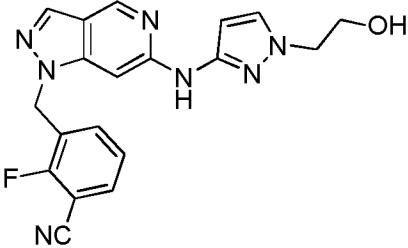
	4-fluoro-2-((6-((1-methyl-1H-pyrazol-3-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)benzonitrile	38	C	348	5.83	>90%
	2-(4-((1-(2,5-difluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)ethanol	39	C	371	5.32	>95%
	2-(3-((1-(2,5-difluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-5-methyl-1H-pyrazol-1-yl)ethanol	40	C	385	6.92	>95%
	5-((1-(2,5-difluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-N-methyl-1H-pyrazole-3-carboxamide	41	C	384	6.23	>95%

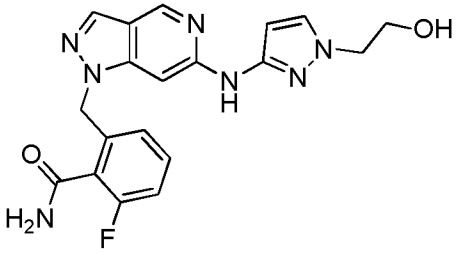
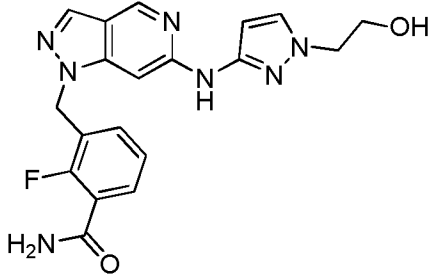
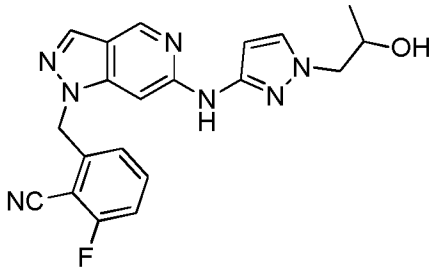
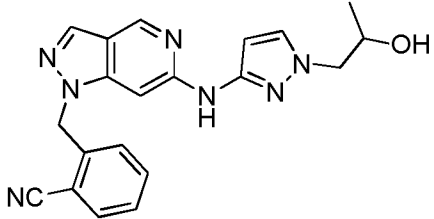
	<p>N-(1,5-dimethyl-1H-pyrazol-4-yl)-1-(2-fluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-amine</p>	42	C	337	5.5	>95%
	<p>N-(1,5-dimethyl-1H-pyrazol-3-yl)-1-(2-fluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-amine</p>	43	C	337	6.13	>90%
	<p>1-(3,5-dimethylpiperazin-1-yl)-2-(3-((1-(2-fluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)ethanone</p>	44	C	463	4.26	>90%
	<p>4-(3-fluoro-5-(((6-((1-(2-hydroxyethyl)-1H-pyrazol-3-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)phenyl)carbamoyl)morpholine</p>	45	C	452	4.9	>95%

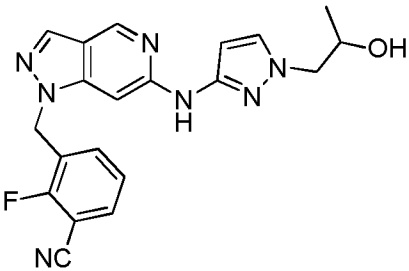
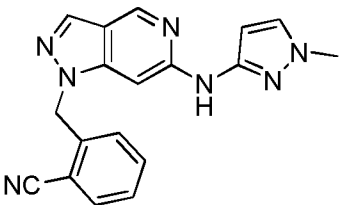
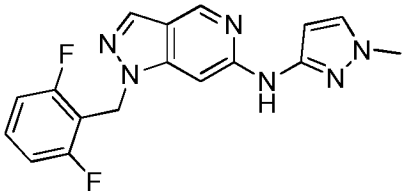
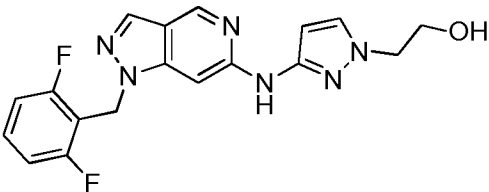
	yl)morpholin-3-one					
	3-(3-((1-(3-fluoro-5-(3-oxomorpholino)benzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)propanenitrile	46	C	461	5.43	>95%
	4-(3-fluoro-5-(((6-((1-methyl-1H-pyrazol-3-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)phenyl)morpholin-3-one	47	C	422	5.22	>95%
	2-((6-((1-(2-hydroxyethyl)-1H-pyrazol-3-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)benzonitrile	48	C	360	5.07	>95%
	1-benzyl-N-(1-(2,2-difluoroethyl)-1H-pyrazol-3-yl)-1H-pyrazolo[4,3-c]pyridin-6-amine	49	C	355	6.60	>95%

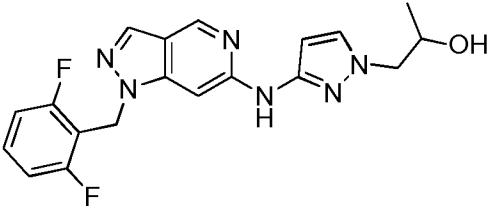
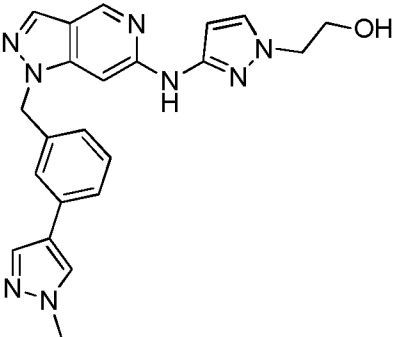
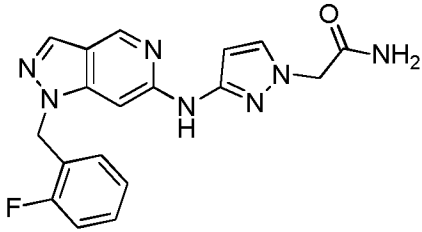
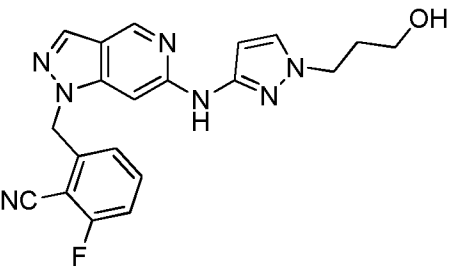
	2-((6-((1-(2,2-difluoroethyl)-1H-pyrazol-3-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)benzonitrile	50	C	380	6.60	>95%
	2-((6-((1-(2-hydroxyethyl)-1H-pyrazol-4-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)benzonitrile	51	C	360	4.85	>95%
	N-(1-(2,2-difluoroethyl)-1H-pyrazol-3-yl)-1-(pyridin-2-ylmethyl)-1H-pyrazolo[4,3-c]pyridin-6-amine	52	C	356	5.09	>95%
	1-(2,3-difluorobenzyl)-N-(1-methyl-1H-pyrazol-3-yl)-1H-pyrazolo[4,3-c]pyridin-6-amine	53	C	341	6.09	>90%
	2-(3-((1-(2,3-difluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-5-yl)ethanol	54	C	371	5.52	>90%

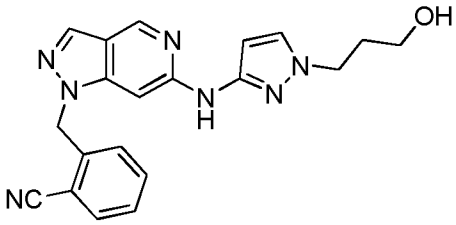
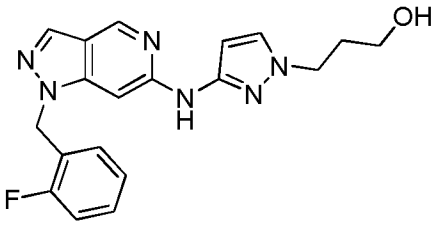
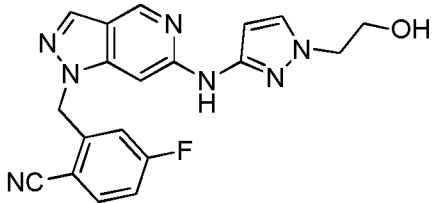
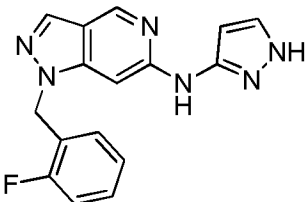
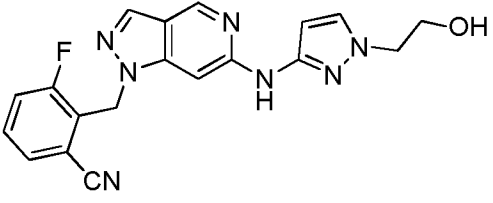
	yl)amino)-1H-pyrazol-1-yl)ethanol					
	1-(2,3-difluorobenzyl)-N-(1-(2,2-difluoroethyl)-1H-pyrazol-3-yl)-1H-pyrazolo[4,3-c]pyridin-6-amine	55	C	391	7.12	>90%
	3-((6-((1-(2-hydroxyethyl)-1H-pyrazol-3-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)benzonitrile	56	C	360	5.12	>90%
	2-((6-((1-(2,2-difluoroethyl)-1H-pyrazol-3-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)-6-fluorobenzonitrile	57	C	398	6.88	>95%
	3-((6-((1-(2,2-difluoroethyl)-1H-pyrazol-3-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)-2-fluorobenzonitrile	58	C	398	6.69	>95%

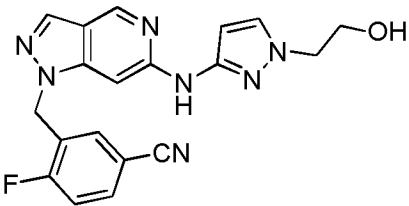
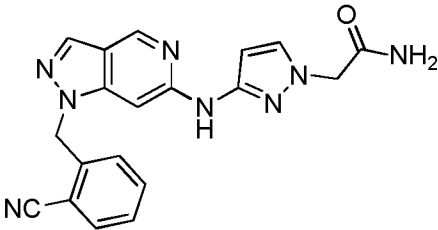
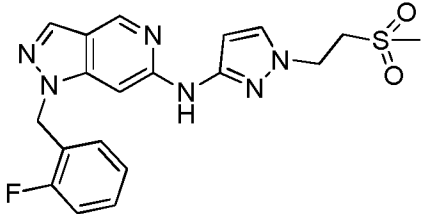
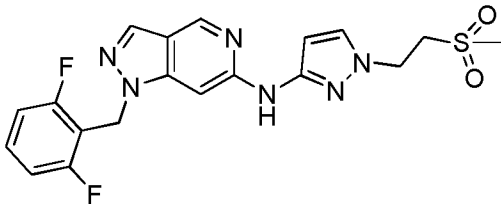
	le					
	2-(3-((1-(2-fluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)-1-(piperazin-1-yl)ethanone	59	C	435	3.90	>95%
	2-(((6-((1-(2,2-difluoroethyl)-1H-pyrazol-3-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)-4-fluorobenzonitrile	60	C	398	6.87	>90%
	2-fluoro-6-(((6-((1-(2-hydroxyethyl)-1H-pyrazol-3-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)benzo nitrile	61	C	378	5.40	>95%
	2-fluoro-3-(((6-((1-(2-hydroxyethyl)-1H-pyrazol-3-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)benzo nitrile	62	C	378	5.34	>95%

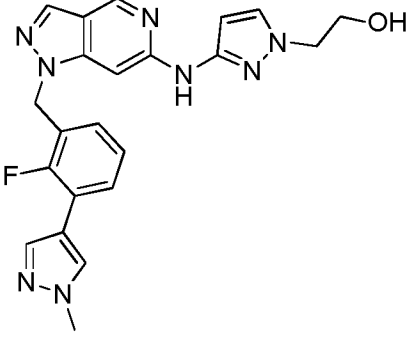
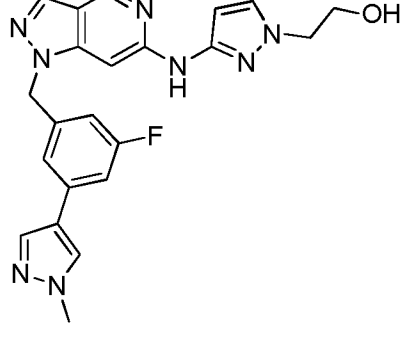
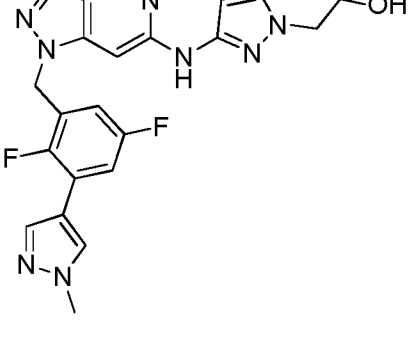
	2-fluoro-6-(((1-(2-hydroxyethyl)-1H-pyrazol-3-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)benzamide	63	C	396	4.32	>95%
	2-fluoro-3-(((1-(2-hydroxyethyl)-1H-pyrazol-3-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)benzamide	64	C	396	4.35	>95%
	2-fluoro-6-(((1-(2-hydroxypropyl)-1H-pyrazol-3-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)benzonitrile	65	C	392	5.70	>95%
	2-(((1-(2-hydroxypropyl)-1H-pyrazol-3-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)benzonitrile	66	C	374	5.42	>95%

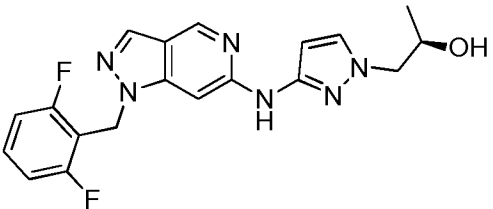
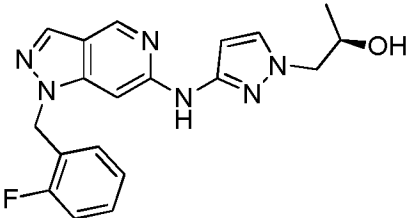
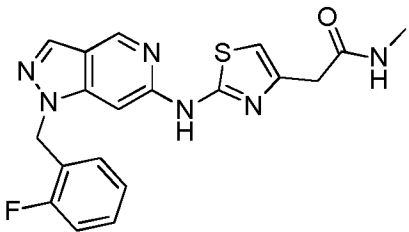
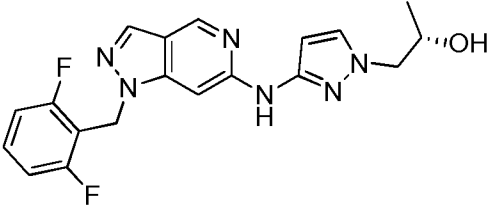
	2-fluoro-3-((6-((1-(2-hydroxypropyl)-1H-pyrazol-3-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)benzo nitrile	67	C	392	5.64	>95%
	2-((6-((1-methyl-1H-pyrazol-3-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)benzo nitrile	68	C	330	5.65	>95%
	1-(2,6-difluorobenzyl)-N-(1-methyl-1H-pyrazol-3-yl)-1H-pyrazolo[4,3-c]pyridin-6-amine	69	C	341	5.91	>90%
	2-(3-((1-(2,6-difluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)ethanol	70	C	371	5.45	>90%

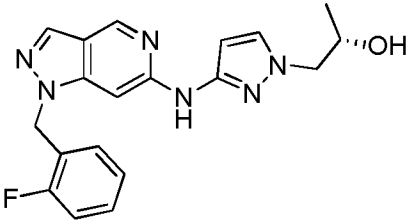
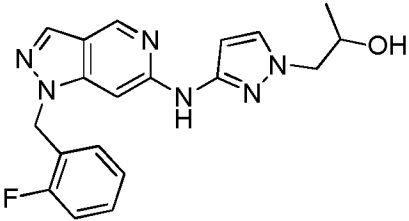
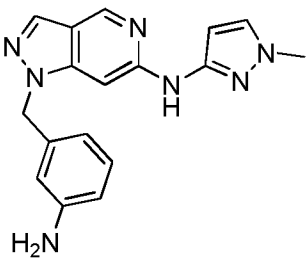
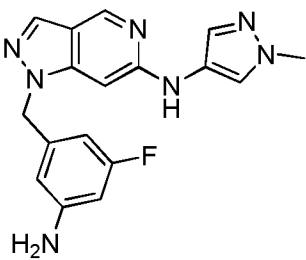
	1-(3-((1-(2,6-difluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)propan-2-ol	71	C	385	5.74	>90%
	2-(3-((1-(3-(1-methyl-1H-pyrazol-4-yl)benzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)ethanol	72	C	415	5.45	>90%
	2-(3-((1-(2-fluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)acetamide	73	C	366	5.19	>95%
	2-fluoro-6-((6-((1-(3-hydroxypropyl)-1H-pyrazol-3-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)benzonitrile	74	C	392	5.61	>95%

	2-((6-((1-(3-hydroxypropyl)-1H-pyrazol-3-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)benzonitrile	75	C	374	5.33	>95%
	3-(3-((1-(2-fluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)propan-1-ol	76	C	367	5.51	>95%
	4-fluoro-2-((6-((1-(2-hydroxyethyl)-1H-pyrazol-3-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)benzonitrile	77	C	378	5.38	>90%
	1-(2-fluorobenzyl)-N-(1H-pyrazol-3-yl)-1H-pyrazolo[4,3-c]pyridin-6-amine	78	C	309	5.44	>95%
	3-fluoro-2-((6-((1-(2-hydroxyethyl)-1H-pyrazol-3-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)benzonitrile	79	C	378	5.05	>90%

	pyrazolo[4,3-c]pyridin-1-yl)methyl)benzo nitrile					
	4-fluoro-3-((6-((1-(2-hydroxyethyl)-1H-pyrazol-3-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)benzo nitrile	80	C	378	5.26	>90%
	2-(3-((1-(2-cyanobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)acetamide	81	C	373	4.88	>95%
	1-(2-fluorobenzyl)-N-(1-(2-(methylsulfonyl)ethyl)-1H-pyrazol-3-yl)-1H-pyrazolo[4,3-c]pyridin-6-amine	82	C	415	6.37	>95%
	1-(2,6-difluorobenzyl)-N-(1-(2-(methylsulfonyl)ethyl)-1H-pyrazol-3-yl)-1H-pyrazolo[4,3-c]pyridin-6-amine	83	C	433	5.86	>90%

	1H-pyrazolo[4,3-c]pyridin-6-amine					
	2-(3-((1-(2-fluoro-3-(1-methyl-1H-pyrazol-4-yl)benzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)ethanol	84	C	433	5.54	>95%
	2-(3-((1-(3-fluoro-5-(1-methyl-1H-pyrazol-4-yl)benzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)ethanol	85	C	433	5.90	>95%
	2-(3-((1-(2,5-difluoro-3-(1-methyl-1H-pyrazol-4-yl)benzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)ethanol	86	C	451	5.77	>95%

	(R)-1-(3-((1-(2,6-difluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)propan-2-ol	87	C	385	5.70	>80%
	(R)-1-(3-((1-(2-fluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)propan-2-ol	88	C	367	5.72	>80%
	2-(2-((1-(2-fluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)thiazol-4-yl)-N-methylacetamide	89	C	397	7.39	>90%
	(S)-1-(3-((1-(2,6-difluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)propan-2-ol	90	C	385	5.65	>80%

	(S)-1-(3-((1-(2-fluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)propan-2-ol	91	C	367	5.70	>80%
	1-(3-((1-(2-fluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)propan-2-ol	92	C	367	5.65	>80%
	1-(3-aminobenzyl)-N-(1-methyl-1H-pyrazol-3-yl)-1H-pyrazolo[4,3-c]pyridin-6-amine	93	C	320	4.53	>80%
	1-(3-amino-5-fluorobenzyl)-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-c]pyridin-6-amine	94	C	338	5.27	>85%

Example 95: Biology Assays

- 5 Determination of the effect of the compounds according to the invention on JAK

The compounds of the present invention as described in the previous examples were tested in a Kinobeads™ assay as described for ZAP-70 (WO-A 2007/137867). Briefly, test compounds (at various concentrations) and the affinity matrix with the immobilized aminopyrido-pyrimidine ligand 24 were added to cell lysate aliquots and allowed to bind to the proteins in the lysate sample. After the incubation time the beads with captured proteins were separated from the lysate. Bound proteins were then eluted and the presence of JAK2 and JAK3 was detected and quantified using specific antibodies in a dot blot procedure and the Odyssey infrared detection system. Dose response curves for individual kinases were generated and IC₅₀ values calculated. Kinobeads™ assays for ZAP-70 (WO-A 2007/137867) and for kinase selectivity profiling (WO-A 2006/134056) have been previously described.

Protocols

Washing of affinity matrix

The affinity matrix was washed two times with 15mL of 1x DP buffer containing 0.2% NP40 (IGEPAL® CA-630, Sigma, #I3021) and then resuspended in 1xDP buffer containing 0.2% NP40 (3% beads slurry).

5xDP buffer: 250mM Tris-HCl pH 7.4, 25% Glycerol, 7.5mM MgCl₂, 750mM NaCl, 5mM Na₃VO₄; filter the 5xDP buffer through a 0.22µm filter and store in aliquots at -80°C. The 5xDP buffer is diluted with H₂O to 1xDP buffer containing 1mM DTT and 25mM NaF.

Preparation of test compounds

Stock solutions of test compounds were prepared in DMSO. In a 96 well plate 30µL solution of diluted test compounds at 5mM in DMSO were prepared. Starting with this solution a 1:3 dilution series (9 steps) was prepared. For control experiments (no test compound) a buffer containing 2% DMSO was used.

Cell culture and preparation of cell lysates

Molt4 cells (ATCC catalogue number CRL-1582) and Ramos cells (ATCC catalogue number CRL-1596) were grown in 1L Spinner flasks (Integra Biosciences, #182101) in suspension in RPMI 1640 medium (Invitrogen, #21875-034) supplemented with 10% Fetal Bovine Serum (Invitrogen) at a density between 0.15×10^6 and 1.2×10^6 cells/mL. Cells were harvested by centrifugation, washed once with 1 x PBS buffer (Invitrogen, #14190-094) and cell pellets were frozen in liquid nitrogen and subsequently stored at -80°C. Cells were homogenized in a

Potter S homogenizer in lysis buffer: 50mM Tris-HCl, 0.8% NP40, 5% glycerol, 150mM NaCl, 1.5mM MgCl₂, 25 mM NaF, 1mM sodium vanadate, 1mM DTT, pH 7.5. One complete EDTA-free tablet (protease inhibitor cocktail, Roche Diagnostics, 1873580) per 25mL buffer was added. The material was dounced 10 times using a mechanized POTTER S, transferred to 50mL falcon tubes, incubated for 30 minutes on ice and spun down for 10 minutes at 20,000 g at 4°C (10,000 rpm in Sorvall SLA600, precooled). The supernatant was transferred to an ultracentrifuge (UZ)-polycarbonate tube (Beckmann, 355654) and spun for 1hour at 100.000g at 4°C (33.500 rpm in Ti50.2, precooled). The supernatant was transferred again to a fresh 50mL falcon tube, the protein concentration was determined by a Bradford assay (BioRad) and samples containing 50mg of protein per aliquot were prepared. The samples were immediately used for experiments or frozen in liquid nitrogen and stored frozen at -80°C.

Dilution of cell lysate

Cell lysate (approximately 50mg protein per plate) was thawed in a water bath at room temperature and then stored on ice. To the thawed cell lysate 1xDP 0.8% NP40 buffer containing protease inhibitors (1 tablet for 25mL buffer; EDTA-free protease inhibitor cocktail; Roche Diagnostics 1873580) was added in order to reach a final protein concentration of 10mg/mL total protein. The diluted cell lysate was stored on ice. Mixed Molt4/Ramos lysate was prepared by combining one volume of Molt4 lysate and two volumes of Ramos lysate (ratio 1:2).

Incubation of lysate with test compound and affinity matrix

To a 96 well filter plate (Multiscreen HTS, BV Filter Plates, Millipore #MSBVN1250) were added per well: 100µL affinity matrix (3% beads slurry), 3µL of compound solution, and 50µL of diluted lysate. Plates were sealed and incubated for 3 hours in a cold room on a plate shaker (Heidolph tiramax 1000) at 750rpm. Afterwards the plate was washed 3 times with 230µL washing buffer (1xDP 0.4% NP40). The filter plate was placed on top of a collection plate (Greiner bio-one, PP-microplate 96 well V-shape, 65120) and the beads were then eluted with 20µL of sample buffer (100 mM Tris, pH 7.4, 4% SDS, 0.00025% bromophenol blue, 20% glycerol, 50 mM DTT). The eluate was frozen quickly at -80°C and stored at -20°C.

Detection and quantification of eluted kinases

The kinases in the eluates were detected and quantified by spotting on nitrocellulose membranes and using a first antibody directed against the kinase of interest and a fluorescently labelled secondary antibody (anti-rabbit IRDyeTM antibody 800 (Licor, # 926-32211). The Odyssey Infrared Imaging system from LI-COR Biosciences (Lincoln, Nebraska, USA) was operated according to instructions provided by the manufacturer (Schutz-Geschwendener *et al.*, 2004. Quantitative, two-color Western blot detection with infrared fluorescence. Published May 2004 by LI-COR Biosciences, www.licor.com).

After spotting of the eluates the nitrocellulose membrane (BioTrace NT; PALL, #BTNT30R) was first blocked by incubation with Odyssey blocking buffer (LICOR, 927-40000) for 1 hour at room temperature. Blocked membranes were then incubated for 16 hours at the temperature shown in table 4 with the first antibody diluted in Odyssey blocking buffer (LICOR #927-40000). Afterwards the membrane was washed twice for 10 minutes with PBS buffer containing 0.2% Tween 20 at room temperature. The membrane was then incubated for 60 minutes at room temperature with the detection antibody (anti-rabbit IRDyeTM antibody 800, Licor, # 926-32211) diluted in Odyssey blocking buffer (LICOR #927-40000). Afterwards the membrane was washed twice for 10 minutes each with 1 x PBS buffer containing 0.2% Tween 20 at room temperature. Then the membrane was rinsed once with PBS buffer to remove residual Tween 20. The membrane was kept in PBS buffer at 4°C and then scanned with the Odyssey instrument. Fluorescence signals were recorded and analysed according to the instructions of the manufacturer.

Table 6: Sources and dilutions of antibodies

Target kinase	Primary antibody (dilution)	Temp of Primary incubation	Secondary antibody (dilution)
Jak2	Cell signaling #3230 (1:100)	Room temperature	Licor anti-rabbit 800 (1:15000)
Jak3	Cell signaling #3775 (1:100)	4°C	Licor anti-rabbit 800 (1:5000)

Results

Table 7: Inhibition values (IC_{50} in μM) as determined in the Kinobeads™ assay (Activity level: A < 0.1 μM ; 0.1 μM \leq B < 1 μM ; 1 μM \leq C < 10 μM ; D \geq 10 μM).

Example Number	JAK3 IC_{50} (μM)	JAK2 IC_{50} (μM)
1	A	B
2	A	C
3	A	B
4	A	C
5	B	D
6	A	C
7	A	C
8	A	C
9	A	C
10	A	C
11	A	B
12	B	D
13	A	C
14	A	C
15	A	D
16	A	C
17	A	C
18	A	B
19	A	D
20	A	C
21	A	C
22	A	D
23	C	D
24	C	D
25	A	D
26	A	B
27	A	C
28	A	C

29	C	D
30	C	D
31	A	D
32	C	D
33	B	D
34	A	C
35	B	C
36	A	C
37	A	C
38	A	B
39	A	B
40	C	D
41	A	B
42	B	D
43	A	D
44	A	C
45	A	C
46	A	C
47	A	D
48	A	B
49	B	D
50	A	C
51	A	C
52	B	D
53	A	C
54	A	B
55	A	D
56	A	C
57	A	C
58	B	D
59	A	C
60	A	B
61	A	B
62	A	C
63	B	D

64	A	C
65	A	B
66	A	B
67	A	C
68	A	C
69	A	C
70	A	B
71	A	C
72	A	C
73	A	C
74	A	C
75	A	C
76	A	C
77	A	A
78	A	D
79	A	B
80	A	C
81	A	C
82	A	C
83	A	C
84	A	C
85	A	B
86	A	B
87	A	B
88	A	B
89	B	D
90	A	C
91	A	C
92	A	C
93	B	D
94	A	D

Cell assays

pSTAT5 assay

5 Assay principle

STAT5 phosphorylation represents one of the proximal events in the signalling cascade downstream of JAK3 activation. Therefore STAT5 phosphorylation is an appropriate readout to assess the mechanistic effect of JAK3 inhibition. Stimulation of human YT cells, an NK-like cell line, with interleukin-2 (IL-2) results in phosphorylation of STAT5 at tyrosine residue 694 (Tyr694) that can be quantitatively measured by immunodetection with specific antibodies and an appropriate detection method, in this case AlphaScreen assay technology.

Assay protocol

Cell culture and cell seeding

15 Human YT cells were grown in RPMI medium (Lonza, BE12-167) with 2mM L-Glutamine (Invitrogen, 25030-024) and 10% heat-inactivated FBS (Invitrogen, 10106-169) and kept in a humidified incubator (37°C, 5% CO₂). Cells were harvested by centrifugation, washed once with HBSS (Invitrogen, 14180-046), resuspended in HBSS at 1.5x10⁶ cells/ml and 0.9x10⁴ cells were seeded in 6µl per well in a 96 well White plate (PerkinElmer, 6005569).

20

Treatment with test compounds and IL-2 stimulation

Test compounds were dissolved in DMSO and a 1:3 dilution series (9 steps) was prepared. To generate a dose response curve, 3µl of fourfold concentrated compound in 4% DMSO/HBSS were added to each cell sample in the 96 well plate resulting in a final DMSO concentration of 1% DMSO. Cells were incubated for one hour in a humidified incubator (37°C, 5% CO₂). To each well 3µl of a fourfold concentrated IL-2 solution (Recombinant human IL-2, Peprotech 200-02; 120 nM solution in HBSS) was added and incubated for 30 minutes at room temperature. Cells were lysed by adding 3µl of 5x lysis buffer (SureFire lysis buffer; Perkin Elmer, TGRS5S10K) and incubated for 10 minutes at room temperature with gentle shaking.

30

Signal detection

For signal detection by AlphaScreen® technology the SureFire phospho-STAT5 (Tyr694/Tyr699) kit was used according to instructions provided by the manufacturer (Perkin

Elmer, TGRS5S10K). Acceptor beads were added as recommended by the manufacturer (Reactivation buffer / Activation buffer / Acceptor beads at a ratio of 40:10:1) and incubated at room temperature for 1.5 hours with gentle shaking. Then donor beads were added as recommended (Dilution buffer / Donor beads at a ratio of 20:1) and incubated at room temperature for 1.5 hours with gentle shaking. Plates were read on an Envision instrument (Perkin Elmer) with the AlphaScreen protocol. Data were analysed in BioAssay using the nonlinear regression for a sigmoidal dose-response with a variable slope.

Table 8 provides data for selected compounds of the invention in the pSTAT5 cell assay.

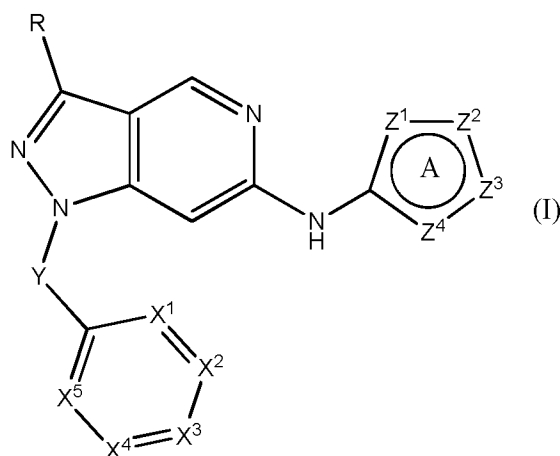
Table 8: Inhibition values (IC_{50} in μM) as determined in the pSTAT5 cell assay (Activity level: $A < 0.1\mu M$; $0.1\mu M \leq B < 1\mu M$; $1\mu M \leq C < 10\mu M$; $D \geq 10\mu M$).

Example Number	pSTAT5 IC_{50} (μM)
1	B
2	C
3	B
4	C
6	C
7	C
8	C
9	B
10	A
11	B
13	B
15	C
17	B
18	A
20	B
21	B
26	C
27	C
28	C
34	B

37	D
38	B
39	B
44	C
45	D
46	C
48	A
50	B
54	B
59	C
61	A
62	B
64	C
66	B
70	A
71	B
72	A
73	B
74	B
75	B
76	C
77	A
79	B
82	C
83	B
88	B

Patent Claims

1. A compound of formula (I)



or a pharmaceutically acceptable salt thereof, wherein

R is H or F;

Ring A is a 5 membered aromatic heterocycle in which Z^1 , Z^2 , Z^3 and Z^4 are independently selected from the group consisting of $C(R^1)$, N, $N(R^1)$, O and S, provided that at least one of Z^1 , Z^2 , Z^3 , Z^4 is N or $N(R^1)$;

Each R^1 is independently H, halogen; CN; $C(O)OR^2$; OR^2 ; $C(O)R^2$; $C(O)N(R^{2a}R^{2b})$; $S(O)_2N(R^{2a}R^{2b})$; $S(O)N(R^{2a}R^{2b})$; $S(O)_2R^2$; $S(O)R^2$; $N(R^2)S(O)_2N(R^{2a}R^{2b})$; $N(R^2)S(O)N(R^{2a}R^{2b})$; SR^2 ; $N(R^{2a}R^{2b})$; NO_2 ; $OC(O)R^2$; $N(R^2)C(O)R^{2a}$; $N(R^2)S(O)_2R^{2a}$; $N(R^2)S(O)R^{2a}$; $N(R^2)C(O)N(R^{2a}R^{2b})$; $N(R^2)C(O)OR^{2a}$; $OC(O)N(R^{2a}R^{2b})$; T^1 ; or C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more R^3 , which are the same or different;

R^2 , R^{2a} , R^{2b} are independently selected from the group consisting of H; T^1 ; and C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more R^3 , which are the same or different;

R^3 is halogen; CN; $C(O)OR^4$; OR^4 ; $C(O)R^4$; $C(O)N(R^4R^{4a})$; $S(O)_2N(R^4R^{4a})$; $S(O)N(R^4R^{4a})$; $S(O)_2R^4$; $S(O)R^4$; $N(R^4)S(O)_2N(R^{4a}R^{4b})$; $N(R^4)S(O)N(R^{4a}R^{4b})$; SR^4 ; $N(R^4R^{4a})$; NO_2 ; $OC(O)R^4$; $N(R^4)C(O)R^{4a}$; $N(R^4)S(O)_2R^{4a}$; $N(R^4)S(O)R^{4a}$; $N(R^4)C(O)N(R^{4a}R^{4b})$; $N(R^4)C(O)OR^{4a}$; $OC(O)N(R^4R^{4a})$; or T^1 ;

5

R^4 , R^{4a} , R^{4b} are independently selected from the group consisting of H; T^1 ; and C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different;

10 T^1 is C_{3-7} cycloalkyl; saturated 4 to 7 membered heterocyclyl; or saturated 7 to 11 membered heterobicyclyl, wherein T^1 is optionally substituted with one or more R^{10} , which are the same or different;

Y is $(C(R^5R^{5a}))_n$;

15

n is 0, 1, 2, 3 or 4;

R^5 , R^{5a} are independently selected from the group consisting of H; and unsubstituted C_{1-6} alkyl; or jointly form oxo (=O);

20

Optionally, R^5 , R^{5a} are joined to form an unsubstituted C_{3-7} cycloalkyl;

X^1 is $C(R^6)$ or N; X^2 is $C(R^{6a})$ or N; X^3 is $C(R^{6b})$ or N; X^4 is $C(R^{6c})$ or N; X^5 is $C(R^{6d})$ or N, provided that at most two of X^1 , X^2 , X^3 , X^4 , X^5 are N;

25

R^6 , R^{6a} , R^{6b} , R^{6c} , R^{6d} are independently selected from the group consisting of H; halogen; CN; $C(O)OR^7$; OR^7 ; $C(O)R^7$; $C(O)N(R^7R^{7a})$; $S(O)_2N(R^7R^{7a})$; $S(O)N(R^7R^{7a})$; $S(O)_2R^7$; $S(O)R^7$; $N(R^7)S(O)_2N(R^{7a}R^{7b})$; $N(R^7)S(O)N(R^{7a}R^{7b})$; SR^7 ; $N(R^7R^{7a})$; NO_2 ; $OC(O)R^7$; $N(R^7)C(O)R^{7a}$; $N(R^7)S(O)_2R^{7a}$; $N(R^7)S(O)R^{7a}$; $N(R^7)C(O)N(R^{7a}R^{7b})$; $N(R^7)C(O)OR^{7a}$; $OC(O)N(R^7R^{7a})$; T^2 ; and C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more R^{11} , which are the same or different;

30

Optionally one of the pairs R^6/R^{6a} , R^{6a}/R^{6b} is joined to form a ring T^3 ;

R^7 , R^{7a} , R^{7b} are independently selected from the group consisting of H; T^2 ; and C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more R^8 , which are the same or different;

5 R^8 is halogen; CN; $C(O)OR^9$; OR^9 ; $C(O)R^9$; $C(O)N(R^9R^{9a})$; $S(O)_2N(R^9R^{9a})$; $S(O)N(R^9R^{9a})$; $S(O)_2R^9$; $S(O)R^9$; $N(R^9)S(O)_2N(R^{9a}R^{9b})$; $N(R^9)S(O)N(R^{9a}R^{9b})$; SR^9 ; $N(R^9R^{9a})$; NO_2 ; $OC(O)R^9$; $N(R^9)C(O)R^{9a}$; $N(R^9)S(O)_2R^{9a}$; $N(R^9)S(O)R^{9a}$; $N(R^9)C(O)N(R^{9a}R^{9b})$; $N(R^9)C(O)OR^{9a}$; $OC(O)N(R^9R^{9a})$; or T^2 ;

10 R^9 , R^{9a} , R^{9b} are independently selected from the group consisting of H; T^2 ; and C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more R^{12} , which are the same or different;

15 R^{10} is halogen; CN; $C(O)OR^{13}$; OR^{13} ; oxo (=O), where the ring is at least partially saturated; $C(O)R^{13}$; $C(O)N(R^{13}R^{13a})$; $S(O)_2N(R^{13}R^{13a})$; $S(O)N(R^{13}R^{13a})$; $S(O)_2R^{13}$; $S(O)R^{13}$; $N(R^{13})S(O)_2N(R^{13a}R^{13b})$; $N(R^{13})S(O)N(R^{13a}R^{13b})$; SR^{13} ; $N(R^{13}R^{13a})$; NO_2 ; $OC(O)R^{13}$; $N(R^{13})C(O)R^{13a}$; $N(R^{13})S(O)_2R^{13a}$; $N(R^{13})S(O)R^{13a}$; $N(R^{13})C(O)N(R^{13a}R^{13b})$; $N(R^{13})C(O)OR^{13a}$; $OC(O)N(R^{13}R^{13a})$; or C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more R^{14} , which are the same or different;

20

R^{13} , R^{13a} , R^{13b} are independently selected from the group consisting of H; and C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more R^{14} , which are the same or different;

25 R^{11} , R^{12} are independently selected from the group consisting of halogen; CN; $C(O)OR^{15}$; OR^{15} ; $C(O)R^{15}$; $C(O)N(R^{15}R^{15a})$; $S(O)_2N(R^{15}R^{15a})$; $S(O)N(R^{15}R^{15a})$; $S(O)_2R^{15}$; $S(O)R^{15}$; $N(R^{15})S(O)_2N(R^{15a}R^{15b})$; $N(R^{15})S(O)N(R^{15a}R^{15b})$; SR^{15} ; $N(R^{15}R^{15a})$; NO_2 ; $OC(O)R^{15}$; $N(R^{15})C(O)R^{15a}$; $N(R^{15})S(O)_2R^{15a}$; $N(R^{15})S(O)R^{15a}$; $N(R^{15})C(O)N(R^{15a}R^{15b})$; $N(R^{15})C(O)OR^{15a}$; $OC(O)N(R^{15}R^{15a})$; and T^2 ;

30

R^{15} , R^{15a} , R^{15b} are independently selected from the group consisting of H; T^2 ; and C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different;

5 R^{14} is halogen; CN; C(O)OR¹⁶; OR¹⁶; C(O)R¹⁶; C(O)N(R¹⁶R^{16a}); S(O)₂N(R¹⁶R^{16a}); S(O)N(R¹⁶R^{16a}); S(O)₂R¹⁶; S(O)R¹⁶; N(R¹⁶)S(O)₂N(R^{16a}R^{16b}); N(R¹⁶)S(O)N(R^{16a}R^{16b}); SR¹⁶; N(R¹⁶R^{16a}); NO₂; OC(O)R¹⁶; N(R¹⁶)C(O)R^{16a}; N(R¹⁶)S(O)₂R^{16a}; N(R¹⁶)S(O)R^{16a}; N(R¹⁶)C(O)N(R^{16a}R^{16b}); N(R¹⁶)C(O)OR^{16a}; or OC(O)N(R¹⁶R^{16a});

10 R^{16} , R^{16a} , R^{16b} are independently selected from the group consisting of H; and C₁₋₆ alkyl, wherein C₁₋₆ alkyl is optionally substituted with one or more halogen, which are the same or different;

T^2 is phenyl; naphthyl; indenyl; indanyl; C₃₋₇ cycloalkyl; 4 to 7 membered heterocyclyl; or 7 to 11 membered heterobicycyl, wherein T^2 is optionally substituted with one or more R^{17} , which are the same or different;

15 T^3 is phenyl; C₃₋₇ cycloalkyl; or 4 to 7 membered heterocyclyl, wherein T^3 is optionally substituted with one or more R^{18} , which are the same or different;

20 R^{17} , R^{18} are independently selected from the group consisting of halogen; CN; C(O)OR¹⁹; OR¹⁹; oxo (=O), where the ring is at least partially saturated; C(O)R¹⁹; C(O)N(R¹⁹R^{19a}); S(O)₂N(R¹⁹R^{19a}); S(O)N(R¹⁹R^{19a}); S(O)₂R¹⁹; S(O)R¹⁹; N(R¹⁹)S(O)₂N(R^{19a}R^{19b}); N(R¹⁹)S(O)N(R^{19a}R^{19b}); SR¹⁹; N(R¹⁹R^{19a}); NO₂; OC(O)R¹⁹; N(R¹⁹)C(O)R^{19a}; N(R¹⁹)S(O)₂R^{19a}; N(R¹⁹)S(O)R^{19a}; N(R¹⁹)C(O)N(R^{19a}R^{19b}); N(R¹⁹)C(O)OR^{19a}; OC(O)N(R¹⁹R^{19a}); and C₁₋₆ alkyl, wherein C₁₋₆ alkyl is optionally substituted with one or more R^{20} , which are the same or different;

25 R^{19} , R^{19a} , R^{19b} are independently selected from the group consisting of H; and C₁₋₆ alkyl, wherein C₁₋₆ alkyl is optionally substituted with one or more R^{20} , which are the same or different;

30 R^{20} is halogen; CN; C(O)OR²¹; OR²¹; C(O)R²¹; C(O)N(R²¹R^{21a}); S(O)₂N(R²¹R^{21a}); S(O)N(R²¹R^{21a}); S(O)₂R²¹; S(O)R²¹; N(R²¹)S(O)₂N(R^{21a}R^{21b}); N(R²¹)S(O)N(R^{21a}R^{21b}); SR²¹; N(R²¹R^{21a}); NO₂; OC(O)R²¹; N(R²¹)C(O)R^{21a}; N(R²¹)S(O)₂R^{21a}; N(R²¹)S(O)R^{21a}; N(R²¹)C(O)N(R^{21a}R^{21b}); N(R²¹)C(O)OR^{21a}; or OC(O)N(R²¹R^{21a});

R^{21} , R^{21a} , R^{21b} are independently selected from the group consisting of H; and C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different.

- 5 2. A compound of claim 1, wherein R is H.
3. A compound of claim 1 or 2, wherein ring A is a pyrazole, an oxazole, an isoxazole or a triazole.
- 10 4. A compound of claim 1 or 2, wherein 0, 1, or 2 R^1 , which are the same or different, are other than H.
5. A compound of any one of claims 1 to 4, wherein R^1 is C_{1-4} alkyl, which is optionally substituted with 1 or 2 R^3 , which are the same or different.
- 15 6. A compound of any one of claims 1 to 5, wherein R^3 is halogen; CN; OR^4 ; $C(O)N(R^4R^{4a})$; $S(O)_2R^4$; or $C(O)T^1$.
7. A compound of any one of claims 1 to 6, wherein n is 0, 1 or 2.
- 20 8. A compound of any of claims 1 to 7, wherein R^5 , R^{5a} are H.
9. A compound of any one of claims 1 to 8, wherein none or one of X^1 , X^2 , X^3 , X^4 , X^5 is N.
- 25 10. A compound of any one of claims 1 to 9, wherein R^6 , R^{6a} , R^{6b} , R^{6c} , R^{6d} are H.
11. A compound of any one of claims 1 to 9, wherein at least one of R^6 , R^{6a} , R^{6b} , R^{6c} , R^{6d} is other than H.
- 30 12. A compound of claim 11, wherein R^6 , R^{6a} , R^{6b} , R^{6c} , R^{6d} are independently selected from the group consisting of H; halogen; CN; $C(O)N(R^7R^{7a})$; $N(R^7R^{7a})$; T^2 , provided that 1 or 2 or 3 of R^6 , R^{6a} , R^{6b} , R^{6c} , R^{6d} are other than H.

13. A compound of any one of claims 1 to 12, wherein T² is unsubstituted morpholine; substituted morpholine; unsubstituted pyrazole; or substituted pyrazole, and wherein substituted morpholine and substituted pyrazole are independently substituted with one or more R¹⁷, which are the same or different.

5

14. A compound of any one of claims 1 to 13 or a pharmaceutically acceptable salt thereof selected from the group consisting of

10

N-(1,3-Dimethyl-1H-pyrazol-4-yl)-1-(2-fluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-amine;

1-(2-Fluorobenzyl)-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-c]pyridin-6-amine;

15

1-(2-Fluorobenzyl)-N-(1-methyl-1H-pyrazol-3-yl)-1H-pyrazolo[4,3-c]pyridin-6-amine;

2-(4-((1-(2-Fluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)ethanol;

20

1-(2,5-Difluorobenzyl)-N-(1-methyl-1H-pyrazol-3-yl)-1H-pyrazolo[4,3-c]pyridin-6-amine;

25

3-(3-((1-(2,5-Difluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)propanenitrile;

1-(2,5-Difluorobenzyl)-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-c]pyridin-6-amine;

30

2-(3-((1-(2-Fluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)ethanol;

1-(2-Fluorobenzyl)-N-(1-methyl-1H-1,2,4-triazol-3-yl)-1H-pyrazolo[4,3-c]pyridin-6-amine;

3-(3-((1-(2-Fluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)propanenitrile;

5 1-(2,5-Difluorobenzyl)-N-(1-methyl-1H-1,2,4-triazol-3-yl)-1H-pyrazolo[4,3-c]pyridin-6-amine;

4-(3-Fluoro-5-((6-((1-methyl-1H-pyrazol-4-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)phenyl)morpholin-3-one;

10 4-(3-Fluoro-5-((6-((1-(2-hydroxyethyl)-1H-pyrazol-4-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)phenyl)morpholin-3-one;

15 4-Fluoro-2-((6-((1-methyl-1H-pyrazol-3-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)benzonitrile;

4-Fluoro-2-((6-((1-methyl-1H-pyrazol-4-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)benzonitrile;

20 2-(4-((1-(2,5-Difluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)ethanol;

2-(3-((1-(2,5-Difluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-5-methyl-1H-pyrazol-1-yl)ethanol;

25 5-((1-(2,5-Difluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-N-methyl-1H-pyrazole-3-carboxamide;

30 N-(1,5-Dimethyl-1H-pyrazol-4-yl)-1-(2-fluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-amine;

N-(1,5-Dimethyl-1H-pyrazol-3-yl)-1-(2-fluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-amine;

1-(3,5-Dimethylpiperazin-1-yl)-2-(3-((1-(2-fluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)ethanone;

4-(3-Fluoro-5-((6-((1-(2-hydroxyethyl)-1H-pyrazol-3-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)phenyl)morpholin-3-one;

3-(3-((1-(3-Fluoro-5-(3-oxomorpholino)benzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)propanenitrile;

4-(3-Fluoro-5-((6-((1-methyl-1H-pyrazol-3-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)phenyl)morpholin-3-one;

tert-Butyl 5-(2-(3-((1-(2-fluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)acetyl)-2,5-diazabicyclo[2.2.2]octane-2-carboxylate;

3-(4-((1-(2,5-Difluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)propanenitrile;

2-(3-((1-(2,5-Difluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)ethanol;

3-(4-((1-(3-Fluoro-5-(3-oxomorpholino)benzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)propanenitrile;

2-(4-((1-(2,5-Difluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)-N-methylacetamide;

2-(4-((1-(2,5-Difluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)-N,N-dimethylacetamide;

3-(4-((1-(2-Fluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)propanenitrile;

N-(1-(2,5-Difluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-methylisothiazol-5-amine;

N-(1-(2-Fluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)oxazol-2-amine;

5

1-(2-Fluorobenzyl)-N-(5-methyl-1H-pyrazol-3-yl)-1H-pyrazolo[4,3-c]pyridin-6-amine;

10

1-(2,5-Diazabicyclo[2.2.2]octan-2-yl)-2-(3-((1-(2-fluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)ethanone;

2-(3-((1-(2-Fluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)-N-methylacetamide;

15

2-(3-((1-(2-Fluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)-N,N-dimethylacetamide;

N-(1-(2-Fluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)thiazol-2-amine;

20

N-(1-(2-Fluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)-5-methylthiazol-2-amine;

4-(2,5-Difluoro-3-((6-((1-methyl-1H-pyrazol-4-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)phenyl)morpholin-3-one;

25

4-(2,5-Difluoro-3-((6-((1-(2-hydroxyethyl)-1H-pyrazol-4-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)phenyl)morpholin-3-one;

N-(1-(2-Fluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)-4-methylthiazol-2-amine;

30

1-Benzyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-c]pyridin-6-amine;

2-(3-((1-Benzyl-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)ethanol;

2-(4-((1-Benzyl-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)ethanol;

2-(3-((1-Benzyl-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)-N-methylacetamide;

5 2-(3-((1-Benzyl-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)-N,N-dimethylacetamide;

2-(((6-((1-(2-Hydroxyethyl)-1H-pyrazol-3-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)benzonitrile;

10 1-Benzyl-N-(1-(2,2-difluoroethyl)-1H-pyrazol-3-yl)-1H-pyrazolo[4,3-c]pyridin-6-amine;

15 2-(((6-((1-(2,2-Difluoroethyl)-1H-pyrazol-3-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)benzonitrile;

2-(((6-((1-(2-Hydroxyethyl)-1H-pyrazol-4-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)benzonitrile;

20 N-(1-(2,2-Difluoroethyl)-1H-pyrazol-3-yl)-1-(pyridin-2-ylmethyl)-1H-pyrazolo[4,3-c]pyridin-6-amine;

1-(2,3-Difluorobenzyl)-N-(1-methyl-1H-pyrazol-3-yl)-1H-pyrazolo[4,3-c]pyridin-6-amine;

25 2-(3-((1-(2,3-Difluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)ethanol;

30 1-(2,3-Difluorobenzyl)-N-(1-(2,2-difluoroethyl)-1H-pyrazol-3-yl)-1H-pyrazolo[4,3-c]pyridin-6-amine;

3-(((6-((1-(2-Hydroxyethyl)-1H-pyrazol-3-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)benzonitrile;

2-(((6-((1-(2,2-Difluoroethyl)-1H-pyrazol-3-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)-6-fluorobenzonitrile;

5

3-(((6-((1-(2,2-Difluoroethyl)-1H-pyrazol-3-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)-2-fluorobenzonitrile;

2-(3-((1-(2-Fluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)-1-(piperazin-1-yl)ethanone;

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2-(((6-((1-(2,2-Difluoroethyl)-1H-pyrazol-3-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)-4-fluorobenzonitrile;

2-Fluoro-6-(((6-((1-(2-hydroxyethyl)-1H-pyrazol-3-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)benzonitrile;

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2-Fluoro-3-(((6-((1-(2-hydroxyethyl)-1H-pyrazol-3-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)benzonitrile;

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2-Fluoro-6-(((6-((1-(2-hydroxyethyl)-1H-pyrazol-3-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)benzamide;

2-Fluoro-3-(((6-((1-(2-hydroxyethyl)-1H-pyrazol-3-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)benzamide;

25

2-Fluoro-6-(((6-((1-(2-hydroxypropyl)-1H-pyrazol-3-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)benzonitrile;

2-(((6-((1-(2-hydroxypropyl)-1H-pyrazol-3-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)benzonitrile;

30

2-Fluoro-3-(((6-((1-(2-hydroxypropyl)-1H-pyrazol-3-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)benzonitrile;

2-(((6-((1-Methyl-1H-pyrazol-3-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)benzonitrile;

1-(2,6-Difluorobenzyl)-N-(1-methyl-1H-pyrazol-3-yl)-1H-pyrazolo[4,3-c]pyridin-6-amine;

2-(3-(((1-(2,6-Difluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)ethanol;

1-(3-(((1-(2,6-Difluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)propan-2-ol;

2-(3-(((1-(3-(1-Methyl-1H-pyrazol-4-yl)benzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)ethanol;

2-(3-(((1-(2-Fluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)acetamide;

2-Fluoro-6-(((6-(((1-(3-hydroxypropyl)-1H-pyrazol-3-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)benzonitrile;

2-(((6-(((1-(3-Hydroxypropyl)-1H-pyrazol-3-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)benzonitrile;

3-(3-(((1-(2-Fluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)propan-1-ol;

4-Fluoro-2-(((6-(((1-(2-hydroxyethyl)-1H-pyrazol-3-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)benzonitrile;

1-(2-Fluorobenzyl)-N-(1H-pyrazol-3-yl)-1H-pyrazolo[4,3-c]pyridin-6-amine;

3-Fluoro-2-(((6-(((1-(2-hydroxyethyl)-1H-pyrazol-3-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)benzonitrile;

4-Fluoro-3-((6-((1-(2-hydroxyethyl)-1H-pyrazol-3-yl)amino)-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)benzonitrile;

5 2-(3-((1-(2-Cyanobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)acetamide;

1-(2-Fluorobenzyl)-N-(1-(2-(methylsulfonyl)ethyl)-1H-pyrazol-3-yl)-1H-pyrazolo[4,3-c]pyridin-6-amine;

10

1-(2,6-Difluorobenzyl)-N-(1-(2-(methylsulfonyl)ethyl)-1H-pyrazol-3-yl)-1H-pyrazolo[4,3-c]pyridin-6-amine;

15

2-(3-((1-(2-Fluoro-3-(1-methyl-1H-pyrazol-4-yl)benzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)ethanol;

2-(3-((1-(3-Fluoro-5-(1-methyl-1H-pyrazol-4-yl)benzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)ethanol;

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2-(3-((1-(2,5-Difluoro-3-(1-methyl-1H-pyrazol-4-yl)benzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)ethanol;

(*R*)-1-(3-((1-(2,6-Difluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)propan-2-ol;

25

(*R*)-1-(3-((1-(2-Fluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)propan-2-ol;

30

2-(2-((1-(2-Fluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)thiazol-4-yl)-N-methylacetamide;

(*S*)-1-(3-((1-(2,6-Difluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)propan-2-ol;

(S)-1-(3-((1-(2-Fluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)propan-2-ol;

1-(3-((1-(2-Fluorobenzyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-1H-pyrazol-1-yl)propan-2-ol;

1-(3-Aminobenzyl)-N-(1-methyl-1H-pyrazol-3-yl)-1H-pyrazolo[4,3-c]pyridin-6-amine; and

1-(3-Amino-5-fluorobenzyl)-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-c]pyridin-6-amine.

15. A pharmaceutical composition comprising a compound or a pharmaceutically acceptable salt thereof of any one of claims 1 to 14 together with a pharmaceutically acceptable carrier, optionally in combination with one or more other pharmaceutical compositions.

16. A compound or a pharmaceutically acceptable salt thereof of any one of claims 1 to 14 for use as a medicament.

17. A compound or a pharmaceutically acceptable salt thereof of any one of claims 1 to 14 for use in a method of treating or preventing a disease or disorder associated with JAK.

18. Use of a compound of any one of claims 1 to 14 or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment or prophylaxis of diseases and disorders associated with JAK.

19. A method for treating, controlling, delaying or preventing in a mammalian patient in need thereof one or more conditions selected from the group consisting of diseases and disorders associated with JAK, wherein the method comprises the administration to said patient a therapeutically effective amount of a compound according to any one of claims 1 to 14 or a pharmaceutically acceptable salt thereof.

20. A compound or a pharmaceutically acceptable salt thereof of any one of claims 1 to 14 for use in a method of treating or preventing an immunological, inflammatory, autoimmune, or allergic disorder or disease of a transplant rejection or a Graft-versus host disease.

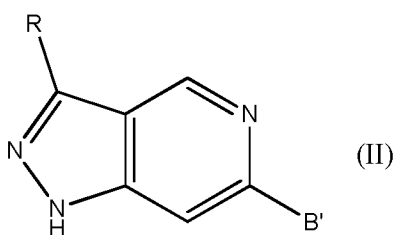
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21. A compound or a pharmaceutically acceptable salt thereof of any one of claims 1 to 14 for use in a method of treating or preventing a proliferative disease.

22. A method for the preparation of a compound of any one of claims 1 to 14 comprising the steps of

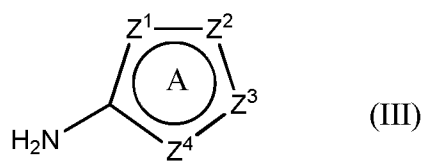
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- reacting a compound of formula (II)



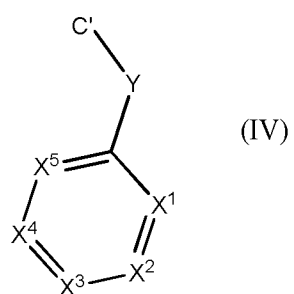
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wherein B' is a suitable leaving group and R has the meaning as indicated in any one of claims 1 to 14 with a compound of formula (III)



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wherein A, Z¹ to Z⁴ have the meaning as indicated in any one of claims 1 to 14 and subsequently with a compound of formula (IV)



wherein X^1 to X^5 and Y have the meaning as indicated in any of claims 1 to 14 and C' is suitable reactive group, or first with a compound of formula (IV) followed by reaction with compound (III) to yield a compound of formula (I).

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2012/064510

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04 A61K31/437 A61P29/00 A61P35/00 A61P37/00
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2011/048082 A1 (CELLZOME LTD [GB]; RAMSDEN NIGEL [GB]; HARRISON RICHARD JOHN [GB]; OXE) 28 April 2011 (2011-04-28) cited in the application the whole document	1-22
Y	WO 2007/140222 A2 (NOVARTIS AG [CH]; NOVARTIS PHARMA GMBH [AT]; BRAIN CHRISTOPHER THOMAS) 6 December 2007 (2007-12-06) the whole document	1-22
A	WO 2008/094575 A2 (BIOGEN IDEC INC [US]; KASIBHATLA SRINIVAS RAO [US]; HONG KEVIN [US]; Z) 7 August 2008 (2008-08-07) the whole document	1-22



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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

"&" document member of the same patent family

Date of the actual completion of the international search

30 August 2012

Date of mailing of the international search report

13/09/2012

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

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