Title: SUBSTITUTED PYRAZOLO[1,5-a]PYRIMIDINE COMPOUNDS AS TRK KINASE INHIBITORS

Abstract: Compounds of Formula (I) in which R¹, R², R³, R⁴, X, Y and n have the meanings given in the specification, are inhibitors of Trk kinases and are useful in the treatment of diseases which can be treated with a Trk kinase inhibitor.
The present invention relates to novel compounds, to pharmaceutical compositions comprising the compounds, to a process for making the compounds and to the use of the compounds in therapy. More particularly, it relates to certain substituted pyrazolo[1,5-a]pyrimidine compounds which exhibit Trk family protein tyrosine kinase inhibition, and which are useful in the treatment of pain, inflammation, cancer, and certain infectious diseases.

The current treatment regimes for pain conditions utilize several classes of compounds. The opioids (such as morphine) have several drawbacks including emetic, constipatory and negative respiratory effects, as well as the potential for addictions. Non-steroidal anti-inflammatory analgesics (NSAIDs, such as COX-I or COX-2 types) also have drawbacks including insufficient efficacy in treating severe pain. In addition, COX-I inhibitors can cause ulcers of the mucosa. Accordingly, there is a continuing need for new and more effective treatments for the relief of pain, especially chronic pain.

Trk's are the high affinity receptor tyrosine kinases activated by a group of soluble growth factors called neurotrophins (NT). The Trk receptor family has three members —TrkA, TrkB and TrkC. Among the neurotrophins are (i) nerve growth factor (NGF) which activates TrkA, (ii) brain-derived neurotrophic factor (BDNF) and NT-4/5 which activate TrkB and (iii) NT3 which activates TrkC. Trk's are widely expressed in neuronal tissue and are implicated in the maintenance, signaling and survival of neuronal cells (Patapoutian, A. et al, Current Opinion in Neurobiology, 2001, 11, 272-280).

decrease signaling through the BDNF/TrkB pathway inhibit neuronal hypersensitization and the associated pain (Chang-Qi, L et al. Molecular Pain 2008, 4:27).

In addition, it has been shown that tumor cell sand tumor invading macrophages directly stimulates TrkA located on peripheral pain fibers. Using various tumor models in both mice and rats it was demonstrated that neutralizing NGF with a monoclonal antibody inhibits cancer related pain to a degree similar or superior to the highest tolerated dose of morphine. In addition, activation of the BDNF/TrkB pathway has been implicated in numerous studies as a modulator of various types of pain including inflammatory pain (Matayoshi, S., J. Physiol. 2005, 569:685-95), neuropathic pain (Thompson, S.W., Proc. Natl. Acad. Sci. USA 1999, 96:7714-18) and surgical pain (Li, C-Q. et al., Molecular Pain, 2008, 4(28), 1-11). Because TrkA and TrkB kinases may serve as a mediator of NGF driven biological responses, inhibitors of TrkA and/or other Trk kinases may provide an effective treatment for chronic pain states.

Therefore, an inhibitor of the Trk family of kinases is expected to have utility in the treatment of cancer.

[0007] In addition, inhibition of the neurotrophin/Trk pathway has been shown to be effective in treatment of pre-clinical models of inflammatory diseases. For example, inhibition of the neurotrophin/Trk pathway has been implicated in preclinical models of inflammatory lung diseases including asthma (Freund-Michel, V.; Frossard, N.; Pharmacology & Therapeutics (2008), 117(1), 52-76), interstitial cystitis (Hu Vivian Y; et. al. The Journal of Urology (2005), 173(3), 1016-21), inflammatory bowel diseases including ulcerative colitis and Crohn's disease (Di Moia, F. F, et. al., Gut (2000), 46(5), 670-678) and inflammatory skin diseases such as atopic dermatitis (Dou, Y.-C; et. al. Archives of Dermatological Research (2006), 298(1), 31-37), eczema and psoriasis (Raychaudhuri, S. P.; et. al. Journal of Investigative Dermatology (2004), 122(3), 812-819).

[0008] The neurotrophin/Trk pathway, particularly BDNF/TrkB, has also been implicated in the etiology of neurodegenerative diseases including multiple sclerosis, Parkinson's disease and Alzheimer's disease (Sohrabji, Farida; Lewis, Danielle K. Frontiers in Neuroendocrinology (2006), 27(4), 404-414). Modulation of the neurotrophin/Trk pathway may have utility in treatment of these and related diseases.

[0009] The TrkA receptor is also thought to be critical to the disease process in the infection of the parasitic infection of Trypanosoma cruzi (Chagas disease) in human hosts (de Melo-Jorge, M. et al. Cell Host & Microbe (2007), 1(4), 251-261). Thus, TrkA inhibition may have utility in treating Chagas disease and related protozoan infections.

[0010] Trk inhibitors may also find use in treating disease related to an imbalance of the regulation of bone remodeling, such as osteoporosis, rheumatoid arthritis, and bone metastases. Bone metastases are a frequent complication of cancer, occurring in up to 70 percent of patients with advanced breast or prostate cancer(1) and in approximately 15 to 30 percent of patients with carcinoma of the lung, colon, stomach, bladder, uterus, rectum, thyroid, or kidney. Osteolytic metastases can cause severe pain, pathologic fractures, life-threatening hypercalcemia, spinal cord compression, and other nerve-compression syndromes. For these reasons, bone metastasis is a serious and costly complication of cancer. Therefore, agents that can induce apoptosis of proliferating osteoblasts would be highly advantageous. Expression of TrkA and TrkC receptors has been observed in the bone forming area in mouse models of bone fracture (K. Asaumi, et al., Bone (2000) 26(6) 625-633). In addition, localization of NGF was observed in almost all bone forming cells (K.
Asaumi, et al.). Recently, it was demonstrated that a pan-Trk inhibitor inhibits the tyrosine signaling activated by neurotrophins binding to all three of the Trk receptors in human hFOB osteoblasts (J. Pinski, et al., (2002) 62, 986-989). These data support the rationale for the use of Trk inhibitors for the treatment of bone remodeling diseases, such as bone metastases in cancer patients.

Several classes of small molecule inhibitors of Trk kinases said to be useful for treating pain or cancer are known (Expert Opin. Ther. Patents (2009) 19(3)).

International Patent Application Publications WO 2006/115452 and WO 2006/087538 describe several classes of small molecules said to be inhibitors or Trk kinases which could be useful for treating pain or cancer.

Pyrazolo[1,5-a]pyrimidine compounds are known. For example, International Patent Application Publication WO 2008/037477 discloses pyrazolo[1,5-a]pyrimidine compounds bearing an alkyl, aryl or heterocyclic group at the 3-position. These compounds are asserted to be PI3K and/or mTOR Lipid Kinase inhibitors.

International Patent Application Publication WO 2008/058126 discloses pyrazolo[1,5-a]pyrimidine compounds bearing a phenyl group at the 3-position. These compounds are asserted to be Pim-kinase inhibitors.

U.S. Publication US 2006/0094699 discloses pyrazolo[1,5-a]pyrimidine compounds bearing a -C(=O)NH-phenyl, -C(=O)(4-methylpiperidinyl) or -C(=O)NMe(CH2-trimethylpyrazolyl) group at the 3-position for use in combination therapy with a glucocorticoid receptor agonist.

It has now been found that certain pyrazolo[1,5-a]pyrimidine compounds bearing an aryl or heteroaryl-substituted heterocyclic group at the 5-position and a group having the formula NR1C(=O)R2 at the 3-position, wherein R1 and R2 are as defined herein, are inhibitors of Trk kinases, in particular inhibitors of TrkA and/or TrkB, which are useful for treating disorders and diseases which can be treated by inhibiting TrkA and/or TrkB kinases, such as pain, including chronic and acute pain, or cancer. Certain compounds which are dual inhibitors of TrkA and TrkB may be useful in the treatment of multiple types of pain including inflammatory pain, neuropathic pain, surgical pain, and pain associated with cancer, surgery and bone fracture. Selectivity for TrkA and/or TrkB is particularly desirable in compounds for use in treating pain. In addition, compounds of the invention may be useful for treating cancer, inflammation, neurodegenerative diseases and certain infectious diseases.
Accordingly, one embodiment of this invention provides a compound of the general Formula I:

![Chemical structure](image)

or a pharmaceutically acceptable salt thereof, wherein:

- \( R^1 \) is H or (1-OC alkyl);
- \( R^2 \) is \( NR^bR^c \), (1-4C)alkyl, (1-4C)fluoroalkyl, CF\(_3\), (1-4C)hydroxyalkyl, -(1-4C alkyl)hetAr\(_e\), -(1-4C alkyl)NH\(_2\), -(1-4C alkyl)NH-(1-4C alkyl), -(1-4C alkyl)N(l-4C alkyl)\(_2\), hetAr\(_2\), hetCyc\(_1\), hetCyc\(_2\), phenyl which is optionally substituted with NH\(_2\)SO\(_2\)(1-4C alkyl), or (3-6C)\(_e\)cycloalkyl which is optionally substituted with (1-4C alkyl), CN, OH, OMe, NH\(_2\), NHMe, N(CH\(_3\))\(_2\), F, CF\(_3\), CO\(_2\)(1-4C alkyl), CO\(_2\)H, C(=O)NR\(_e\)R\(_f\) or C(=O)OR\(_g\);
- \( R^b \) is H or (1-6C alkyl);
- \( R^c \) is H, (1-4C)alkyl, (1-4C)hydroxyalkyl, hetAr\(_3\), or phenyl, wherein said phenyl is optionally substituted with one or more substituents independently selected from halogen, CN, CF\(_3\) and -O(1-4C alkyl);
- \( R^bR^c \) forms a 4-membered heterocyclic ring having a ring nitrogen atom wherein said heterocyclic ring is optionally substituted with one or more substituents independently selected from halogen, OH, (1-4C alkyl), (1-4 Qalkoxy, -OC(=O)(1-4C alkyl), NH\(_2\), -NH(=O)O(1-4C alkyl) and (1-4C)hydroxyalkyl,
- \( R^bR^c \) forms a 5-6 membered heterocyclic ring having a ring heteroatom which is nitrogen and optionally having a second ring heteroatom or group selected from N, O and SO\(_2\), wherein the heterocyclic ring is optionally substituted with one or more substituents independently selected from OH, halogen, CF\(_3\), (1-4C)alkyl, CO\(_2\)(1-4C alkyl), CO\(_2\)H, NH\(_2\), NH(=O)O(1-4C alkyl) and oxo,
- \( R^bR^c \) forms a 7-8 membered bridged heterocyclic ring having a ring nitrogen atom and optionally having a second ring heteroatom selected from N and O, wherein said ring is optionally substituted with CO\(_2\)(1-4C alkyl);
- \( \text{hetAr}^1 \) is a 5-membered heteroaryl ring having 1-3 ring nitrogen atoms;
- \( \text{hetAr}^2 \) is 5-6 membered heteroaryl ring having at least one nitrogen ring atom and optionally having a second ring heteroatom independently selected from N and S,
wherein said heteroaryl ring is optionally substituted with one or more substituents independently selected from (1-4C alkyl), halogen, -(1-4 Qalkoxy, and NH(I -4C alkyl);

hetCyc is a carbon-linked 4-6 membered azacyclic ring optionally substituted with one or more substituents independently selected from (1-4C alkyl), and CO₂(I-4C alkyl);

hetCyc₂ is a pyridinone or pyridazinone ring which is optionally substituted with a substituent selected from (1-4C)alkyl;

hetAr is a 5-6 membered heteroaryl ring having 1-2 ring heteroatoms independently selected from N and O and optionally substituted with one or more substituents independently selected from (l-4C)alkyl;

Rₑ is H or (l-4C)alkyl;

[0034] R₇ is H or (1-6C)alkyl;

[0035] Y is (i) phenyl optionally substituted with one or more substituents independently selected from halogen, (l-4C)alkoxy, CF₃ and CHF₂, or (ii) a 5-6 membered heteroaryl ring having a ring heteroatom selected from N and S, wherein said heteroaryl ring is optionally substituted with one or more halogen atoms;

X is null, -CH₂-, -CH₂CH₂-, -CH₂O- or -CH₂NRᵈ⁻;

[0036] Rᵈ is H or (1-4C alkyl);

[0037] R₃ is H or (1-4C alkyl);

[0038] each Rᵈ is independently selected from halogen, (1-4C)alkyl, OH, (1-4C)alkoxy, NH₂, NH(I -4C alkyl) and CH₂OH; and

n is o, 1, 2, 3, 4, 5 or 6.

[0040] In certain embodiments of Formula I, R² is selected from any of the values described above, other than C(=O)NRₑRᶠ or C(=O)OR₇.

[0041] In certain embodiments of Formula I, R¹ is hydrogen.

[0042] In certain embodiments of Formula I, R¹ is (l-6C)alkyl. A particular example is methyl.
In certain embodiments of Formula I, R² is a group having the formula NRᵇRᶜ, such that the group at the 3 position of the pyrazolo[1,5-a]pyrimidine core of Formula I has the formula -NR⁻(CC=O)NRᵥ.

In certain embodiments, Rᵇ is H or (1-6C alkyl).

In certain embodiments, Rᵇ is H. In certain embodiments, Rᵇ is (1-6C alkyl), for example Me.

In certain embodiments, R² is NRᵇRᶜ where Rᶜ is H, (1-4C)alkyl, (1-4C)hydroxyalkyl, hetAr³, or phenyl, wherein said phenyl is optionally substituted with one or more substituents independently selected from halogen, CN, CF₃ and -O-(1-4C alkyl).

In certain embodiments, R² is NRᵇRᶜ, where Rᶜ is hydrogen. In particular embodiments, the group represented by NRᵇRᶜ is NH₂.

In certain embodiments, R² is NRᵇRᶜ, where Rᶜ is (1-4C)alkyl. Examples include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, and the like. In particular embodiments, the group represented by NRᵇRᶜ includes NHMe, NMe₂ and NH(t-butyl).

In certain embodiments, R² is NRᵇRᶜ, where Rᶜ is (1-4C)hydroxyalkyl. Examples include CH₂CH₂OH and CH₂CH₂CH₂OH. In particular embodiments, the group represented by NRᵇRᶜ includes NMe(CH₂CH₂OH).

In certain embodiments, R² is NRᵇRᶜ, where Rᶜ is hetAr³, and hetAr³ is an optionally substituted 5-6 membered heteroaryl ring having 1-2 ring heteroatoms independently selected from N and O. An example of hetAr³ includes an isoxazolyl ring. In certain embodiments, hetAr³ is unsubstituted. In other embodiments, hetAr³ is substituted with one or more substituents independently selected from (1-4C)alkyl, for example one or more substituents independently selected from methyl and ethyl. Examples of hetAr³ include dimethylisoxazolyl. In particular embodiments, the group represented by NRᵇRᶜ includes the group having the structure:

![Structure](image)

In certain embodiments, R² is NRᵇRᶜ, where Rᶜ is a phenyl group optionally substituted with one or more substituents independently selected from halogen, CN, CF₃ and O-(1-4C alkyl). Examples of Rᶜ include phenyl, fluorophenyl, chlorophenyl, cyanophenyl, methoxyphenyl, trifluoromethylphenyl, dichlorophenyl, and trimethoxyphenyl. More
particular examples include 4-fluorophenyl, 3-chlorophenyl, 4-chlorophenyl, 3-cyanophenyl, 4-cyanophenyl, 4-methoxyphenyl, 2,4-dichlorophenyl, 3-(trifluoromethyl)phenyl, 3,5-dichlorophenyl, and 3,4,5-trimethoxyphenyl. In particular embodiments, the group represented by NR^bR^c includes the structures:

![Chemical Structures](image)

[0053] In certain embodiments, R^2 is NR^bR^c where R^c is selected from H, Me, t-butyl, CH_2CH_2OH and CH_2CH_2CH_2OH, dimethylisoxazolyl, phenyl, fluorophenyl, chlorophenyl, cyanophenyl, methoxyphenyl, trifluoromethylphenyl, dichlorophenyl, and trimethoxyphenyl. More particular examples include 4-fluorophenyl, 3-chlorophenyl, 4-chlorophenyl, 3-cyanophenyl, 4-cyanophenyl, 4-methoxyphenyl, 2,4-dichlorophenyl, 3-(trifluoromethyl)phenyl, 3,5-dichlorophenyl, and 3,4,5-trimethoxyphenyl. In one embodiment, R^b is H. In one embodiments, R^b is (1-6C alkyl), for example methyl.

[0054] In certain embodiments, R^2 is -NR^bR^c, wherein:

[0055] (i) NR^bR^c forms a 4 membered heterocyclic ring having a ring nitrogen atom, wherein said ring is optionally substituted with one or more substituents independently selected from halogen, OH, (1-4C alkyl), (1-4 Qalkoxy, -OC(=O)(1-4C alkyl), NH_2, -NHC(=O)O(1-4C alkyl) and (1-4C)hydroxyalkyl, or

[0056] (ii) NR^bR^c forms a 5-6 membered heterocyclic ring having a ring heteroatom which is nitrogen and optionally having a second ring heteroatom or group selected from N, O and SO_2, wherein the heterocyclic ring is optionally substituted with one or more substituents independently selected from OH, halogen, CF_3, (1-4C)alkyl, CO_2(1-4C alkyl), CO_2H, NH_2, NH(=O)O(1-4C alkyl) and oxo, or

[0057] (iii) NR^bR^c forms a 7-8 membered bridged heterocyclic ring having a ring nitrogen atom and optionally having a second ring heteroatom selected from N and O, wherein said ring is optionally substituted with CO_2(1-4C alkyl).
In certain embodiments, $R_2$ is $-NR^bR^c$, wherein $-NR^bR^c$ forms a 4 membered heterocyclic ring having a ring nitrogen atom, wherein said ring is optionally substituted with one or more substituents independently selected from halogen, OH, (1-4C alkyl), -O(1-4C alkyl), -OC(OH)(1-4C alkyl), NH$_2$, -NHC(OH)(1-4C alkyl) and (1-4C)hydroxyalkyl. Examples include azetidinyl rings optionally substituted with one or more substituents independently selected from OH, methyl, OMe, OC(OH)(CH$_3$)$_2$, NH$_2$, -NHC(OH)(CH$_3$)$_3$ and CH$_2$OH. Particular examples of $R^2$ when represented by $-NR^bR^c$, wherein $-NR^bR^c$ forms a 4 membered heterocyclic ring, include the structures:

[0059] In certain embodiments, $R^2$ is $-NR^bR^c$, wherein $-NR^bR^c$ forms a 4 membered azacyclic ring optionally substituted with one or two substituents independently selected from OH, (1-4C alkyl), and -O(1-4C alkyl), for example OH, Me and OMe.

[0060] In certain embodiments, $R^2$ is $-NR^bR^c$, wherein $-NR^bR^c$ forms a 5-6 membered heterocyclic ring having a ring heteroatom which is nitrogen and optionally having a second ring heteroatom or group selected from N, O and SO$_2$, wherein the heterocyclic ring is optionally substituted with one or more substituents independently selected from OH, halogen, CF$_3$, (1-4C)alkyl, CO$_2$(1-4C alkyl), CO$_2$H, NH$_2$, NHC(OH)(1-4C alkyl) and oxo. Examples include optionally substituted pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl and piperidinesulfone rings. Examples of substituents on the 5-6 membered heterocyclic ring include OH, F, NH$_2$, CO$_2$H, CO$_2$Et, NHCO$_2$C(CH$_3$)$_3$, CF$_3$, methyl, ethyl, isopropyl, CO$_2$C(CH$_2$)$_3$ and oxo. In one embodiment, the heterocyclic ring is optionally substituted with one or two of said substituents. Particular examples of $R^2$ when represented by $-NR^bR^c$, wherein $-NR^bR^c$ forms a 5-6 membered heterocyclic ring, include the structures:
In certain embodiments, \( R_2 \) is \(-\text{NR}^b\text{R}^c\), wherein \(-\text{NR}^b\text{R}^c\) forms a 5-membered heterocyclic ring optionally substituted with one or two substituents independently selected from \( \text{OH} \) and (1-4C) alkyl, for example \( \text{OH} \) and \( \text{Me} \). In certain embodiments, \(-\text{NR}^b\text{R}^c\) forms an azacyclic ring optionally substituted with one to two substituted independently selected from \( \text{OH} \) and \( \text{Me} \).

In certain embodiments, \( R_2 \) is \(-\text{NR}^b\text{R}^c\), wherein \(-\text{NR}^b\text{R}^c\) forms a 6-membered heterocyclic ring optionally substituted with one or two substituents independently selected from \( \text{OH} \) and (1-4C) alkyl, for example \( \text{OH} \) and \( \text{Me} \).

In certain embodiments, \( R_2 \) is \(-\text{NR}^b\text{R}^c\), wherein \( \text{NR}^b\text{R}^c \) forms a 7-8 membered bridged heterocyclic ring having a ring nitrogen atom and optionally having a second ring heteroatom selected from \( \text{N} \) and \( \text{O} \), wherein said ring is optionally substituted with \( \text{CO}_2(1-4\text{C alkyl}) \). Examples of bridged heterocyclic rings include diazabicyclooctane rings such as 3,8-diazabicyclo[3.2.1]octane and oxa-azabicyclo[2.2.1]heptane rings, which are optionally substituted with \( \text{CO}_2(1-4\text{C alkyl}) \), such as \( \text{CO}_2\text{C(CH}_3)_3 \). Particular examples of \( R_2 \) when represented by \(-\text{NR}^b\text{R}^c\), wherein \(-\text{NR}^b\text{R}^c\) forms a 7-8 membered bridged heterocyclic ring, include the structures:

In certain embodiments, \( R_2 \) is selected from (1-4C)alkyl, (1-4C)fluoroalkyl, \( \text{CF}_3 \), (1-4C)hydroxyalkyl, (1-4C alkyl)hetAr and (1-4C alkyl)NH(1-4C alkyl).
In certain embodiments, R<sub>2</sub> is (1-4C)alkyl. Particular examples include methyl, isopropyl and tert-butyl.

In certain embodiments, R<sub>2</sub> is (1-4C)fluoroalkyl. A particular example includes CF(CH<sub>3</sub>)<sub>2</sub>.

In certain embodiments, R<sub>2</sub> is CF.<br>

In certain embodiments, R<sub>2</sub> is (1-4C)hydroxyalkyl. Particular examples include C(CH<sub>3</sub>)<sub>2</sub>OH and C(CH<sub>3</sub>)<sub>2</sub>CH<sub>2</sub>OH.<br>

In certain embodiments, R<sub>2</sub> is -(1-4C<sub>2</sub>)alkyl<sup>hetAr</sup><sub>1</sub>, where hetAr<sup>1</sup> is a 5-membered heteroaryl ring having 1-3 ring nitrogen atoms. An example of hetAr<sup>1</sup> is a triazolyl ring, such as 1,2,4-triazolyl. Examples of the (1-4C)alkyl portion include methylene, ethylene, dimethylmethylene, and the like. A particular value for R<sub>2</sub> when represented by -(1-4C alkyl)hetAr<sup>1</sup> is the structure:<br>

\[
\text{N} \equiv \text{N}
\]

In certain embodiments, R<sub>2</sub> is -(1-4C alkyl)NH(l-4C alkyl). Examples include groups having the formula (1-4C alkyl)NHCH<sub>3</sub>. A particular value include - C(CH<sub>3</sub>)<sub>2</sub>NHCH<sub>3</sub>.

In certain embodiments, R<sub>2</sub> is selected from methyl, isopropyl, tert-butyl, CF(CH<sub>3</sub>)<sub>2</sub>, CF<sub>3</sub>, C(CH<sub>3</sub>)<sub>2</sub>OH and C(CH<sub>3</sub>)<sub>2</sub>CH<sub>2</sub>OH, 2-(1,2,4-triazolyl)propan-2-yl, and -C(CH<sub>3</sub>)<sub>2</sub>NHCH<sub>3</sub>.

In certain embodiments, R<sub>2</sub> is (3-6C cycloalkyl) which is optionally substituted with (l-4C)alkyl, CN, OH, OMe, NH<sub>2</sub>, NHMe, N(CH<sub>3</sub>)<sub>2</sub>, F, CF<sub>3</sub>, CO<sub>2</sub>l-4C alkyl) or CO<sub>2</sub>H. In certain embodiments, R<sub>2</sub> is a cyclopropyl ring optionally substituted with (1-4C alkyl), CN, OH, CF<sub>3</sub>, CO<sub>2</sub>l-4C alkyl) or CO<sub>2</sub>H. Particular examples of R<sub>2</sub> include the structures:

![Structures](image)

In certain embodiments R<sub>2</sub> is a (3-6C cycloalkyl) include cyclopropyl, cyclobutyl and cyclopentyl rings optionally substituted with (1-4C alkyl), CN, OH, CF<sub>3</sub>, CO<sub>2</sub>l-4C alkyl) or CO<sub>2</sub>H. Examples include cyclobutyl and cyclopentyl rings optionally substituted with OH. Further examples of R<sub>2</sub> include the structures:
In certain embodiments, \( R^2 \) is selected from \( \text{hetAr}^2 \), \( \text{hetCyc}^1 \), and \( \text{hetCyc}^2 \).

In certain embodiments, \( R^2 \) is \( \text{hetAr}^2 \). Examples of \( \text{hetAr}^2 \) include pyridyl, pyrimidyl, pyrazinyl, pyrazolyl, imidazolyl and thiazolyl rings optionally substituted with one or more substituents independently selected from \((1-4\text{C} \text{ alkyl}), \text{halogen}, (1-4\text{C})\text{alkoxy}\) and \(\text{NH}(1-4\text{C} \text{ alkyl})\). Particular examples of substituents for \( \text{hetAr}^2 \) include methyl, ethyl, chloro, OMe, and NHCH(CH\(_3\))\(_2\). In certain embodiments, \( \text{hetAr}^2 \) is optionally substituted with 1 or 2 of said substituents. Particular values of \( R^2 \) when represented by \( \text{hetAr}^2 \) include the structures:

![Chemical structures](image)

In certain embodiments, \( R^2 \) is \( \text{hetCyc}^1 \). Examples of \( \text{hetCyc}^1 \) include carbon-linked azetidinyl, pyrrolidinyl and piperidinyl rings optionally substituted with one or more substituents independently selected from \((1-4\text{C} \text{ alkyl}), \text{CO}_2\text{H} \) and \(\text{CO}_2(1-4\text{C} \text{ alkyl})\). Examples of substituents include methyl, ethyl, propyl, \(\text{CO}_2\text{Me}, \text{CO}_2\text{Et} \) and \(\text{CO}_2\text{C(CH}_3\text{)}\text{)}\(_3\). In one embodiment, \( \text{hetCyc}^1 \) is optionally substituted with one or two of said substituents. Particular values for \( R^2 \) represented by \( \text{hetCyc}^1 \) include the structures:

![Chemical structures](image)
[0077] In certain embodiments, \( R^2 \) is \( \text{hetCyc}^2 \). Examples include a pyridinone or pyridazinone ring which is optionally substituted with a substituent selected from (1-4C)alkyl such as a methyl or ethyl group. Particular values of \( R^2 \) when represented by \( \text{hetCyc}^2 \) include the structures:

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[0078] In certain embodiments, \( R^2 \) is selected from (i) pyridyl, pyrimidyl, pyrazinyl, pyrazolyl, imidazolyl and thiazolyl rings optionally substituted with one or more substituents independently selected from (1-4C alkyl), halogen, (1-4C)alkoxy and NH(1-4C alkyl); (ii) carbon-linked azetidinyl, pyrrolidinyl and piperidinyl rings optionally substituted with one or more substituents independently selected from (1-4C alkyl), CO\(_2\)H and CO\(_2\)(1-4C alkyl); and (iii) a pyridinone or pyridazinone ring which is optionally substituted with a substituent selected from (1-4C)alkyl.

[0079] In certain embodiments, \( R^2 \) is selected from the structures:

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In certain embodiments, \( R^2 \) is phenyl which is optionally substituted with a \( \text{NHSO}_2(1-4\text{C alkyl}) \) group such a methanesulfonamido or an ethanesulfonamido group. Particular values for \( R^2 \) include the structures:

\[ \text{NHSO}_2\text{Me} \quad \text{NHSO}_2\text{Et} \]

In certain embodiments, \( R^2 \) is \( \text{C} (=\text{O})\text{NR}^6\text{R}^f \) or \( \text{C} (=\text{O})\text{OR}^g \).

In certain embodiments, \( R^2 \) is \( \text{C} (=\text{O})\text{NR}^6\text{R}^f \). In certain embodiments, \( R^6 \) is H or (1-4C)alkyl and \( R^f \) is H, (1-4C)alkyl, or (3-6C)cycloalkyl. Particular values for \( R^2 \) include \( \text{C} (=\text{O})\text{NH}_2 \), \( \text{C} (=\text{O})\text{NMe} \), \( \text{C} (=\text{O})\text{NMe}_2 \) and \( \text{C} (=\text{O})\text{NH}-\text{cyclopropyl} \).

In certain embodiments \( R^2 \) is \( \text{C} (=\text{O})\text{NR}^6\text{R}^f \), where \( \text{NR}^6\text{R}^f \) forms a 4-6-membered azacyclic ring optionally having an additional ring heteroatom selected from N and O, wherein the azacyclic ring is optionally substituted with OH. Particular values for \( R^2 \) include the structures:

\[ \text{OH} \quad \text{OH} \quad \text{OH} \]

In certain embodiments where \( R^2 \) is \( \text{C} (=\text{O})\text{OR}^g \). Particular examples include \( \text{C} (=\text{O})\text{OH} \) and \( \text{C} (=\text{O})\text{Me} \).
Referring now to the substituents on the ring at the 5-position of Formula I, in one embodiment Y is phenyl optionally substituted with one or more substituents independently selected from halogen, (1-4C)alkoxy, CF₃ and CHF₂. In one embodiment, Y is phenyl optionally substituted with one or more substituents independently selected from F, Cl, OMe, CF₃ and CHF₂. In certain embodiments, Y is phenyl optionally substituted with one or two of said substituents. Particular values for Y include phenyl, 3-fluorophenyl, 2,5-difluorophenyl, 2-chloro-5-fluorophenyl, 2-methoxyphenyl, 2-methoxy-5-fluorophenyl, 2-trifluoromethyl-5-fluorophenyl, 2-difluoromethyl-5-fluorophenyl and 3-chloro-5-fluorophenyl.

In one embodiment, Y is a 5-6 membered heteroaryl ring having a ring heteroatom selected from N and S and optionally substituted with one or more halogen atoms. Examples include pyridyl and thienyl groups optionally substituted with one or more halogen atoms, for example one or more fluoro atoms. Particular values for Y include 2-pyridyl, 3-pyridyl, 5-fluoropyrid-3-yl and 2-thienyl.

In one embodiment, the Y group has the absolute configuration shown in Figure Ia:

![Figure Ia](image)

With reference to the R³ substituent, in one embodiment R³ is H. In one embodiment, R³ is (1-4C)alkyl, for example, methyl, ethyl, propyl, isopropyl or butyl. Particular values for R³ include hydrogen and methyl.

With reference to the R⁴ substituent, in one embodiment R⁴ is halogen. Particular examples are fluoro and chloro.

In one embodiment, R⁴ is (1-4C)alkyl, such as methyl, ethyl, propyl, isopropyl, or butyl. A particular example is methyl.

In one embodiment, R⁴ is OH.

In one embodiment, R⁴ is (1-4alkoxy, for example OMe and OEt.

In one embodiment, R⁴ is NH₂.

In one embodiment, R⁴ is NH(1-4C alkyl), for example NHMe, NHEt, NHP, NHiPr or NHBu. A particular example is NHMe.
In one embodiment, \( R^4 \) is \( \text{CH}_2\text{OH} \).

In one embodiment, each \( R^4 \) is independently selected from \( \text{F}, \text{Cl}, \text{OH}, \text{OMe}, \text{NH}_2, \text{Me}, \text{CH}_2\text{OH} \) and \( \text{NHMe} \).

In one embodiment, \( n \) is 0, 1, 2, 3 or 4. In one embodiment, \( n \) is 0, 1, 2 or 3. In one embodiment, \( n \) is 0, 1 or 2.

With continued reference to the ring at the 5-position of Formula I, in certain embodiments, \( X \) is null, \(-\text{CH}_2-\) or \(-\text{CH}_2\text{CH}_2-\).

In one embodiment \( X \) is null, such that the heterocyclic ring at the 5-position of Formula I has the structure:

![Diagram](image)

where \( R^3, R^4, Y \) and \( n \) are as defined herein. In one embodiment, \( Y \) is phenyl optionally substituted with one or more substituents independently selected from halogen, \((1\text{-}4\text{C})\text{alkoxy}, \text{CF}_3\) and \( \text{CHF}_2 \). In one embodiment, \( Y \) is 5-6 membered heteroaryl ring having a ring heteroatom selected from \( \text{N} \) and \( \text{S} \), wherein said heteroaryl ring is optionally substituted with one or more halogen atoms. In one embodiment, \( R^3 \) is hydrogen. In another embodiment, \( R^3 \) is methyl. A particular example of the ring at the 5-position of Formula I when \( X \) is null includes the structures:

![Diagrams](image)

In one embodiment, \( X \) is \( \text{CH}_2 \), such that the heterocyclic ring at the 5-position of Formula I has the structure:

![Diagram](image)

where \( R^3, R^4, Y \) and \( n \) are as defined herein. In one embodiment \( Y \) is phenyl optionally substituted with one or more substituents independently selected from halogen, \((1\text{-}4\text{C})\text{alkoxy}, \text{CF}_3\) and \( \text{CHF}_2 \). In one embodiment, \( Y \) is a 5-6 membered heteroaryl ring having a ring heteroatom selected from \( \text{N} \) and \( \text{S} \), wherein said heteroaryl ring is optionally
substituted with one or more halogen atoms. In one embodiment, R³ is hydrogen. In another embodiment, R³ is methyl. In one embodiment, each R⁴ is independently selected from F, Cl, Me, OH, OMe, NH₂, NHMe, CH₂OH, CHF₂ and CF₃. In one embodiment, n is 0, 1 or 2. Particular examples of the ring at the 5-position of Formula I when X is CH₂ include the structures:

![Chemical structures](image)

[00103] In one embodiment, X is CH₂CH₂, such that the heterocyclic ring at the 5-position of Formula I has the structure:
where $R^3$, $R^4$, $Y$ and $n$ are as defined herein. In one embodiment, phenyl optionally substituted with one or more substituents independently selected from halogen, (1-4C)alkoxy, CF$_3$ and CHF$_2$. In one embodiment, $Y$ is a 5-6 membered heteroaryl ring having a ring heteroatom selected from N and S, wherein said heteroaryl ring is optionally substituted with one or more halogen atoms. In one embodiment, $R^3$ is hydrogen. In another embodiment, $R^3$ is methyl. In one embodiment, $n$ is 0, 1 or 2. In one embodiment, $n$ is 0. Particular examples of the ring at the 5-position of Formula I when $X$ is CH$_2$CH$_2$ include the structures:

![Structures](image)

In one embodiment, $X$ is -CH$_2$O-. In one embodiment, the heterocyclic ring at the 5-position of Formula I has the structure:

![Structure](image)

where $R^3$, $R^4$, $Y$ and $n$ are as defined herein. In one embodiment, $Y$ is phenyl optionally substituted with one or more substituents independently selected from halogen, (1-4C)alkoxy, CF$_3$ and CHF$_2$. In one embodiment, $Y$ is phenyl optionally substituted with one or more substituents independently selected from F and (1-4C)alkoxy. In one embodiment, $Y$ is a 5-6 membered heteroaryl ring having a ring heteroatom selected from N and S, wherein said heteroaryl ring is optionally substituted with one or more halogen atoms. In one embodiment, $R^3$ is hydrogen. In another embodiment, $R^3$ is methyl. In one embodiment, $n$ is 0, 1 or 2. Particular examples of the ring at the 5-position of Formula I when $X$ is -CH$_2$O- include the structures:

![Structures](image)
In one embodiment, X is -CH$_2$NR$^d$. In one embodiment, the heterocyclic ring at the 5-position of Formula I has the structure:

\[
\begin{array}{c}
\text{Y} \\
\text{R}^3 \\
\text{N} \\
\text{R}^d \\
\end{array}
\]

where $R^3$, $R^4$, $Y$, $R^d$ and $n$ are as defined herein. In one embodiment, $R^d$ is H. In one embodiment, $R^d$ is (1-4C alkyl), for example methyl, ethyl, propyl, isopropyl, or butyl. A particular example is methyl. In one embodiment, $Y$ is phenyl optionally substituted with one or more substituents independently selected from halogen, (1-4C)alkoxy, CF$_3$ and CHF$_2$. In one embodiment, $Y$ is a 5-6 membered heteroaryl ring having a ring heteroatom selected from N and S, wherein said heteroaryl ring is optionally substituted with one or more halogen atoms. In one embodiment, $n$ is 0. Particular examples of the ring at the 5-position of Formula I when X is -CH$_2$NR$^d$ include the structures:

Compounds of Formula I include compound of Formula Ib, wherein

- $R^1$ is H or (1-6C alkyl);
- $R^2$ is NR$^b$R$^c$;
- NR$^b$R$^c$ forms a 4 membered heterocyclic ring having a ring nitrogen atom, wherein said heterocyclic ring is optionally substituted with one or more substituents independently selected from halogen, OH, (1-4C alkyl), (1-4 Qalkoxy, -OC(=O)(1-4C alkyl), NH$_2$, -NHC(=O)O(1-4C alkyl) and (1-4C)hydroxyalkyl,
- or NR$^b$R$^c$ forms a 5-6 membered heterocyclic ring having a ring heteroatom which is nitrogen and optionally having a second ring heteroatom or group selected from N, O and SO$_2$, wherein the heterocyclic ring is optionally substituted with one or more
substituents independently selected from OH, halogen, CF₃, (1-4C)alkyl, CO₂(1-4C alkyl), CO₂H, NH₂, NHC(=O)O(1-4C alkyl) and oxo;

[00114] Y is phenyl optionally substituted with one or more substituents independently selected from halogen, (1-4C)alkoxy, CF₃ and CHF₂;

[00115] X is null, -CH₂ -, or -CH₂CH₂ -;

[00116] R³ is H or (1-4C alkyl);

[00117] each R⁴ is independently selected from halogen, (1-4C)alkyl, OH, (1-4 Qalkoxy, NH₂, NH(I -4C alkyl) and CH₂OH; and

[00118] n is 0, 1, or 2.

[00119] In one embodiment of Formula Ib, Y is phenyl optionally substituted with one or more halogen atoms. In one embodiment of Formula Ib, Y is phenyl optionally substituted with one or two fluorine atoms.

[00120] In one embodiment of Formula Ib, NRᵇRᶜ forms a 4 membered heterocyclic ring having a ring nitrogen atom, wherein said ring is optionally substituted with one or more substituents independently selected from halogen, OH, (1-4C alkyl), (1-4 Qalkoxy, -OC(=O)(1-4C alkyl), NH₂, -NHC(=O)O(1-4C alkyl) and (1-4C)hydroxyalkyl, or (ii) NRᵇRᶜ forms a 5-6 membered heterocyclic ring having a ring heteroatom which is nitrogen and optionally having a second ring heteroatom or group selected from N, O and SO₂, wherein the heterocyclic ring is optionally substituted with one or more substituents independently selected from OH, halogen, CF₃, (1-4C)alkyl, CO₂(1-4C alkyl), CO₂H, NH₂, NHC(O)O(1-4C alkyl) and oxo.

[00121] In one embodiment of Formula Ib, NRᵇRᶜ forms a 5-6 membered heterocyclic ring having a ring heteroatom which is nitrogen and optionally having a second ring heteroatom or group selected from N, O and SO₂, wherein the heterocyclic ring is optionally substituted with one or more substituents independently selected from OH, halogen, CF₃, (1-4C)alkyl, CO₂(1-4C alkyl), CO₂H, NH₂, NHC(O)O(1-4C alkyl) and oxo.

[00122] In one embodiment of Formula Ib, n is zero or one.

[00123] In one embodiment of Formula Ib, R³ is hydrogen.

[00124] Compounds of Formula Ib include compounds of Formula Ic wherein:

[00125] R¹ is H or (1-6C alkyl);

[00126] R² is NRᵇRᶜ;

[00127] NRᵇRᶜ forms a 4 membered heterocyclic ring having a ring nitrogen atom, wherein said heterocyclic ring is optionally substituted with one or more substituents
independently selected from halogen, OH, (1-4C alkyl), (1-4 Qalkoxy, -OC(=O)(1-4C alkyl), NH₂, -NHC(=O)O(1-4C alkyl) and (1-4C)hydroxyalkyl;

Y is phenyl optionally substituted with one or more substituents independently selected from halogen, (l-4C)alkoxy, CF₃ and CHF₂;

X is -CH₂-

R³ is H or (1-4C alkyl);

each R⁴ is independently selected from halogen, (l-4C)alkyl, OH, (1-4 Qalkoxy, NH₂, NH(l-4C alkyl) and CH₂OH; and

n is 0, 1, or 2.

In one embodiment of Formula Ic, the heterocyclic ring formed by NRᵇRᶜ is optionally substituted with one or two substituents independently selected from F, OH, methyl, OMe, OC(=O)C(CH₃)₂, NH₂, -NHC(=O)OC(CH₃)₃ and CH₂OH.

In one embodiment of Formula Ic, the heterocyclic ring formed by NRᵇRᶜ is 4 membered azcyclic ring optionally substituted with one or two substituents independently selected from OH, (1-4C alkyl), and -O(1-4C alkyl), for example OH, Me and OMe.

In one embodiment of Formula Ic, Y is phenyl optionally substituted with one or more halogen atoms. In one embodiment of Formula Ic, Y is phenyl optionally substituted with one or two fluorine atoms.

Compounds of Formula Ib also include compounds of Formula Id wherein:

R¹ is H or (1-6C alkyl);

R² is NRᵇRᶜ;

NRᵇRᶜ forms a 5-6 membered heterocyclic ring having a ring heteroatom which is nitrogen and optionally having a second ring heteroatom or group selected from N, O and SO₂, wherein the heterocyclic ring is optionally substituted with one or more substituents independently selected from OH, halogen, CF₃, (1-4C)alkyl, CO₂(1-4C alkyl), CO₂H, NH₂, NHC(=O)O(1-4C alkyl) and oxo;

Y is phenyl optionally substituted with one or more substituents independently selected from halogen, (1-4C)alkoxy, CF₃ and CHF₂;

X is -CH₂-

R³ is H or (1-4C alkyl);

each R⁴ is independently selected from halogen, (l-4C)alkyl, OH, (1-4 Qalkoxy, NH₂, NH(l-4C alkyl) and CH₂OH; and

n is 0, 1, or 2.
In one embodiment of Formula Id, the heterocyclic ring formed by NR\textsuperscript{b}R\textsuperscript{c} is optionally substituted with one or two substituents independently selected from OH, F, NH\textsubscript{2}, CO\textsubscript{2}H, CO\textsubscript{2}Et, NHCO\textsubscript{2}C(CH\textsubscript{s})\textsubscript{3}, CF\textsubscript{3}, methyl, ethyl, isopropyl, CO\textsubscript{2}C(CH\textsubscript{2})\textsubscript{3} and oxo.

In one embodiment of Formula Id, the heterocyclic ring formed by NR\textsuperscript{b}R\textsuperscript{c} is a 5-6 membered azacyclic ring optionally substituted with one or more substituents independently selected from OH, F, NH\textsubscript{2}, CO\textsubscript{2}H, CO\textsubscript{2}Et, NHCO\textsubscript{2}C(CH\textsubscript{3})\textsubscript{3}, CF\textsubscript{3}, methyl, ethyl, isopropyl, CO\textsubscript{2}C(CH\textsubscript{2})\textsubscript{3} and oxo.

In one embodiment of Formula Id, the heterocyclic ring formed by NR\textsuperscript{b}R\textsuperscript{c} is a 5 membered azacyclic ring optionally substituted with one or more substituents independently selected from OH, F, NH\textsubscript{2}, CO\textsubscript{2}H, CO\textsubscript{2}Et, NHCO\textsubscript{2}C(CH\textsubscript{3})\textsubscript{3}, CF\textsubscript{3}, methyl, ethyl, isopropyl, CO\textsubscript{2}C(CH\textsubscript{2})\textsubscript{3} and oxo.

In certain embodiments of Formula Ia, -NR\textsuperscript{b}R\textsuperscript{c} forms a 5-membered azacyclic ring optionally substituted with one to two substituted independently selected from OH and Me.

In one embodiment of Formula Id, the heterocyclic ring formed by NR\textsuperscript{b}R\textsuperscript{c} is a 6 membered azacyclic ring optionally substituted with one or more substituents independently selected from OH, F, NH\textsubscript{2}, CO\textsubscript{2}H, CO\textsubscript{2}Et, NHCO\textsubscript{2}C(CH\textsubscript{3})\textsubscript{3}, CF\textsubscript{3}, methyl, ethyl, isopropyl, CO\textsubscript{2}C(CH\textsubscript{2})\textsubscript{3} and oxo.

In one embodiment of Formula Id, the heterocyclic ring formed by NR\textsuperscript{b}R\textsuperscript{c} is a 6 membered azacyclic ring optionally substituted with one or two substituents independently selected from OH and (1-4C) alkyl, for example OH and Me.

In one embodiment of Formula Id, Y is phenyl optionally substituted with one or more halogen atoms. In one embodiment of Formula Id, Y is phenyl optionally substituted with one or two fluorine atoms.

In one embodiment of Formula Ic or Id, n is zero or one.

In one embodiment of Formula Ic or Id, R\textsuperscript{3} is hydrogen.

In one embodiment of Formula Ic or Id, R\textsuperscript{1} is hydrogen.

Compounds of Formula I include compound of Formula Ie, wherein:

R\textsuperscript{1} is H or (1-6C alkyl);

R\textsuperscript{2} is NR\textsuperscript{b}R\textsuperscript{c};

NR\textsuperscript{b}R\textsuperscript{c} forms a 4 membered heterocyclic ring having a ring nitrogen atom, wherein said heterocyclic ring is optionally substituted with one or more substituents
independently selected from halogen, OH, (1-4C alkyl), (1-4 Qalkoxy, -OC(=O)(1-4C alkyl), NH₂, -NHC(=O)O(1-4C alkyl) and (1-4C)hydroxyalkyl,

or NR⁵R⁶ forms a 5-6 membered heterocyclic ring having a ring heteroatom which is nitrogen and optionally having a second ring heteroatom or group selected from N, O and SO₂, wherein the heterocyclic ring is optionally substituted with one or more substituents independently selected from OH, halogen, CF₃, (1-4C)alkyl, CO₂(1-4C alkyl), CO₂H, NH₂, NHC(=O)O(1-4C alkyl) and oxo;

Y is a 5-6 membered heteroaryl ring having a ring heteroatom selected from N and S, wherein said heteroaryl ring is optionally substituted with one or more halogen atoms;

X is null, -CH₂-, or -CH₂CH₂-;

R³ is H or (1-4C alkyl);

each R⁴ is independently selected from halogen, (1-4C)alkyl, OH, (1-4 Qalkoxy, NH₂, NH(I-4C alkyl) and CH₂OH; and

n is 0, 1, or 2.

Compounds of Formula I include compounds of Formula If, wherein:

R¹ is H or (1-6C alkyl); 

R² is (1-4C)alkyl, (1-4C)fluoroalkyl, CF₃, (1-4C)hydroxyalkyl, -(1-4C alkyl)hetAr\ -(1-4C alkyl)NH₂, -(1-4C alkyl)NH(l-4C alkyl), -(1-4C alkyl)N(l-4C alkyl)₂, hetAr², hetCyc¹, hetCyc², phenyl which is optionally substituted with NHSO₂(1-4C alkyl), or (3-6C)cycloalkyl which is optionally substituted with (1-4C alkyl), CN, OH, OMe, NH₂, NHMe, N(CH₃)₂, F, CF₃, CO₂(1-4C alkyl), CO₂H, C(=O)NR⁵R⁶ or C(=O)OR⁸;

hetAr¹ is a 5-membered heteroaryl ring having 1-3 ring nitrogen atoms;

hetAr² is 5-6 membered heteroaryl ring having at least one nitrogen ring atom and optionally having a second ring heteroatom independently selected from N and S, wherein said heteroaryl ring is optionally substituted with one or more substituents independently selected from (1-4C alkyl), halogen, -(1-4 Qalkoxy, and NH(I-4C alkyl);

hetCyc¹ is a carbon-linked 4-6 membered azacyclic ring optionally substituted with one or more substituents independently selected from (1-4C alkyl), and CO₂(1-4C alkyl);

hetCyc² is a pyridinone or pyridazinone ring which is optionally substituted with a substituent selected from (1-4C)alkyl;

R⁵ is H or (1-4C)alkyl;

R⁶ is H, (1-4C)alkyl, or (3-6C)cycloalkyl;
or NR\textsuperscript{e}R\textsuperscript{f} forms a 5-6-membered azacyclic ring optionally having an additional ring heteroatom selected from N and O, wherein the azacyclic ring is optionally substituted with OH;

R\textsuperscript{g} is H or (1-6C)alkyl;

Y is (i) phenyl optionally substituted with one or more substituents independently selected from halogen, (1-4C)alkoxy, CF\textsubscript{3} and CHF\textsubscript{2}, or (ii) a 5-6 membered heteroaryl ring having a ring heteroatom selected from N and S, wherein said heteroaryl ring is optionally substituted with one or more halogen atoms;

X is null, -CH\textsubscript{2}-, -CH\textsubscript{2}CH\textsubscript{2}-;

R\textsuperscript{d} is H or (1-4C alkyl);

R\textsuperscript{3} is H or (1-4C alkyl);

each R\textsuperscript{4} is independently selected from halogen, (1-4C)alkyl, OH, (1-4C)alkoxy, NH\textsubscript{2}, NH(I -4C alkyl) and CH\textsubscript{2}OH; and

n is 0, 1, 2, 3, 4, 5 or 6.

In one embodiment of Formula I, Y is phenyl optionally substituted with one or more substituents independently selected from halogen, (1-4C)alkoxy, CF\textsubscript{3} and CHF\textsubscript{2}.

In one embodiment of Formula I, Y is a 5-6 membered heteroaryl ring having a ring heteroatom selected from N and S, wherein said heteroaryl ring is optionally substituted with one or more halogen atoms.

In one embodiment of Formula I, R\textsuperscript{2} is selected from (1-4C)alkyl, (1-4C)fluoroalkyl, CF\textsubscript{3}, -(1-4C)hydroxyalkyl, (1-4C alkyl)hetAr and -(1-4C alkyl)NH(I-4C alkyl)

In one embodiment of Formula I, R\textsuperscript{2} is selected from methyl, isopropyl, tert-butyl, CF(CH\textsubscript{3})\textsubscript{2}, CF\textsubscript{3}, C(CH\textsubscript{3})\textsubscript{2}OH and C(CH\textsubscript{3})\textsubscript{2}CH\textsubscript{2}OH, 2-(1,2,4-triazolyl)propan-2-yl, and -C(CH\textsubscript{3})\textsubscript{2}NHCH\textsubscript{3}.

In one embodiment of Formula I, R\textsuperscript{2} is a cyclopropyl, cyclobutyl and cyclopentyl ring optionally substituted with (1-4C alkyl), CN, OH, CF\textsubscript{3}, CO\textsubscript{2}(I-4C alkyl) or CO\textsubscript{2}H.

In one embodiment of Formula I, R\textsuperscript{2} is selected from hetAr\textsuperscript{2}, hetCyc\textsuperscript{1}, and hetCyc\textsuperscript{2}.

In one embodiment of Formula I, R\textsuperscript{2} is selected from (i) pyridyl, pyrimidyl, pyrazinyl, pyrazolyl, imidazolyl and thiazolyl rings optionally substituted with one or more substituents independently selected from (1-4C alkyl), halogen, (1-4C)alkoxy and NH(I-4C alkoxy).
alkyl); (ii) carbon-linked azetidinyl, pyrrolidinyl and piperidinyl rings optionally substituted with one or more substituents independently selected from (1-4C alkyl), CO$_2$H and CO$_2$(1-4C alkyl); and (iii) a pyridinone or pyridazinone ring which is optionally substituted with a substituent selected from (1-4C)alkyl.

[00189] In one embodiment of Formula I, R$^2$ is C(=O)NR$_2$R$^f$ or C(=O)OR$^f$.

[00190] Compounds of Formula I include compound of Formula Ig, wherein

[00191] R$^1$ is H or (1-6C alkyl);

[00192] R$^2$ is NR$^b$R$^c$;

[00193] R$^b$ is H or (1-6C alkyl);

[00194] R$^c$ is H, (1-4C)alkyl, (1-4C)hydroxyalkyl, hetAr$^3$, or phenyl, wherein said phenyl is optionally substituted with one or more substituents independently selected from halogen, CN, CF$_3$ and -0(1-4C alkyl);

[00195] hetAr$^3$ is a 5-6 membered heteroaryl ring having 1-2 ring heteroatoms independently selected from N and O and optionally substituted with one or more substituents independently selected from (1-4C)alkyl;

[00196] Y is (i) phenyl optionally substituted with one or more substituents independently selected from halogen, (1-4C)alkoxy, CF$_3$ and CHF$_2$, or (ii) a 5-6 membered heteroaryl ring having a ring heteroatom selected from N and S, wherein said heteroaryl ring is optionally substituted with one or more halogen atoms;

[00197] X is null, -CH$_2$-, or -CH$_2$CH$_2$-;

[00198] R$^d$ is H or (1-4C alkyl);

[00199] R$^3$ is H or (1-4C alkyl);

[00200] each R$^4$ is independently selected from halogen, (1-4C)alkyl, OH, (1-4C)alkoxy, NH$_2$, NH(I-4C alkyl) and CH$_2$OH; and

[00201] n is 0, 1, 2, 3, 4, 5 or 6.

[00202] In one embodiment of Formula Ig, Y is phenyl optionally substituted with one or more substituents independently selected from halogen, (1-4C)alkoxy, CF$_3$ and CHF$_2$.

[00203] In one embodiment of Formula Ig, Y is a 5-6 membered heteroaryl ring having a ring heteroatom selected from N and S, wherein said heteroaryl ring is optionally substituted with one or more halogen atoms.

[00204] In one embodiment of Formula Ig, R$^c$ is selected from H, Me, t-butyl, CH$_2$CH$_2$OH and CH$_2$CH$_2$CH$_2$OH, dimethylisoxazolyl, phenyl, fluorophenyl, chlorophenyl, cyanophenyl, methoxyphenyl, trifluoromethylphenyl, dichlorophenyl, and trimethoxyphenyl.
More particular examples include 4-fluorophenyl, 3-chlorophenyl, 4-chlorophenyl, 3-cyanophenyl, 4-cyanophenyl, 4-methoxyphenyl, 2,4-dichlorophenyl, 3-(trifluoromethyl)phenyl, 3,5-dichlorophenyl, and 3,4,5-trimethoxyphenyl.

[00205] In one embodiment of Formula I, n is 0, 1 or 2.

[00206] It will be appreciated that certain compounds according to the invention may contain one or more centers of asymmetry and may therefore be prepared and isolated in a mixture of isomers such as a racemic or diastereomeric mixture, or in an enantiomerically pure form. It is intended that all stereoisomeric forms of the compounds of the invention, including but not limited to, diastereomers, enantiomers and atropisomers, as well as mixtures thereof such as racemic mixtures, form part of the present invention.

[00207] In the structures shown herein, where the stereochemistry of any particular chiral atom is not specified, then all stereoisomers are contemplated and included as the compounds of the invention. Where stereochemistry is specified by a solid wedge or dashed line representing a particular configuration, then that stereoisomer is so specified and defined.

[00208] It will also be appreciated that certain compounds of Formula I may be used as intermediates for further compounds of Formula I.

[00209] The compounds of Formula I include pharmaceutically acceptable salts thereof. In addition, the compounds of Formula I also include other salts of such compounds which are not necessarily pharmaceutically acceptable salts, and which may be useful as intermediates for preparing and/or purifying compounds of Formula I and/or for separating enantiomers of compounds of Formula I. Examples of particular salts include hydrogen sulfate salts, hydrochloride salts and trifluoroacetate salts.

[00210] It will further be appreciated that the compounds of Formula I and their salts may be isolated in the form of solvates, and accordingly that any such solvate is included within the scope of the present invention.

[00211] The compounds of Formula I also include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds of the invention include compounds wherein one or more hydrogen atoms are replaced deuterium or tritium, or one or more carbon atoms are replaced by a $^{13}$C- or $^{14}$C-enriched carbon are within the scope of this invention.

[00212] The term "(1-4C) alkyl" as used herein refers to saturated linear or branched-chain monovalent hydrocarbon radicals of one to four carbon atoms, respectively. Examples
include, but are not limited to, methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-methyl-1-propyl, 2-butyl, and 2-methyl-2-propyl.

[00213] The term "(1-4C) alkoxy" as used herein refers to saturated linear or branched-chain monovalent radicals of one to four carbon atoms, respectively, wherein the radical is on the oxygen atom.

[00214] The term "(1-4C) hydroxyalkyl" as used herein refers to saturated linear or branched-chain monovalent hydrocarbon radicals of one to four carbon atoms, respectively, wherein one of the hydrogen atoms is replaced with an OH group.

[00215] The term "halogen" includes fluoro, chloro, bromo and iodo.

[00216] According to another aspect, the present invention provides a process for the preparation of a compound of Formula I or a pharmaceutically acceptable salt thereof as defined herein which comprises:

[00217] (a) for a compound of Formula I wherein R² is NRᵇRᶜ, reacting a corresponding compound of formula II

\[ \text{II} \]

with a compound having the formula HNRᵇRᶜ in the presence of a coupling reagent; or

[00219] (b) for a compound of Formula I wherein R² is NRᵇRᶜ and Rᵇ is H, reacting a corresponding compound of formula II with a compound having the formula O=C=N-R⁰; or

[00220] (c) for a compound of Formula I wherein R² is hetAr² or a phenyl ring which is optionally substituted with NH₂SO₂(I-4C alkyl), reacting a corresponding compound of Formula II with a corresponding compound having the formula HOC(=O)R² in the presence of a coupling reagent and a base; or

[00221] (d) for a compound of Formula I wherein R² is (1-4C) alkyl, (1-4C) fluoroalkyl, CF₃, (1-4C) hydroxyalkyl, or (3-6C) cycloalkyl which is optionally substituted with (1-4C alkyl), CN, OH, CF₃, CO₂(1-4C alkyl) or CO₂H, reacting a corresponding compound of Formula II with a corresponding compound having the formula (R²CO)₂O in the presence of a base; or

[00222] (e) for a compound of Formula I wherein R² is (1-4C) alkyl, (1-4C) fluoroalkyl, CF₃, (1-4C) hydroxyalkyl, or (3-6C) cycloalkyl which is optionally substituted
with (1-4C alkyl), CN, OH, CF₃, CO₂(1-4C alkyl) or CO₂H, reacting a corresponding compound of Formula II with a corresponding compound having the formula HOC(=O)R in the presence of a coupling reagent and a base; or

(ii) for a compound of Formula I wherein R² is C(=O)NR eRf, reacting a compound of Formula VII with a compound having the formula HNR eRf in the presence of a base; or

(g) for a compound of Formula I wherein R² is C(=O)OR e, reacting a compound of Formula II with methyl 2-chloro-2-oxoacetate, and treating with an alkali hydroxide to prepare a compound of formula I where R e is H; and

removing or adding any protecting groups if desired, and forming a salt if desired.

Referring to methods (a) and (e), examples of suitable coupling reagents include CDI (carbonyl diimidazole), phosgene, and bis(trichloromethyl) carbonate. The reaction is optionally performed in the presence of a tertiary amine base, such as DIEA (diisopropylethylamine). Suitable solvents include dichloromethane, dichloroethane, THF, and DMF. The reaction is conveniently performed at ambient temperature.

Compounds of formula II

Can be prepared by reducing a corresponding compound of formula III

under standard reducing conditions, for example reacting a compound of formula II with zinc dust under acidic conditions, such as in the presence of NH₄Cl (saturated
aqueous), HCl, or acetic acid. Another example of such standard reducing conditions includes reacting compounds of formula III under a hydrogen atmosphere in the presence of a precious metal catalyst to corresponding compounds of formula II.

Compounds of Formula III can be prepared by nitrating a corresponding compound having the formula IV

![IV]

using standard nitrating conditions known in the art, for example by reacting a corresponding compound of Formula IV with nitric acid in the presence of an activating agent such as TFA or concentrated sulfuric acid.

Compounds of the formula IV can be prepared by coupling a corresponding compound of Formula V

![V]

where Z is a leaving group or atom, such as a halogen (for example Cl), with a corresponding compound having the formula VI

![VI]

where \( R^3, R^4, n, X \), and \( Y \) are as defined herein, in a suitable solvent such as an alcohol (for example n-butanol or isopropanol), at elevated temperatures, for example at temperatures between 100 and 180 °C, for example at a temperature of about 140 °C. Compounds of Formula V are commercially available or can be prepared by standard methods known in the art.

Compounds of Formula II and III are also believed to be novel and provide a further embodiment of this invention.

Referring to method (b), suitable solvents include dichloromethane, dichloroethane, THF, and DMF. The reaction is conveniently performed at ambient temperature.
Referring to method (c), suitable coupling reagents include HATU, HBTU, TBTU, DCC (N,N'-dicyclohexylcarbodiimide), DIEC (l-(3-dimethylaminopropyl)-3-ethylcarbodiimide) and any other amide coupling reagents well known to persons skilled in the art. Suitable bases include tertiary amine bases such as diisopropylethylamine (DIEA) and triethylamine. Suitable solvents include DMF and CH₃CN. The reaction is conveniently performed at temperatures between 0°C and ambient temperature.

Referring to method (d), suitable bases include amine bases such as pyridine or triethylamine, and suitable coupling reagents include HATU, HBTU, TBTU, DCC (N,N'-dicyclohexylcarbodiimide), DIEC (l-(3-dimethylaminopropyl)-3-ethylcarbodiimide) and any other amide coupling reagents well known to persons skilled in the art. Suitable solvents include dichloromethane and dichloroethane. The reaction is conveniently performed at temperatures between 0°C and ambient temperature.

The ability of compounds to act as TrkA inhibitors may be demonstrated by the assays described in Examples A and B. The ability of compounds to act as TrkB inhibitors may be demonstrated by the assay described in Example B.

Compounds of Formula I are useful for treating chronic and acute pain, including pain associated with cancer, surgery, and bone fracture. Certain compounds which are inhibitors of TrkA and/or TrkB may be useful in the treatment of multiple types of pain including inflammatory pain, neuropathic pain, and pain associated with cancer, surgery, and bone fracture.

Compounds of Formula I are also useful for treating cancers including neuroblastoma, ovarian, pancreatic and colorectal cancer.

Compounds of Formula I are also useful for treating inflammation and certain infectious diseases.

In addition, compounds of Formula I may also be used to treat interstitial cystitis (IC), painful bladder syndrome (PBS), urinary incontinence, asthma, anorexia, atopic dermatitis, and psoriasis.

Compounds of Formula I may also be used to treat demyelination and dysmyelination by promoting myelination, neuronal survival, and oligodendrocyte differentiation via blocking Sp35-TrkA interaction.

Compounds of Formula I which are dual inhibitors of TrkA and TrkB may be useful in the treatment of multiple types of pain including inflammatory pain, neuropathic pain, surgical pain and pain associated with cancer.
Compounds of Formula I may be of therapeutic value for the useful in the treatment of bone-related diseases (such as those involving bone resorption). Examples of bone-related diseases include metastatic bone disease, treatment-induced bone loss, osteoporosis, rheumatoid arthritis, ankylosing spondylitis, Paget's disease, and periodontal disease. The osteoporosis may be attributed to (1) menopause in women, (2) aging in men or women, (3) suboptimal bone growth during childhood and adolescence that resulted in failure to reach peak bone mass, and/or (4) bone loss secondary to other disease conditions, eating disorders, medications and/or medical treatments.

Other osteolytic diseases that can be treated according to the present invention are more localized. A particular example is metastatic tumor-induced osteolysis. In this condition, bone cancers or bone metastases induce localized osteolysis that causes pain, bone weakness and fractures. Such localized osteolysis also permits tumors to grow larger by creating more space for them in the bone and releasing growth factors from the bone matrix. Cancers presently known to cause tumor-induced osteolysis include hematological malignancies (e.g., myeloma and lymphoma) and solid tumors (e.g., breast, prostate, lung, renal and thyroid), all of which the present invention contemplates treating.

As used herein, the term treatment includes prophylaxis as well as treatment of an existing condition.

Accordingly, another aspect of this invention provides a method of treating diseases or medical conditions in a mammal, wherein said disease or condition is treatable with an inhibitor of TrkA and/or TrkB, comprising administering to said mammal one or more compounds of Formula I or a pharmaceutically acceptable salt thereof in an amount effective to treat or prevent said disorder. In a particular embodiment, the invention provides a method of treating pain, cancer, inflammation, neurodegenerative disease or Trypanosoma cruzi infection in a mammal, which comprises administering to said mammal a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

In another embodiment, the invention provides a method of treating osteolytic disease in a mammal, which comprises administering to said mammal a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt thereof.

The compounds of the present invention can be used in combination with one or more additional drugs that work by the same or a different mechanism of action. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate
administration of the individual components of the treatment. Examples include anti-inflammatory compounds, steroids (e.g., dexamethasone, cortisone and fluticasone), analgesics such as NSAIDs (e.g., aspirin, ibuprofen, indomethacin, and ketoprofen), and opioids (such as morphine), and chemotherapeutic agents.

In the field of medical oncology it is normal practice to use a combination of different forms of treatment to treat each patient with cancer. In medical oncology the other component(s) of such conjoint treatment in addition to compositions of the present invention may be, for example, surgery, radiotherapy, chemotherapy, signal transduction inhibitors and/or monoclonal antibodies.

Accordingly, the compounds of Formula I may be administered in combination with one or more agents selected from mitotic inhibitors, alkylating agents, antimetabolites, antisense DNA or RNA, intercalating antibiotics, growth factor inhibitors, signal transduction inhibitors, cell cycle inhibitors, enzyme inhibitors, retinoid receptor modulators, proteasome inhibitors, topoisomerase inhibitors, biological response modifiers, anti-hormones, angiogenesis inhibitors, cytostatic agents anti-androgens, targeted antibodies, HMG-CoA reductase inhibitors, and prenyl-protein transferase inhibitors.

The phrase "effective amount" means an amount of compound that, when administered to a mammal in need of such treatment, is sufficient to (i) treat or prevent a particular disease, condition, or disorder which can be treated with an inhibitor of TrkA and/or TrkB, (ii) attenuate, ameliorate, or eliminate one or more symptoms of the particular disease, condition, or disorder, or (iii) prevent or delay the onset of one or more symptoms of the particular disease, condition, or disorder described herein.

The amount of a compound of Formula I that will correspond to such an amount will vary depending upon factors such as the particular compound, disease condition and its severity, the identity (e.g., weight) of the mammal in need of treatment, but can nevertheless be routinely determined by one skilled in the art.

As used herein, the term "mammal" refers to a warm-blooded animal that has or is at risk of developing a disease described herein and includes, but is not limited to, guinea pigs, dogs, cats, rats, mice, hamsters, and primates, including humans.

Compounds of the invention may be administered by any convenient route, e.g. into the gastrointestinal tract (e.g. rectally or orally), the nose, lungs, musculature or vasculature, or transdermally or dermally. Compounds may be administered in any convenient administrative form, e.g. tablets, powders, capsules, solutions, dispersions,
suspensions, syrups, sprays, suppositories, gels, emulsions, patches etc. Such compositions may contain components conventional in pharmaceutical preparations, e.g. diluents, carriers, pH modifiers, sweeteners, bulking agents, and further active agents. If parenteral administration is desired, the compositions will be sterile and in a solution or suspension form suitable for injection or infusion. Such compositions form a further aspect of the invention.

[00259] According to another aspect, the present invention provides a pharmaceutical composition, which comprises a compound of Formula I or a pharmaceutically acceptable salt thereof, as defined hereinabove. In one embodiment, the pharmaceutical composition includes the compound of Formula I together with a pharmaceutically acceptable diluent or carrier.

[00260] According to another aspect, the present invention provides a compound of Formula I or a pharmaceutically acceptable salt thereof, for use in therapy, such as the treatment of a condition treatable with an inhibitor or TrkA and/or TrkB, such as a TrkA and/or TrkB mediated condition, such as one or more conditions described herein.

[00261] According to a further aspect, the present invention provides the use of a compound of Formula I or a pharmaceutically acceptable salt thereof, in the treatment of a condition that can be treated with an inhibitor of TrkA and/or TrkB, such as a TrkA and/or TrkB mediated condition, such as a condition as defined hereinabove. In one embodiment, the invention provides a compound of Formula I, or a pharmaceutically acceptable salt thereof, for use in the treatment of pain, cancer, inflammation, neurodegenerative disease or Trypanosoma cruzi infection.

[00262] In one embodiment, a compound of the invention is selected from any one of:

[00263] (R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

[00264] (R)-3-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,1-dimethylurea;

[00265] (R)-I-tert-butyl-3-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)urea;

[00266] (R)-I-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-phenylurea;

[00267] (R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)isobutyramide;
(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1-methyl-6-oxo-1,6-dihydropyridazine-3-carboxamide;

(R)-N-(5-(4,4-difluoro-2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)morpholine-4-carboxamide;

N-(5-(2-(3-fluorophenyl)-2-methylpyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-N-(5-(2-(3-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-N-(5-(2-(2-(difluoromethyl)-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)morpholine-4-carboxamide;

(S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide;

(3R,4R)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3,4-dihydroxypyrrolidine-1-carboxamide;

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)methoxyazetidine-1-carboxamide;

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-I-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-(4-fluorophenyl)urea;

(R)-I-(4-chlorophenyl)-3-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)urea;

(R)-I-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-(4-methoxyphenyl)urea;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)methoxyazetidine-1-carboxamide;
(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-N-(5-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)morpholine-4-carboxamide;

(S)-tert-butyl 4-(5-((R)-2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-ylcarbamoyl)-2-methylpiperazine-1-carboxylate;

(S)-N-(5-((R)-2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-methylpiperazine-1-carboxamide;

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-4-isopropylpiperazine-1-carboxamide;

(R)-N-(5-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-4-ethylpiperazine-1-carboxamide;

(R)-N-(5-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-4-methylpiperazine-1-carboxamide;

(S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3,5-dimethylpiperazine-1-carboxamide;

(S)-tert-butyl 4-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-ylcarbamoyl)-2-methylpiperazine-1-carboxylate;

(S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-methylpiperazine-1-carboxamide hydrochloride;

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-methyl 1-(5-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-ylcarbamoylcyclopropanecarboxylate;

(R)-I-(5-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-ylcarbamoylcyclopropanecarboxylic acid;

(S)-N-(5-((R)-2-(3-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide;

(R)-N-(5-((R)-2-(2-(difluoromethyl)-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide;

(S)-N-(5-((R)-2-(2-(difluoromethyl)-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide;
(R)-N<5-(2-(2-(difluoromethyl)-5-fluorophenyl)pyrrolidin-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-4-hydroxypiperidine-1-carboxamide;

(R)-N-(5-((R)-2-(2-(difluoromethyl)-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypiperidine-1-carboxamide;

(S)-N-(5-((R)-2-(2-(difluoromethyl)-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypiperidine-1-carboxamide;

(R)-N-(5-((R)-2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypiperidine-1-carboxamide;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-4-hydroxypiperidine-1-carboxamide;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypiperidine-1-carboxamide;

(S)-N-(5-((R)-2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypiperidine-1-carboxamide;

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)pivalamide;

(R)-tert-butyl 3-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)carbamoyl)azetidine-1-carboxylate;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)azetidine-3-carboxamide;

(R)-tert-butyl 4-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)carbamoyl)-4-methylpiperidine-1-carboxylate;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-4-methylpiperidine-4-carboxamide;

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-2-hydroxy-2-methylpropanamide;

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1-(trifluoromethyl)cyclopropanecarboxamide;

(R)-l-cyano-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)cyclopropanecarboxamide;

(R)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-2-methylpyrrolidine-2-carboxamide;
(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-2-fluoro-2-methylpropanamide;

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-2-(isopropylamino)thiazole-4-carboxamide;

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-2-methyl-2-(1H-1,2,4-triazol-1-yl)propanamide;

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)pyrazine-2-carboxamide;

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-5-methylpyrazine-2-carboxamide;

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)picolinamide;

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-6-methylpicolinamide;

(R)-5-chloro-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)picolinamide;

(R)-4-chloro-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)picolinamide;

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-methylpicolinamide;

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxy-2,2-dimethylpropanamide;

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1-hydroxy eylopopenacarboxamide;

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-2-methyl-2-(methylamino)propanamide;

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)pyrimidine-2-carboxamide;

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)picolinamide;

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-methylpicolinamide;
(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1-methyl-2-oxo-1,2-dihydropyridine-4-carboxamide;

(R)-6-chloro-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)picolinamide;

(R)-4-(ethylsulfonamido)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)benzamide;

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1-methyl-1H-pyrazole-3-carboxamide;

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1H-pyrazole-3-carboxamide;

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-6-methoxypicolinamide;

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)nicotinamide;

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)isonicotinamide;

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-6-methylnicotinamide;

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-2-methoxynicotinamide;

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-methylisonicotinamide;

(S)-N-(5-((R)-2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide;

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-5-methylpyrazine-2-carboxamide;

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1-methyl-1H-imidazole-2-carboxamide;

(S)-N-(5-((R)-2-(5-fluoro-2-(trifluoromethyl)phenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide;

(R)-N-(5-((R)-2-(5-fluoro-2-(trifluoromethyl)phenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide;
(R)-N-(5-((R)-2-(5-fluoro-2-(trifluoromethyl)phenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypiperidine-1-carboxamide;

(S)-N-(5-((R)-2-(5-fluoro-2-(trifluoromethyl)phenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypiperidine-1-carboxamide;

(S)-N-(5-((R)-2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide;

(R)-N-(5-((R)-2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide;

(S)-N-(5-((R)-2-(5-fluoro-2-methoxyphenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide;

(S)-N-(5-((R)-2-(5-fluoro-2-methoxyphenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide;

(I,S,4S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-2-oxa-5-azabicyclo[2.2.1]heptane-5-carboxamide;

(R)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxytetrahydropyran-4-carboxamide;

(I,S,3R)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxycyclopentanecarboxamide;

(I,S,3S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxycyclopentanecarboxamide;

(R)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxytetrahydropyran-4-carboxamide;

(I,S,3S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxytetrahydropyran-4-carboxamide;

(R)-N-1-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-N2,N2-dimethyloxalamide;

(R)-N-1-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-N2-methyloxalamide;

(R)-N-1-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)oxalamide;

(R)-N-1-cyclopropyl-N2-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)oxalamide;

(R)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-2-(3-hydroxyazetidin-1-yl)-2-o xoacetamide;
[00364] N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-2-((S)-3-hydroxypyrrolidin-1-yl)-2-oxoacetamide;
[00365] (R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-2-morpholino-2-oxoacetamide;
[00366] (R)-methyl 2-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-ylamino)-2-oxoacetate;
[00367] (R)-2-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-ylamino)-2-oxoacetic acid;
[00368] and salts thereof.
[00369] Particular examples of salts of the above compounds include hydrogen sulfate salts, hydrochloride salts and trifluoroacetate salts.

Examples

[00370] The following examples illustrate the invention. In the examples described below, unless otherwise indicated all temperatures are set forth in degrees Celsius. Reagents were purchased from commercial suppliers such as Aldrich Chemical Company, Lancaster, TCI or Maybridge, and were used without further purification unless otherwise indicated. Tetrahydrofuran (THF), dichloromethane (DCM, methylene chloride), toluene, and dioxane were purchased from Aldrich in Sure/Seal™ bottles and used as received.

[00371] The reactions set forth below were done generally under a positive pressure of nitrogen or argon or with a drying tube (unless otherwise stated) in anhydrous solvents, and the reaction flasks were typically fitted with rubber septa for the introduction of substrates and reagents via syringe. Glassware was oven dried and/or heat dried.

[00372] Column chromatography was done on a Biotage system (Manufacturer: Dyax Corporation) having a silica gel or C-18 reverse phase column, or on a silica SepPak cartridge (Waters).

[00373] Acronyms found in the examples have the following meanings:

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>CDI</td>
<td>carbonyldiimidazole</td>
</tr>
<tr>
<td>DIEA</td>
<td>diisopropylethylamine</td>
</tr>
<tr>
<td>DCM</td>
<td>dichloromethane</td>
</tr>
<tr>
<td>DME</td>
<td>dimethoxyethane</td>
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<td>DMF</td>
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<td>O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate</td>
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<tr>
<td>PS-DMAP</td>
<td>polystyrene-bound dimethylaminopyridine</td>
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<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
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</table>
An enzyme-linked immunosorbent assay (ELISA) was used to assess TrkA kinase activity in the presence of inhibitors. Immulon 4HBX 384-well microtiter plates (Thermo part #8755) were coated with a 0.025 mg/mL solution of poly (Glu, Ala, Tyr; 6:3:1; Sigma P3899). Various concentrations of test compound, 2.5 nM TrkA (Invitrogen Corp., histidine-tagged recombinant human TrkA, cytoplasmic domain), and 500 µM ATP were incubated for 25 minutes at ambient temperature in the coated plates while shaking. The assay buffer consisted of 25 mM MOPS pH 7.5, 0.005% (v/v) Triton X-100 and 5 mM MgCl₂. The reaction mixture was removed from the plate by washing with PBS containing 0.1% (v/v) Tween 20. The phosphorylated reaction product was detected using 0.2 µg/mL of a phosphotyrosine specific monoclonal antibody (clone PY20) conjugated to horseradish peroxidase in conjunction with the TMB Peroxidase Substrate System (KPL). After the addition of 1M phosphoric acid, the chromogenic substrate color intensity was quantitated via absorbance at 450 nm. IC50 values were calculated using either a 4 or 5-parameter logistic curve fit.

In this assay, compounds of the invention had an average IC₅₀ below 1000 nM. Certain compounds had an average IC₅₀ below 100 nM. Table 1 provides specific IC₅₀ values for compounds of this invention when tested in this assay.

Table 1

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<th>TrkA Elisa Enzyme IC₅₀ (nM)</th>
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Example B
TrkA and TrkB Omnia Assay

Trk enzymatic selectivity was assessed using Omnia™ Kinase Assay reagents from Invitrogen Corp. Enzyme (either TrkA or TrkB from Invitrogen Corp.) and test compound (various concentrations) were incubated for 10 minutes at ambient temperature in a 384-well white polypropylene plate (Nunc catalog# 267462). Omnia Tyr Peptide #4 (for TrkA) or #5 (for TrkB), as well as ATP, were then added to the plate. Final concentrations were as follows: 20 nM enzyme, 500 µM of ATP for TrkA assay or 1 mM ATP for TrkB assay, 10 µM peptide substrate. The assay buffer consisted of 25 mM MOPS pH 7.5, 0.005% (v/v) Triton X-100 and 5 mM MgCl₂. The production of phosphorylated peptide was monitored continuously for 70 minutes using a Molecular Devices FlexStation II microplate reader (excitation = 360 nm; emission = 485 nm). Initial rates were calculated from the progress curves. IC₅₀ values were then calculated from these rates using either a 4 or 5-parameter logistic curve fit.

In this assay, compounds of the invention had an average IC₅₀ below 1000 nM. Certain compounds had an average IC₅₀ below 100 nM.

Preparation A

Preparation of (R)-2-(2,5-difluorophenyl)pyrrolidine

Step A: Preparation of (PQ-tert-butyl 2-(2,5-difluorophenyl)pyrrolidine-1-carboxylate: A solution of tert-butylpyrrolidine-1-carboxylate (20 g, 116.8 mmol) and (-)sparteine (32.9, 140 mmol) in MTBE (360 mL) was cooled to -78 °C, and sec-BuU (100 mL, 140 mmol, 1.4 M in cyclohexane) was introduced dropwise via cannula, keeping the internal temperature under -70 °C. The resulting solution was stirred for 3 hours at -78 °C, followed by addition of a solution of ZnCl₂ (93.4 mL, 93.4 mmol, 1 M in Et₂O) drop-wise with rapid stirring, keeping the internal temperature below -65 °C. The resulting light suspension was stirred at -78 °C for 30 minutes and then warmed to ambient temperature. The resulting mixture was charged with 2-bromo-1,4-difluorobenzene (14.5 mL, 128 mmol), followed by Pd(OAc)₂ (1.31 g, 5.8 mmol) and t-Bu₃P-HBF₄ (2.03 g, 7.0 mmol) in one portion. After stirring overnight at ambient temperature, 10.5 mL of NH₄OH solution was added and the reaction was stirred for another hour. The resulting slurry was filtered through
CELITE and washed with Et₂O (1 L). The filtrate was washed with HCl (0.5 L, 1M aq.) and brine. The organic layer was filtered and concentrated, and the crude product was purified by silica column chromatography, eluting with 5-10% EtOAc/hexanes to give product (R)-tert-butyl 2-(2,5-difluorophenyl)pyrrolidine-1-carboxylate as yellow oil (23.9 g, 72% yield).

[00379] Step B: Preparation of (RV2-(2.5-difluorophenyl)pyrrolidine: To (R)-tert-butyl 2-(2,5-difluorophenyl)pyrrolidine-1-carboxylate (23.9 g, 84.4 mmol) was added 56.2 mL 4N HCl (dioxane). After stirring at ambient temperature for 2 hours, 200 mL of ether was added and the mixture was stirred for 10 minutes. The resulting slurry was filtered, yielding the hydrochloride salt of the product as a white solid (17.2 g). To obtain the free base, the HCl salt product was dispersed in a mixture of EtOAc (200 mL) and NaOH solution (100 mL, 2 N aq.) The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic extracts were filtered and concentrated to give the desired product as a liquid (13.2 g, 85% yield).

[00380] Step C: Determination of Enantiomeric Excess (ee%) of (RV2-(2.5-difluorophenyl)pyrrolidine: To an ethanol solution of (R)-2-(2,5-difluorophenyl)pyrrolidine was added excess N-(2,4-dinitro-5-fluorophenyl)-L-alanine amide (FDAA, Marfey's reagent). The mixture was heated to reflux for approximately two minutes. After cooling to ambient temperature, the reaction mixture was diluted with acetonitrile and injected onto HPLC (YMC ODS-AQ 4.6 x 50 mm 3 μm 120A column; mobile phase: 5-95% solvent B in A; solvent A: H₂O/ 1% IPA/ 10 mM ammonium acetate, and solvent B: ACN/1% IPA/10 mM ammonium acetate; flow rate: 2 mL/min) to determine the enantiomeric excess of the product by calculating the peak areas of the two diastereomeric derivatives formed. A 1:1 racemic sample was prepared according the same procedure described herein, replacing (R)-2-(2,5-difluorophenyl)pyrrolidine with (rac)-2-(2,5-difluorophenyl)pyrrolidine. The ee% of the product obtained as described above was determined to be > 93%.

**Preparation B**

![Preparation of (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo π,5-alpyrimidin-3-amine](image-url)
Step A: Preparation of (RV5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine : In a pressure reaction tube was added 5-chloropyrazolo[1,5-a]pyrimidine (4.2 g, 27 mmol), (R)-2-(2,5-difluorophenyl)pyrrolidine (Preparation A; 5.3 g, 29 mmol), anhydrous n-butanol (5 ml, 55 mmol), and DIEA (9.5 ml, 55 mmol). The yellowish suspension was sealed and heated in an oil bath (160 °C) overnight. The reaction was cooled to ambient temperature, diluted with EtOAc (250 mL), and filtered, rinsing the solid with EtOAc. The filtrate (330 mL) was washed with water (2 x 150 mL), brine (100 mL), concentrated, and purified by silica chromatography, eluting with 2:1 EtOAc/hexanes to give the product as a bright yellowish solid (5.6 g, 68% yield).

Step B: Preparation of (RV5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-3-nitropyrazolo[1,5-a]pyrimidine : (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine (3.3 g, 10.99 mmol), was dissolved in 25 mL TFA at ambient temperature to give a clear yellowish solution, then nitric acid (3.434 mL, 54.94 mmol) was added drop-wise to the solution with rapid stirring. After addition, the reaction mixture was stirred for another 15 minutes at ambient temperature, then quenched by pouring onto ice with rapid stirring. The resulting yellowish suspension was filtered, rinsed with water, then the solid was triturated with MeOH (50 mL, with brief sonication), and vacuum-filtered, giving the pure product as a fine off-white powder (2.2 g, 58% yield).

Step C: Preparation of (RV5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine: To a yellowish solution of (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-3-nitropyrazolo[1,5-a]pyrimidine (2.3 g, 6.66 mmol), in a 1:1 mixture of MeOH/DCM (30 mL/30 mL) was added Zn dust (4.36 g, 66.6 mmol) [<10 micron, Aldrich] while stirring. Saturated NH₄Cl aqueous solution (30 mL) was added drop-wise to this suspension with rapid stirring. After NH₄Cl addition was complete, the reaction mixture was allowed to cool to ambient temperature and stirred for another 15 minutes. The reaction was diluted with DCM (50 mL) and filtered through a GF/F paper, rinsing the wet cake with DCM. The organic layer of the filtrate was separated, and the aqueous layer was extracted with DCM (2 x 50 mL). The organic layers were combined, washed with brine (100 mL), dried over Na₂SO₄, and concentrated, to provide the basically pure product as a brownish foamy solid (2.08 g, 99% yield), which was used without further purification.
**Example 1**

![Chemical structure](attachment:structure.png)

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)3-hydroxyazetidine-1-carboxamide sulfate (38 mg, 0.074 mmol, 70% yield) as a yellow solid.

**Example IA**

![Chemical structure](attachment:structure.png)

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-alpyrimidin-3-yl)-3 hydroxyazetidine-1-carboxamide sulfate (38 mg, 0.074 mmol, 70% yield) as a yellow solid.

[00384] To a DCM (1.0 mL) solution of (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine (Preparation B; 50 mg, 0.16 mmol), was added CDI (39 mg, 0.24 mmol) at ambient temperature in one portion. After stirring two hours, azetidin-3-ol hydrochloride (35 mg, 0.32 mmol) [purchased from Oakwood] was added in one portion, followed by addition of DIEA (0.083 mL, 0.48 mmol). After stirring for 5 minutes, the reaction was concentrated and directly purified by reverse-phase column chromatography, eluting with 5 to 48% acetonitrile/water to yield the final product as a yellowish foamy powder (66 mg, 100% yield). MS (apci) m/z = 415.2 (M+H).

**Example 1A**

To a solution of (R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-alpyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide (44 mg, 0.11 mmol) in methanol (3 mL) at ambient temperature was added sulfuric acid in methanol (531 µL, 0.11 mmol). The resulting solution was stirred for 30 minutes then concentrated to provide (R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-alpyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide sulfate (38 mg, 0.074 mmol, 70% yield) as a yellow solid.
Example IB

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide hydrochloride

[00386] To a methanol (1 mL) solution of (R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide (5.2 mg, 0.013 mmol) was added HCl as a solution in dioxane (30 µL). After 30 minutes, the reaction was concentrated to provide (R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide hydrochloride (5.7 mg, 0.013 mmol, 101% yield) as a yellow solid.

Example 2

(R)-3-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolyl,5-alpyrimidin-3-yl)-l,l-dimethylurea

[00387] To a DCM (0.8 mL) solution of (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine (Preparation B; 30 mg, 0.095 mmol) was added CDI (31 mg, 0.19 mmol) at ambient temperature in one portion. After stirring two hours, dimethylamine (0.095 mL x 2 N THF, 0.19 mmol) was added in one portion. The reaction was stirred for 5 minutes, then concentrated, and the residue was directly purified by reverse-phase column chromatography, eluting with 0 to 60% acetonitrile/water to yield the final product as a yellowish foamy powder (33 mg, 90% yield). MS (apci) m/z = 387.2 (M+H).

Example 2A
(R)-3-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,1-dimethylurea hydrochloride

[00388] To a methanol (1 mL) solution of (R)-3-(5-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,1-dimethylurea (8.5 mg, 0.022 mmol) was added HCl as a solution is dioxane (30 µL). After 30 minutes, the reaction was concentrated to provide (R)-3-(5-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,1-dimethylurea hydrochloride (6.7 mg, 0.016 mmol, 72% yield) as a yellow solid.

Example 3

(R)-1-tert-butyl-3-(5-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine

[00389] To a DCM (0.8 mL) solution of (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine (Preparation B; 25 mg, 0.079 mmol) was added 2-isocyanatobenzene (9.4 mg, 0.095 mmol) at ambient temperature drop-wise, followed by addition of DIEA (0.028 mL, 0.16 mmol). The reaction was stirred for 4 hours then concentrated, and the residue was directly purified by reverse-phase chromatography, eluting with 5 to 65% acetonitrile/water to yield the final product as a pale-yellowish solid (27 mg, 82% yield). MS (apci) m/z = 415.1 (M+H).

Example 4

(R)-1-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)phenylurea

[00390] To a DCM (0.8 mL) solution of (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine (Preparation B; 25 mg, 0.079 mmol) was added isocyanatobenzene (19 mg, 0.16 mmol) at ambient temperature drop-wise. The reaction was stirred for 5 minutes then concentrated, and the residue was directly purified by reverse-phase
column chromatography, eluting with 5 to 60% acetonitrile/water to yield the final product as a pale-yellowish solid (30 mg, 87% yield). MS (apci) m/z = 435.2 (M+H).

**Example 4A**

(R)-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-phenylurea sulfate

[00391] To a solution of (R)-l-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-phenylurea (10.1 mg, 0.0232 mmol) in methanol (0.5 mL) at ambient temperature was added sulfuric acid in methanol (232 µL, 0.0232 mmol). The resulting solution was stirred for 30 minutes then concentrated to provide (R)-l-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-phenylurea sulfate (12 mg, 0.0225 mmol, 96.9 % yield) as a yellow solid.

**Example 5**

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-vDisobutyramide

[00392] A DCM (0.5 mL) solution of (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine (Preparation B; 20 mg, 0.063 mmol) was cooled in an ice bath, followed by addition of isobutyric anhydride (11.0 mg, 0.070 mmol) and pyridine (10 mg, 0.12 mmol) drop-wise. The reaction was allowed to warm up to ambient temperature and stirred for 1 hour. The reaction mixture was directly purified by reverse-phase column chromatography, eluting with 5 to 60% acetonitrile/water to yield the final product as a yellowish foamy solid (17 mg, 71%). MS (apci) m/z = 386.2 (M+H).
Example 6

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-alpyrimidin-3-yl)-1-methyl-6-oxo-1,6-dihydropyridazine-3-carboxamide

[00393] Step A: Preparation of (RV5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine: Prepared according to the method of Preparation B, substituting (R)-2-(2,5-difluorophenyl)pyrrolidine in Step A with (R)-2-(3-fluorophenyl)pyrrolidine.

[00394] Step B: Preparation of (R)-2-(3-fluorophenyl)pyrrolidine: Prepared by the method of Preparation A, substituting 2-bromo-l,4-difluorobenzene with l-bromo-3-fluorobenzene in step A.

[00395] Step C: Preparation of (R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-alpyrimidin-3-yl)-1-methyl-6-oxo-1,6-dihydropyridazine-3-carboxamide:

To a mixture of (R)-5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine (30 mg, 0.10 mmol), 1-methyl-β-oxo-1,6-dihydropyridazine-S-carboxylic acid (34 mg, 0.22 mmol), and HATU (84 mg, 0.22 mmol) was added 0.8 mL DMF to make a solution. After cooling in an ice bath for 10 minutes, DIEA (0.053 mL, 0.30 mmol) was added to the reaction drop-wise. The reaction was allowed to warm up to ambient temperature and stirred overnight. The resulting fine yellowish suspension from the reaction mixture was filtered, rinsed with first DMF and then ether, to provide the final product as a yellowish solid (14.4 mg, 33% yield). MS (apci) m/z = 434.2 (M+H).

Example 7

(R)-N-(5-(4,4-difluoro-2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazololo 1,5-alpyrimidin-3-yD-3-hydroxyazetidine-1-carboxamide
Steps A1-A6: Preparation of (R)-4,4-difluoro-2-(3-fluorophenyl)-pyrrolidine:

Step A1. Preparation of (R)-3-(tert-butyldimethylsilyloxy)-5-(3-fluorophenyl)-3,4-dihydro-2H-pyrrole: (3-Fluorophenyl)magnesium bromide (203.2 mL x 0.5 M ether, 102 mmol) was slowly added (via syringe) to a solution of (R)-3-(tert-butyldimethylsilyloxy)-4-chlorobutanenitrile (9.5 g, 40.6 mmol) in 120 mL of MTBE. The reaction was stirred for two hours and then DME (35 mL) was slowly added over 15 minutes, followed by EtOH (23 mL). After stirring for overnight, brine and 1 M NaOH (50 mL each) were added to the reaction. After stirring for one hour, the reaction mixture was filtered through Celite, rinsing the solid with EtOAc. The filtrate was washed with 1 N NaOH and brine, filtered through Phase Separator filter paper, and concentrated, yielding the crude product, which was carried to the next step without further purification (12.8 g, 107% yield).

Step A2. Preparation of (3R,5R)-5-(3-fluorophenyl)pyrrolidin-3-ol: (R)-3-(tert-butyldimethylsilyloxy)-5-(3-fluorophenyl)-3,4-dihydro-2H-pyrrole (5.0 g, 17.0 mmol) was dissolved in 50 mL methanol and 10 mL AcOH and cooled to -40 °C. NaBH₄ (1.6 g, 43 mmol) was slowly added in small portions. The reaction was allowed to warm to ambient temperature. Most of the solvent was removed by rotary evaporation. The reaction was taken up in 200 mL of EtOAc, washed with 1 N NaOH, and filtered through Phase Separator filter paper, and concentrated. The crude product was taken up in 20 mL of 2 N HCl in dioxane. The reaction was concentrated, taken up in 200 mL of EtOAc, washed with 1 N NaOH, filtered, and concentrated, yielding the crude product, which was carried to the next step without further purification (2.93 g, 95% yield).

Step A3. Preparation of (2R,4R)-tert-butyl 2-(3-fluorophenyl)-4-hydroxypyrrolidine-1-carboxylate: To a mixture of (3R,5R)-5-(3-fluorophenyl)pyrrolidin-3-ol (3.4 g, 18.8 mmol), di-tert-butyl dicarbonate (4.91 g, 22.5 mmol), and PS-DMAP (2.29 g, 18.8 mmol) were added 100 mL DCM and 50 mL THF, and the reaction was left to stand for one week with periodic sonication treatment. The mixture was filtered, concentrated, and purified by silica column chromatography, eluting with 2-10% MeOH/DCM to yield the pure product (4 g, 76% yield).

Step A4. Preparation of (R)-tert-butyl 2-(3-fluorophenyl)-4-oxopyrrolidine-1-carboxylate: (2R,4R)-tert-Butyl 2-(3-fluorophenyl)-4-hydroxypyrrolidine-1-carboxylate (1.4 g, 4.98 mmol) and Dess-Martin periodinane (2.53 g, 5.97 mmol) were mixed in 50 mL DCM and stirred at ambient temperature overnight. For workup, 20 mL IN NaOH was added to reaction, and stirred for 30 minutes, followed by addition of 20 mL brine. The
reaction mixture was extracted with several portions of DCM. The combined organic extracts were filtered through a Phase Separator filter paper, concentrated, and purified by reverse phase chromatography, eluting with 20-70% acetonitrile/water to yield the product as yellow oil (600 mg, 43% yield.)

Step A5. Preparation of (R)-tert-butyl 4,4-difluoro-2-(3-fluorophenyl)pyrrolidine-1-carboxylate: (R)-tert-butyl 2-(3-fluorophenyl)-4-oxopyrrolidine-1-carboxylate (200 mg, 0.72 mmol) and Bis(2-methoxyethyl)aminosulfur trifluoride (238 mg, 1.07 mmol) were mixed in 25 mL DCM and stirred at ambient temperature overnight. For workup, 5 mL IN NaOH was added and the reaction stirred for 30 minutes. The reaction was filtered through Celite, rinsing with DCM. Brine (2 mL) was added to the filtrate and the mixture was filtered through a Biotage Phase Separator frit, washing with several portions of DCM. The combined organic extracts were concentrated and purified by reverse phase chromatography, eluting with 20-90% acetonitrile/water to yield the product as clear oil (180 mg, 83%).

Step A6. Preparation of (R)-4,4-difluoro-2-(3-fluorophenyl)pyrrolidine: To (R)-tert-butyl 4,4-difluoro-2-(3-fluorophenyl)pyrrolidine-1-carboxylate (180 mg, 0.6 mmol) in a pressure reaction tube was added a solution of HCl (2 mL, 4 N dioxane, 8 mmol), then the reaction was sealed and heated at 60 °C for 4 hours. For workup, the reaction was poured into a mixture of ice and 1 M NaOH, and extracted with several portions of EtOAc. The combined organic extracts were filtered through a Phase Separator filter paper and concentrated, yielding the final product as clear oil, which was used in the next step without further purification.

Step B: Preparation of (R)-5-(4,4-difluoro-2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine: Prepared according to the method of Preparation B, substituting (R)-2-(2,5-difluorophenyl)pyrrolidine in Step 1 with (R)-4,4-difluoro-2-(3-fluorophenyl)pyrrolidine.

Step C: Preparation of (R)-N-(5-(4,4-difluoro-2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)azetidine-1-carboxamide: To a DCM (0.7 mL) solution of (R)-5-(4,4-difluoro-2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine (25 mg, 0.074 mmol), was added CDI (18 mg, 0.11 mmol) at ambient temperature in one portion. After stirring two hours, azetidin-3-ol hydrochloride (16 mg, 0.15 mmol) was added in one portion, followed by addition of DIEA (0.039 mL, 0.22 mmol). The reaction was stirred overnight, then concentrated, and the residue was directly purified by reverse-
phase column chromatography, eluting with 0 to 45% acetonitrile/water to yield the final product as a yellowish oil (15 mg, 48% yield). MS (apci) m/z = 433.1 (M+H).

**Example 8**

![Chemical structure](image)

(R^N-fS-fl-fl-chloro-S-fluoropheny πpyrrolidin-l-ν πpyrazolo^fl-alpyrimidin-S-vD-S- hydroxyazetidine- 1-carboxamide

[00405] Step A: Preparation of (RV5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-vDpyrazolo[1,5-alpyrimidin-3-amine]: Prepared according to the method of Preparation B, substituting (R)-2-(2,5-difluorophenyl)pyrrolidine in Step 1 with (R)-2-(2-chloro-5-fluorophenyl)pyrrolidine.


[00407] Step C: Preparation of (R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-alpyrimidin-3-yl)-3-hydroxyazetidine- 1-carboxamide: To a DCM (0.8 mL) solution of (R)-5-(2-(2-chloro-5-fluorophenyl)pyrrolidin- 1-yl)pyrazolo[1,5-alpyrimidin-3-amine (30 mg, 0.090 mmol) was added CDI (29 mg, 0.18 mmol) at ambient temperature in one portion. After stirring two hours, azetidin-3-ol hydrochloride (20 mg, 0.18 mmol) was added in one portion, followed by addition of DIEA (0.047 mL, 0.27 mmol). The reaction was stirred for 5 minutes before it was concentrated and directly purified by reverse-phase column chromatography, eluting with 5 to 50% acetonitrile/water to yield the final product as a yellowish foamy powder (33 mg, 85% yield). MS (apci) m/z = 431.1 (M+H).

**Example 8A**

![Chemical structure](image)

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolori,5-alpyrimidin-3-yl)-3-hydroxyazetidine- 1-carboxamide
To a solution of (R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-l-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-l-carboxamide (11.1 mg, 0.0258 mmol) in methanol (1 mL) at ambient temperature was added sulfuric acid in methanol (258 µL, 0.0258 mmol). The resulting solution was stirred for 30 minutes then concentrated to provide (R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-l-carboxamide sulfate (10 mg, 0.0189 mmol, 73.4 % yield) as a yellow solid.

Example 9

\[
\text{(R)-N-(5-\text{-(2-(3-fluorophenyl)pyrrolidin-l-yl)pyrazolo[1,5-a]pyrimidin-3-yl})morpholine-4-carboxamide}
\]

Step A: Preparation of (R)-5-(2-(3-fluorophenyl)pyrrolidin-l-ympyrrozolπ.5-alpyrimidin-3-amine: Prepared according to the method of Preparation B, substituting (R)-2-(2,5-difluorophenyl)pyrrolidine in Step A with (R)-2-(3-fluorophenyl)pyrrolidine.

Step B: Preparation of (R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-l-yl)pyrazolo[1,5-a]pyrimidin-3-yl)morpholine-4-carboxamide: To a DCM (0.8 mL) solution of (R)-5-(2-(3-fluorophenyl)pyrrolidin-l-yl)pyrazolo[1,5-a]pyrimidin-3-amine (50 mg, 0.17 mmol) was added CDI (41 mg, 0.25 mmol) at ambient temperature in one portion. After stirring two hours, morpholine (22 mg, 0.25 mmol) was added in one portion. The reaction was stirred for 5 minutes before it was concentrated and directly purified by reverse-phase column chromatography, eluting with 5 to 54% acetonitrile/water to yield the final product as a yellowish foamy powder (69 mg, 100% yield). MS (apci) m/z = 411.2 (M+H).

Example 10
N-(5-(2-(3-fluorophenyl)-2-methylpyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide

[00411] Step A: Preparation of tert-butyl 4-(3-fluorophenyl)O-4-oxobutylcarbamate: In a round-bottomed flask was charged tert-butyl 2-oxopyrrolidine-1-carboxylate (2.2 g, 11.9 mmol) and THF (25 mL). The mixture was cooled down to -78 °C first, followed by slow addition of (3-fluorophenyl)magnesium bromide (17.8 mL, 17.8 mmol, 1.0 M solution in THF) over 15 minutes. The mixture was stirred for 3 hours, during which time the bath temperature rose from -78 °C to -10 °C. The reaction was quenched by drop-wise addition of IN HCl (2 mL) and warmed up to ambient temperature, followed by addition of EtOAc and water. After separating the organic layer, the aqueous layer was extracted with EtOAc three times. The combined organic layers were dried over Na₂SO₄ and concentrated to yield the product as a clear oil.

[00412] Step B: Preparation of 5-(3-fluorophenyl)4,4-dihydro-2H-pyrrole: Crude tert-butyl 4-(3-fluorophenyl)-4-oxobutylcarbamate was dissolved in 10 mL CH₂Cl₂ first, followed by addition of 10 mL 4N HCl (dioxane). The reaction was stirred at ambient temperature for 4 hours and filtered, giving the HCl salt of the desired product as a white solid (~ 2 g). To obtain the free base product, EtOAc and saturated NaHCO₃ (aq.) solution were added to the HCl salt of the product. After separating the organic layer, the aqueous layer was extracted with EtOAc three times. The combined organic extracts was dried over Na₂SO₄ and concentrated to yield 5-(3-fluorophenyl)-3,4-dihydro-2H-pyrrole (1.46g, 75%).

[00413] Step C: Preparation of 2-(3-fluorophenyl)-2-methylpyrrolidine: A solution of 5-(3-fluorophenyl)-3,4-dihydro-2H-pyrrrole (6.1 g, 37.4 mmol) in 100 mL THF was cooled to -78 °C, and boron trifluoride diethyl etherate (9.47 mL, 74.8 mmol) was added drop-wise over 5 minutes. The resulting cloudy reaction mixture was stirred at -78 °C for 40 minutes. MeLi (1.6 M in diethyl ether, 46.7 mL, 74.8 mmol) was added drop-wise over 10 minutes. The mixture was stirred at -78 °C for another 2 hours, then warmed up to ambient temperature overnight. For workup, water and EtOAc were added to the reaction mixture, and the aqueous layer was acidified with HCl solution. After separating and discarding the organic layer, the aqueous layer was basified with NaOH (6 N, aq.) to pH = 12 and extracted twice with EtOAc. The combined organic extracts was dried over Na₂SO₄ and concentrated to get a mixture of the desired product (2-(3-fluorophenyl)-2-methylpyrrolidine) and starting material (4.3 g, 1.3:1 of the desired product:starting material, 37% yield). The crude product was used in the next step without any further purification.
Step D: Preparation of 5-(2-(3-fluorophenyl)-2-methylpyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine: Prepared according to the method of Preparation B, substituting (R)-2-(2,5-difluorophenyl)pyrrolidine in Step 1 with 2-(3-fluorophenyl)-2-methylpyrrolidine.

Step E: Preparation of N-(5-(2-(3-fluorophenyl)-2-methylpyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide: To a DCM (0.7 mL) solution of 5-(2-(3-fluorophenyl)-2-methylpyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine (25 mg, 0.08 mmol) was added CDI (20 mg, 0.12 mmol) at ambient temperature in one portion. After stirring one hour, azetidin-3-ol hydrochloride (20 mg, 0.12 mmol) was added in one portion, followed by addition of DIEA (0.028 mL, 0.16 mmol). The reaction was stirred for 30 minutes before it was concentrated and directly purified by reverse-phase column chromatography, eluting with 0 to 60% acetonitrile/water to yield the final product as a yellowish oil (18 mg, 55% yield). MS (apci) m/z = 411.2 (M+H).

Example 11

(R)-N-(5-(2-(3-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide

Step A: Preparation of (R)-5-(2-(3-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine: Prepared according to the method of Preparation B, substituting (R)-2-(2,5-difluorophenyl)pyrrolidine in Step A with (R)-2-(3-chloro-5-fluorophenyl)pyrrolidine.

Step B: Preparation of (R)-2-(3-chloro-5-fluorophenyl)pyrrolidine: Prepared by the method of Preparation A, substituting 2-bromo-1,4-difluorobenzene with 1-bromo-3-chloro-5-fluorobenzene in step A.

Step C: Preparation of (R)-N-(5-(2-(3-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide: To a DCM (0.7 mL) solution of (R)-5-(2-(3-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine (20 mg, 0.06 mmol, prepared as described in the following paragraph), was added CDI (20 mg, 0.12 mmol) at ambient temperature in one portion. After stirring two hours, azetidin-
3-ol hydrochloride (20 mg, 0.18 mmol) was added in one portion, followed by addition of DIEA (0.032 mL, 0.18 mmol). The reaction was stirred overnight before it was concentrated and directly purified by reverse-phase column chromatography, eluting with 0 to 60% acetonitrile/water to yield the final product as a solid (29 mg, 74% yield). MS (apci) m/z = 431.2 (M+H).

Example 12

(R)-N-(5-(2-(2-(difluoromethyl)-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide

Step A: Preparation of (R)-2-(2-(difluoromethyl)-5-fluorophenyl)pyrrolidin-1-ylpyrazolo[1,5-a]pyrimidin-3-amine: Prepared according to the method of Preparation B, substituting (R)-2-(2,5-difluorophenyl)pyrrolidine in Step A with (R)-2-(2-(difluoromethyl)-5-fluorophenyl)pyrrolidine.

Step B: Preparation of (R)-2-(3-chloro-5-fluorophenyl)pyrrolidine: Prepared by the method of Preparation A, substituting 2-bromo-1,4-difluorobenzene with 2-bromo-1-(difluoromethyl)-4-fluorobenzene in step A.

Step C: Preparation of (R)-5-(2-(2-(difluoromethyl)-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide: To a DCM (0.6 mL) solution of (R)-5-(2-(2-(difluoromethyl)-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine (10 mg, 0.028 mmol, prepared as described in the following paragraph), was added CDI (9 mg, 0.056 mmol) at ambient temperature in one portion. After stirring two hours, azetidin-3-ol hydrochloride (6 mg, 0.056 mmol) was added in one portion, followed by addition of DIEA (0.015 mL, 0.084 mmol). The reaction was stirred overnight before it was concentrated and directly purified by reverse-phase column chromatography, eluting with 0 to 50% acetonitrile/water to yield the final product as a solid. MS (apci) m/z = 447.2 (M+H).
Example 13

\(\text{(-N-fS-fl-fl^difuorophenyDpyrrolidin-l-y \_\_pyrazolorLS-alpyrimidin-S-yl)morpholine-4-carboxamide}\)

To a DCM (0.8 mL) solution of (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-l-yl)pyrazolo[1,5-a]pyrimidin-3-amine (Preparation B; 30 mg, 0.095 mmol) was added CDI (31 mg, 0.19 mmol) at ambient temperature in one portion. After stirring two hours, morpholine (17 mg, 0.19 mmol) was added in one portion. The reaction was stirred for 5 minutes before it was concentrated and directly purified by reverse-phase column chromatography, eluting with 5 to 55% acetonitrile/water to yield the final product as a yellowish foamy powder (37 mg, 91% yield). MS (apci) m/z = 429.2 (M+H).

Example 14

\((S)-\text{N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-l-yl)pyrazolo[1,5-alpyrimidin-3-yl)-__3-hydroxypyrrolidine-1-carboxamide}\)

To a DCM (0.8 mL) solution of (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-l-yl)pyrazolo[1,5-a]pyrimidin-3-amine (Preparation B; 30 mg, 0.095 mmol) was added CDI (31 mg, 0.19 mmol) at ambient temperature in one portion. After stirring two hours, (S)-pyrrolidin-3-ol (17 mg, 0.19 mmol) [purchased from Suven Life Sciences] was added in one portion. The reaction was stirred for 5 minutes before it was concentrated and directly purified by reverse-phase column chromatography, eluting with 0 to 50% acetonitrile/water to yield the final product as a yellowish foamy powder (30 mg, 74% yield). MS (apci) m/z = 429.2 (M+H).
Example 14A

(S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-l-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate

[00424] To a solution of (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-l-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide (4.5 mg, 0.011 mmol) in methanol (1 mL) at ambient temperature was added sulfuric acid in MeOH (105 μL, 0.011 mmol). The resulting solution was stirred for 30 minutes then concentrated to provide (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-l-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate (5.2 mg, 0.0099 mmol, 94 % yield) as a yellow solid.

Example 15

(3R,4R)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-l-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3,4-dihydroxypyrrolidine-1-carboxamide

[00425] To a DCM (0.8 mL) solution of (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-l-yl)pyrazolo[1,5-a]pyrimidin-3-amine (Preparation B; 26 mg, 0.08 mmol) was added CDI (27 mg, 0.16 mmol) at ambient temperature in one portion. After stirring two hours, (3R,4R)-pyrrolidine-3,4-diol (17.3 mg, 0.16 mmol) [obtained from benzyl de-protection of commercially available (3R,4R)-l-benzylpyrrolidine-3,4-diol] was added in one portion. A few drops of DMSO were added to obtain a clear reaction solution. The reaction was stirred for 5 minutes before it was concentrated and directly purified by reverse-phase column chromatography, eluting with 0 to 45% acetonitrile/water to yield the final product as a yellowish foamy powder (27 mg, 74% yield). MS (apci) m/z = 445.2 (M+H).
**Example 16**

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-methoxyazetidine-1-carboxamide

[00426] To a DCM (0.8 mL) solution of (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine (Preparation B; 30 mg, 0.095 mmol) was added CDI (31 mg, 0.19 mmol) at ambient temperature in one portion. After stirring two hours, 3-methoxyazetidine 2,2,2-trifluoroacetate (38 mg, 0.19 mmol) [obtained from N-de-protection of commercially available tert-butyl 3-methoxyazetidine-1-carboxylate using TFA in DCM] was added in one portion, followed by addition of DIEA (0.050 mL, 0.29 mmol). The reaction was stirred for 5 minutes before it was concentrated and directly purified by reverse-phase column chromatography, eluting with 0 to 55% acetonitrile/water to yield the final product as a yellowish foamy powder (34 mg, 83% yield). MS (apci) m/z = 429.2 (M+H).

**Example 16A**

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-methoxyazetidine-1-carboxamide sulfate

[00427] To a solution of (R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-methoxyazetidine-1-carboxamide (6.2 mg, 0.014 mmol) in methanol (1 mL) at ambient temperature was added sulfuric acid in methanol (145 µL, 0.014 mmol). The resulting solution was stirred for 30 minutes then concentrated to provide (R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-methoxyazetidine-1-carboxamide sulfate (7.2 mg, 0.014 mmol, 94 % yield) as a yellow solid.
Example 17

To a DCM (0.8 mL) solution of (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine (Preparation B; 30 mg, 0.095 mmol) was added CDI (31 mg, 0.19 mmol) at ambient temperature in one portion. After stirring two hours, 3-methoxyazetidine 3-methylazetidin-3-ol hydrochloride (26 mg, 0.19 mmol) [obtained from N-de-protection of commercially available 1-benzhydryl-3-methylazetidin-3-ol under hydrogenation conditions facilitated by Pd(OH)$_2$ in EtOH and 1% TFA] was added in one portion, followed by addition of DIEA (0.050 mL, 0.29 mmol). The reaction was stirred for 5 minutes before it was concentrated and directly purified by reverse-phase column chromatography, eluting with 0 to 50% acetonitrile/water to yield the final product as a yellowish foamy powder (27 mg, 66% yield). MS (apci) m/z = 429.2 (M+H).

Example 17A

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-alpyrimidin-3-yl)-3-hydroxy-3-methylazetidine- 1-carboxamide sulfate

To a solution of (R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxy-3-methylazetidine- 1-carboxamide (3.1 mg, 0.0072 mmol) in methanol (1 mL) at ambient temperature was added sulfuric acid in methanol (145 µL, 0.014 mmol). The resulting solution was stirred for 30 minutes then concentrated to provide(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxy-3-methylazetidine- 1-carboxamide sulfate (3.3 mg, 0.0063 mmol, 87% yield) as a yellow solid.
Example 17B

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-l-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-
hydroxy-3-methylazetidine-1-carboxamide hydrochloride

[00430] To a methanol (1 mL) solution of (R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide (10.2 mg, 0.0238 mmol) was added HCl as a solution is dioxane (30 µL). After 30 minutes, the reaction was concentrated to provide (R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide hydrochloride (8.3 mg, 0.0179 mmol, 75.0 % yield) as a yellow solid.

Example 18

(R)-l-(5-(2-(2,5-difluorophenyl)pyrrolidin-l-yl)pyrazolo[1,5-alpyrimidin-3-yl)-3-(4-
fluorophenyl)urea

[00431] To a DCM (0.8 mL) solution of (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-alpyrimidin-3-amine (Preparation B; 25 mg, 0.079 mmol) was added 1-fluoro-4-isocyanatobenzene (13 mg, 0.095 mmol) at ambient temperature drop-wise, followed by addition of DIEA (0.028 mL, 0.16 mmol). The reaction was stirred for 90 minutes before it was concentrated and directly purified by column chromatography on silica, eluting with 3:1 EtOAc/hexanes to yield the final product as a solid (30 mg, 84% yield). MS (apci) m/z = 453.2 (M+H).
Example 19

(R)-l-(4-chlorophenyl)-3-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazololo[1,5-a]pyrimidin-3-yl)pyrrolidin-3-yl)urea

Prepared by the method as described in Example 18, substituting l-fluoro-4-isocyanatobenzene with l-chloro-4-isocyanatobenzene, giving the final product as a fine white solid (33 mg, 89%). MS (apci) m/z = 469.1 (M+H).

Example 20

(R)-l-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-(4-methoxyphenyl)urea

Prepared by the method as described in Example 18, substituting l-fluoro-4-isocyanatobenzene with l-methoxy-4-isocyanatobenzene, and eluting with first 4:1 EtOAc/hexanes and then 100% EtOAc during silica column chromatography purification step, giving the final product as a fine white solid (34 mg, 92%). MS (apci) m/z = 465.2 (M+H).

Example 21

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-alpyrimidin-3-yl]-3-methoxyazetidine-1-carboxamide

Step B: Preparation of (R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yPpyrazolo[1,5-a]pyrimidin-3-yl)-3-methoxyazetidine-1-carboxamide: To a DCM (0.8 mL) solution of (R)-5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine (30 mg, 0.090 mmol) was added CDI (29 mg, 0.18 mmol) at ambient temperature in one portion. After stirring for two hours, 3-methoxyazetidine 2,2,2-trifluoroacetate (36 mg, 0.18 mmol) [obtained from N-de-protection of commercially available tert-butyl 3-methoxyazetidine-1-carboxylate using TFA in DCM] was added in one portion, followed by addition of DIEA (0.047 mL, 0.27 mmol). The reaction was stirred for 5 minutes before it was concentrated and directly purified by reverse-phase column chromatography, eluting with 5 to 60% acetonitrile/water to yield the final product as a yellowish foamy powder (36 mg, 89% yield). MS (apci) m/z = 445.2 (M+H).

Example 22

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-alpyrimidin-3-yl]-3-hydroxy-3-methylazetidine-1-carboxamide

Step 22: To a DCM (0.8 mL) solution of (R)-5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine (Example 8, Step A; 22 mg, 0.066 mmol) was added CDI (22 mg, 0.13 mmol) at ambient temperature in one portion. After stirring two hours, 3-methoxyazetidine 3-methylazetidin-3-ol hydrochloride (18 mg, 0.13 mmol) was added in one portion, followed by addition of DIEA (0.035 mL, 0.20 mmol). The reaction was stirred for 5 minutes before it was concentrated and directly purified by reverse-phase column chromatography, eluting with 5 to 50% acetonitrile/water to yield the final product as a yellowish foamy powder (21 mg, 71% yield). MS (apci) m/z = 445.2 (M+H).
Example 23

\[
\text{\(^{-}N\text{-}fS\text{-}fl\text{-}fl\text{-}chloro\text{-}S\text{-}fluorophenyl\ pyrrolidin-1\text{-}y pyrazolo[1,5-a]pyrimidin-3\text{-}yl\)morpholine-4\text{-}carboxamide}
\]

Prepared according to the method of Example 22, replacing (R)-5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine with morpholine to yield the product as a yellowish foamy powder (26 mg, 76% yield). MS (apci) m/z = 445.1 (M+H).

Example 24

\[
\text{(S)-tert-butyl 4-(5-((R)-2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-ylcarbamoyl)-2-methylpiperazine-1-carboxylate}
\]

Prepared according to the method of Example 22, replacing (R)-5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine with (S)-tert-butyl 2-methylpiperazine-1-carboxylate to yield the product as a yellowish foamy powder (47 mg, 80% yield). MS (apci) m/z = 558.1 (M+H).

Example 25

\[
\text{HCl}
\]
To (S)-tert-butyl 4-(5-((R)-2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-ylcarbamoyl)-2-methylpiperazine-1-carboxylate (Example 24; 47 mg, 0.084 mmol), was added 1 mL 4 N HCl (dioxane) solution and stirred at ambient temperature for 10 minutes. The reaction was concentrated, treated with ether, and filtered, giving the final product HCl salt as a fine beige powder. MS (apci) m/z = 458.1 (M+H).

Example 26

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-4-isopropylpiperazine-1-carboxamide

To a DCM (0.8 mL) solution of (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine (Preparation B; 30 mg, 0.095 mmol) was added CDI (31 mg, 0.19 mmol) at ambient temperature in one portion. After stirring two hours, 1-isopropylpiperazine (24 mg, 0.19 mmol) was added in one portion. The reaction was stirred for 5 minutes before it was concentrated and directly purified by reverse-phase column chromatography, eluting with 5 to 45% acetonitrile/water to yield the final product as a yellowish foamy powder (40 mg, 90% yield). MS (apci) m/z = 470.1 (M+H).

Example 27

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-4-ethylpiperazine-1-carboxamide
Prepared by the method as described in Example 26, substituting 1-isopropylpiperazine with 1-ethylpiperazine, giving the final product as a yellowish solid (40 mg, 92%). MS (apci) m/z = 456.1 (M+H).

Example 28

\[
(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-4-methylpiperazine-1-carboxamide
\]

Prepared by the method as described in Example 26, substituting 1-isopropylpiperazine with 1-methylpiperazine, giving the final product as a yellowish solid (38 mg, 90%). MS (apci) m/z = 442.2 (M+H).

Example 28A

\[
(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-4-methylpiperazine-1-carboxamide hydrochloride
\]

To a methanol (1 mL) solution of (R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-4-methylpiperazine-1-carboxamide was added HCl as a solution is dioxane (30 µL). After 30 minutes, the reaction was concentrated to provide (R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-4-methylpiperazine-1-carboxamide hydrochloride as a yellow solid.
N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-l-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3,5-
dimethylpiperazine-1-carboxamide

[00443] Prepared by the method as described in Example 26, substituting 1-
isopropylpiperazine with 2,6-dimethylpiperazine [predominantly cis, Aldrich], giving the final product as a yellowish solid (34 mg, 78%). MS (apci) m/z = 456.2 (M+H).

Example 30

(S)-tert-butyl 4-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-l-yl)pyrazolo[1,5-a]pyrimidin-3-ylcarbamoyl)-2-methylpiperazine-1-carboxylate

[00444] Prepared by the method as described in Example 26, substituting 1-isopropylpiperazine with (S)-tert-butyl 2-methylpiperazine-1-carboxylate, giving the final product as a yellowish solid (47 mg, 90%). MS (apci) m/z = 542.2 (M+H).

Example 31

(S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-l-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-
3-methylpiperazine-1-carboxamide hydrochloride

[00445] To (S)-tert-butyl 4-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-l-yl)pyrazolo[1,5-a]pyrimidin-3-ylcarbamoyl)-2-methylpiperazine-1-carboxylate (Example 30; 47 mg, 0.087 mmol), was added 1 mL 4 N HCl (dioxane) solution and stirred at ambient temperature for 1 hour. The reaction was concentrated, treated with ether, and filtered, giving the final product HCl salt as a fine yellowish powder. MS (apci) m/z = 442.2 (M+H).
Example 32

(R)-5-(2-(3-fluorophenyl)pyrrolidin-l-yl)pyrazolo[1,5-a]pyrimidin-3-amine

To a DCM (0.8 nL) solution of (R)-5-(2-(3-fluorophenyl)pyrrolidin-l-yl)pyrazolo[1,5-a]pyrimidin-3-amine (Example 6, Step A; 50 mg, 0.17 mmol) was added CDI (41 mg, 0.25 mmol) at ambient temperature in one portion. After stirring two hours, azetidin-3-ol hydrochloride (28 mg, 0.25 mmol) was added in one portion, followed by addition of DIEA (0.059 mL, 0.34 mmol). The reaction was stirred for 5 minutes before it was concentrated and directly purified by reverse-phase column chromatography, eluting with 5 to 55% acetonitrile/water to yield the final product as a yellowish foamy powder (64 mg, 96% yield). MS (apci) m/z = 397.2 (M+H).

Example 33

(R)-methyl 1-(5-(2-(2,5-difluorophenyl)pyrrolidin-l-yl)pyrazolo[1,5-alpyrimidin-3-y1][cyclopropanecarboxylate

To a mixture of (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-l-yl)pyrazolo[1,5-a]pyrimidin-3-amine (Preparation B; 43 mg, 0.14 mmol), 1-(methoxycarbonyl)cyclopropanecarboxylic acid (24 mg, 0.16 mmol), and HATU (62 mg, 0.16 mmol) was added 0.7 mL DMF to make a solution. After cooling in an ice bath for 10 minutes, DIEA (0.053 mL, 0.30 mmol) was added to the reaction drop-wise. The reaction was allowed to warm up to ambient temperature and stirred for 10 minutes. The reaction mixture was diluted with EtOAc (15 mL), washed with water, brine (5 mL each), concentrated, and purified by reverse-phase column chromatography, eluting with 5 to 72%
acetonitrile/water to yield the final product as a yellowish foamy powder (36 mg, 60% yield).
MS (apci) m/z = 442.2 (M+H).

Example 34

![Chemical Structure](attachment:image)

(R)-I-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-ylcarbamoyl)cyclopropanecarboxylic acid

[00448] (R)-methyl 1-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-ylcarbamoyl)cyclopropanecarboxylate (Example 33; 24 mg, 0.054 mmol), was dissolved in a mixture solvent of THF/MeOH/water (0.3/0.3/0.2 mL), followed by addition of lithium hydroxide monohydrate (6 mg, 0.14 mmol). After stirring at ambient temperature for five hours, the reaction mixture was diluted with water (15 mL), acidified with 1 N HCl (aq.) to pH ~ 3, and filtered, giving the final product as a fine white solid (19 mg, 82% yield). MS (apci) m/z = 428.2 (M+H).

Example 35

![Chemical Structure](attachment:image)

(S)-N-(5-((R)-2-(3-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)3-hydroxyxypyrrolidine-1-carboxamide

[00449] To a DCM (0.6 mL) solution of (R)-5-(2-(3-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine (Example 11, Step A; 20 mg, 0.06 mmol), was added CDI (20 mg, 0.12 mmol) at ambient temperature in one portion. After stirring two hours, (S)pyrrolidin-3-ol (16 mg, 0.18 mmol) was added in one portion. The reaction was stirred overnight before it was concentrated and directly purified by reverse-phase column chromatography, eluting with 0 to 60% acetonitrile/water to yield the final product as a solid (50 mg, 83% yield). MS (apci) m/z = 445.2 (M+H).
Example 36

(RVN-CS-CCRV1-Cl-Cdifluoromethyl-S-fluorophenyl-pyrrolidin-1-v-pyrazol-5-alpyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide

[00450] Step A: Preparation of (R)-5-(2-(2-(difluoromethyl)-5-fluorophenyl)pyrrolidin-1-v-pyrazolo[1,5-a]pyrimidin-3-amine: Prepared according to the method of Preparation B, substituting (R)-2-(2,5-difluorophenyl)pyrrolidine in Step 1 with (R)-2-(2-(difluoromethyl)-5-fluorophenyl)pyrrolidine.

[00451] Step B: Preparation of (R)-N-(5-((R)-2-(2-(difluoromethyl)-5-fluorophenyl)pyrrolidin-1-v-pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide: To a DCM (0.6 mL) solution of (R)-5-(2-(2-(difluoromethyl)-5-fluorophenyl)pyrrolidin-1-v-pyrazolo[1,5-a]pyrimidin-3-amine (10 mg, 0.028 mmol, prepared as described in the following paragraph), was added CDI (9 mg, 0.056 mmol) at ambient temperature in one portion. After stirring two hours, (S)-pyrrolidin-3-ol (8 mg, 0.084 mmol) was added in one portion. The reaction was stirred overnight, then concentrated and directly purified by reverse-phase column chromatography, eluting with 0 to 50% acetonitrile/water to yield the final product as a solid (9 mg, 69%). MS (apci) m/z = 461.2 (M+H).

Example 37

(S)-N-(5-((R)-2-(2-(difluoromethyl)-5-fluorophenyl)pyrrolidin-1-v-pyrazol-5-alpyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide

[00452] Prepared by the method as described in Example 36, substituting (S)-pyrrolidin-3-ol with (R)-pyrrolidin-3-ol, giving the final product as a solid (12 mg, 89%). MS (apci) m/z = 461.2 (M+H).
Example 38

(R)-N-(5-(2-(2-(difluoromethyl)-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-4-hydroxypiperidine-1-carboxamide

Prepared by the method as described in Example 36, substituting (S)-pyrrolidin-3-ol with piperidin-4-ol, giving the final product as a solid (11 mg, 80%). MS (apci) m/z = 475.2 (M+H).

Example 39

(R)-N-(5-((R)-2-(2-(difluoromethyl)-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypiperidine-1-carboxamide

Prepared by the method as described in Example 36, substituting (S)-pyrrolidin-3-ol with (R)-piperidin-3-ol hydrochloride (followed by addition of 3 equivalents of DIEA), giving the final product as a solid (10 mg, 74%). MS (apci) m/z = 475.2 (M+H).

Example 40

(S)-N-(5-((R)-2-(2-(difluoromethyl)-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypiperidine-1-carboxamide

Prepared by the method as described in Example 36, substituting (S)-pyrrolidin-3-ol with (S)-piperidin-3-ol hydrochloride (followed by addition of 3 equivalents of DIEA), giving the final product as a solid (11 mg, 80%). MS (apci) m/z = 475.2 (M+H).
Example 41

\[
\text{To a DCM (0.8 mL) solution of (R)-5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)hydroxypyrrolidine-1-carboxamide (10 mg, 0.030 mmol, prepared as described in Example 8) was added CDI (10 mg, 0.06 mmol) at ambient temperature in one portion. After stirring two hours, (S)-pyrrolidin-3-ol (5 mg, 0.06 mmol) was added in one portion. The reaction was stirred at ambient temperature for 20 hours before it was concentrated and directly purified by reverse-phase column chromatography, eluting with 5 to 50% acetonitrile/water to yield the final product as a solid (9 mg, 67% yield). MS (apci) m/z = 445.2 (M+H).}
\]

Example 42

\[
\text{(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-4-hydroxypiperidine-1-carboxamide}
\]

[00457] Prepared by the method as described in Example 41, substituting (S)-pyrrolidin-3-ol with piperidin-4-ol, giving the final product as a solid (8 mg, 60%). MS (apci) m/z = 459.2 (M+H).
(R)-N-(5-((R)-2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypiperidine-1-carboxamide

[00458] Prepared by the method as described in Example 41, substituting (S)-pyrrolidin-3-ol with (R)-piperidin-3-ol hydrochloride (followed by addition of 3 equivalents of DIEA), giving the final product as a solid (9.4 mg, 69%). MS (apci) m/z = 459.1 (M+H).

Example 44

(S)-N-(5-((R)-2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypiperidine-1-carboxamide

[00459] Prepared by the method as described in Example 41, substituting (S)-pyrrolidin-3-ol with (S)-piperidin-3-ol hydrochloride (followed by addition of 3 equivalents of DIEA), giving the final product as a solid (9.3 mg, 68%). MS (apci) m/z = 459.2 (M+H).

Example 45

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-alpyrimidin-3-yl]-3-hydroxypiperidine-1-carboxamide

[00460] A DCM (0.5 mL) solution of (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine (Preparation B; 20 mg, 0.063 mmol) was cooled in an ice bath, followed by addition of pivalic anhydride (26 mg, 0.14 mmol) and pyridine (12 mg, 0.14 mmol) drop-wise. The reaction was allowed to warm up to ambient temperature and stirred for 1 hour. The reaction mixture was directly purified by reverse-phase column chromatography, eluting with 5 to 65% acetonitrile/water to yield the final product as a yellowish foamy solid (19 mg, 75%). MS (apci) m/z = 400.2 (M+H).
Example 46

(R)-tert-butyl 3-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[4,5-a]pyrimidin-3-ylcarbamoyl)azetidine-1-carboxylate

To a mixture of (R)-5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine (Example 8, Step A; 20 mg, 0.06 mmol), L-(tert-butoxycarbonyl)azetidine-3-carboxylic acid (15 mg, 0.072 mmol), and HATU (28 mg, 0.072 mmol) was added 0.6 mL acetonitrile to make a solution. After cooling in an ice bath for 10 minutes, DIEA (0.032 mL, 0.18 mmol) was added to the reaction drop-wise. The reaction was allowed to warm up to ambient temperature and stirred overnight. The reaction mixture was directly purified by reverse-phase column chromatography, eluting with 5 to 70% acetonitrile/water to yield the final product as an off-white solid (19 mg, 61% yield). MS (apci) m/z = 515.0 (M+H).

Example 47

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolori,5-alpyrimidin-3-y]pyrazolylazetidine-3-carboxamide trifluoroacetate

To (R)-tert-butyl 3-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-ylcarbamoyl)azetidine-1-carboxylate (Example 46; 17 mg, 0.033 mmol), was added 0.5 mL 50% TFA solution in DCM and stirred at ambient temperature for 10 minutes. The reaction was concentrated, treated with ether, and filtered, giving the final product (TFA salt) as a fine beige powder (12 mg, 88% yield). MS (apci) m/z = 415.2 (M+H).
Example 48

(R)-tert-butyl 4-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-ylcarbamoyl)-4-methylpiperidine-1-carboxylate

To a mixture of (R)-5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine (Example 8, Step A; 25 mg, 0.075 mmol), L-(tert-butoxycarbonyl)-4-methylpiperidine-4-carboxylic acid (22 mg, 0.090 mmol), and HATU (34 mg, 0.090 mmol) was added 0.6 mL DMF to make a solution. After cooling in an ice bath for 10 minutes, DIEA (0.039 mL, 0.23 mmol) was added to the reaction dropwise. The reaction was allowed to warm up to ambient temperature and stirred overnight. The reaction mixture was directly purified by reverse-phase column chromatography, eluting with 5 to 80% acetonitrile/water to yield the final product as a yellowish powder (28 mg, 67% yield). MS (apci) m/z = 557.1 (M+H).

Example 49

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-alpyrimidin-3-yl)-4-methylpiperidine-4-carboxamide hydrochloride

To (R)-tert-butyl 4-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-alpyrimidin-3-yl)-4-methylpiperidine-1-carboxylate (Example 48; 28 mg, 0.05 mmol), was added 1 mL 4 N HCl solution in dioxane and stirred at ambient temperature for 10 minutes. The reaction was concentrated, treated with ether, and filtered, giving the final product (HCl salt) as a fine beige powder. MS (apci) m/z = 457.1 (M+H).
Example 50

\[ \text{To a mixture of} \ (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1-[\text{[00465]} \text{hydroxy-2-methylpropanamide}\]

\[ \text{[00465]} \text{To a mixture of} \ (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine (Preparation B; 25 mg, 0.079 mmol), 2-hydroxy-2-methylpropanoic acid (10 mg, 0.095 mmol), and HATU (36 mg, 0.095 mmol) was added 0.6 mL acetonitrile to make a solution. After cooling in an ice bath for 10 minutes, DIEA (0.041 mL, 0.24 mmol) was added to the reaction drop-wise. The reaction was allowed to warm up to ambient temperature and stirred overnight. The reaction mixture was concentrated, re-dissolved in methanol, and purified by reverse-phase column chromatography, eluting with 5 to 55% acetonitrile/water to yield the final product as an off-white solid (21 mg, 66% yield). MS (apci) m/z = 402.2 (M+H).\]

Example 51

\[ \text{(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-alpyrimidin-3-yl)-1-} \]

\[\text{(trifluoromethyl)cyclopropanecarboxamide)}\]

\[\text{[00466]} \text{To a mixture of} \ (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine (Preparation B; 25 mg, 0.079 mmol), 1-(trifluoromethyl)cyclopropanecarboxylic acid (15 mg, 0.095 mmol), and HATU (36 mg, 0.095 mmol) was added 0.6 mL DMF to make a solution. After cooling in an ice bath for 10 minutes, DIEA (0.041 mL, 0.24 mmol) was added to the reaction drop-wise. The reaction was allowed to warm up to ambient temperature and stirred overnight. The reaction mixture was diluted with EtOAc (15 mL), washed with water and brine (5 mL each), concentrated, and purified by reverse-phase column chromatography, eluting with 5 to 72% acetonitrile/water to yield the final product as a beige solid (23 mg, 63% yield). MS (apci) m/z = 452.2 (M+H).\]
**Example 52**

![Chemical Structure](attachment:image)

(R)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-alpyrimidin-3-yl]-2-methylpyrrolidine-2-carboxamide

Prepared by the method as described in Example 51, substituting 1-(trifluoromethyl)cyclopropanecarboxylic acid with 1-cyanocyclopropanecarboxylic acid, to provide the final product as a white solid (18 mg, 56% yield). MS (apci) m/z = 409.2 (M+H).

**Example 53**

![Chemical Structure](attachment:image)

(R)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-alpyrimidin-3-yl]-2-methylpyrrolidine-2-carboxamide

To a mixture of (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine (Preparation B; 25 mg, 0.079 mmol), (R)-l-((tert-butoxycarbonyl)-2-methylpyrrolidine-2-carboxylic acid (22 mg, 0.095 mmol), and HATU (36 mg, 0.095 mmol) was added 0.6 mL DMF to make a solution. After cooling in an ice bath for 10 minutes, DIEA (0.041 mL, 0.24 mmol) was added to the reaction drop-wise. The reaction was allowed to warm up to ambient temperature and stirred overnight. The reaction mixture was diluted with EtOAc (15 mL), washed with water and brine (5 mL each), concentrated, and purified by reverse-phase column chromatography, eluting with 5 to 68% acetonitrile/water to yield the N-Boc-protected product, (R)-tert-butyl 2-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)carbamoyl)-2-methylpyrrolidine-1-carboxylate, as a beige solid (32 mg, 73% yield). The de-protection was carried out by adding 1 mL 4 N HCl solution in dioxane to the above protected product. After 1 hour at ambient temperature, the reaction mixture was concentrated, treated with ether (1 mL), and filtered, giving the final product as an off-white solid. MS (apci) m/z = 427.2 (M+H).
Example 54

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-alpyrimidin-3-yl)-2-fluoro-2-methylpropanamide

[00469] Prepared by the method as described in Example 51, substituting 1-(trifluoromethyl)-cyclopropane-carboxylic acid with 2-fluoro-2-methylpropanoic acid, to provide the final product as a pale-yellowish solid (25 mg, 77% yield). MS (apci) m/z = 404.2 (M+H).

Example 55

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-alpyrimidin-3-yl)-2-(isopropylamino)thiazole-4-carboxamide

[00470] Prepared by the method as described in Example 51, substituting 1-(trifluoromethyl)-cyclopropane-carboxylic acid with 2-(isopropylamino)thiazole-4-carboxylic acid hydrobromide, to provide the final product as a beige solid (34 mg, 89% yield). MS (apci) m/z = 484.2 (M+H).

Example 56

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-alpyrimidin-3-yl)-2-methyl-2-(1H-1,2,4-triazol-1-yl)propanamide
Prepared by the method as described in Example 51, substituting 1-(trifluoromethyl)-cyclopropane-carboxylic acid with 2-methyl-2-(IH-1,2,4-triazol-1-yl)propanoic acid, to provide the final product as a pale-yellowish solid (26 mg, 72% yield). MS (apci) m/z = 453.1 (M+H).

Example 57

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-alpyrimidin-3-yl)pyrazine-2-carboxamide

To a mixture of (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-alpyrimidin-3-amine (Preparation B; 25 mg, 0.079 mmol), pyrazine-2-carboxylic acid (12 mg, 0.095 mmol), and HATU (36 mg, 0.095 mmol) was added 0.6 mL DMF to make a solution. After cooling in an ice bath for 10 minutes, DIEA (0.041 mL, 0.24 mmol) was added to the reaction drop-wise. The reaction was allowed to warm up to ambient temperature and stirred for 10 minutes. The reaction mixture was diluted with EtOAc (15 mL), washed with water and brine (5 mL each), concentrated, and purified by reverse-phase column chromatography, eluting with 5 to 65% acetonitrile/water to yield the final product as a yellowish solid (31 mg, 93% yield). MS (apci) m/z = 422.2 (M+H).

Example 58

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-alpyrimidin-3-yl)-5-methylpyrazine-2-carboxamide

Prepared by the method as described in Example 57, substituting pyrazine-2-carboxylic acid with 5-methylpyrazine-2-carboxylic acid, to provide the final product as a yellowish solid (9 mg, 26% yield). MS (apci) m/z = 436.2 (M+H).
Example 59

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-6-methylpicolinamide

Prepared by the method as described in Example 57, substituting pyrazine-2-carboxylic acid with picolinic acid, to provide the final product as a yellowish solid (31 mg, 93% yield). MS (apci) m/z = 421.2 (M+H).

Example 60

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-6-methylpicolinamide

Prepared by the method as described in Example 57, substituting pyrazine-2-carboxylic acid with 6-methylpicolinic acid, to provide the final product as a yellowish solid (30 mg, 87% yield). MS (apci) m/z = 435.2 (M+H).

Example 60A

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-6-methylpicolinamide hydrochloride

To a methanol (1 mL) solution of (R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-6-methylpicolinamide (10.3 mg, 0.0237 mmol) was added HCl as a solution is dioxane (30 µL). After 30 minutes, the reaction was concentrated...
to provide (R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-methylpicolinamide hydrochloride as a yellow solid.

Example 61

![Chemical Structure]

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-methylpicolinamide

[00477] Prepared by the method as described in Example 57, substituting pyrazine-2-carboxylic acid with 5-chloropicolinic acid, to provide the final product as a yellowish solid (24 mg, 67% yield). MS (apci) m/z = 455.2 (M+H).

Example 62

![Chemical Structure]

(R)-4-chloro-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-methylpicolinamide

[00478] Prepared by the method as described in Example 57, substituting pyrazine-2-carboxylic acid with 4-chloropicolinic acid, to provide the final product as a beige solid (30 mg, 83% yield). MS (apci) m/z = 455.2 (M+H).

Example 63

![Chemical Structure]

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-methylpicolinamide
Prepared by the method as described in Example 57, substituting pyrazine-2-carboxylic acid with 3-methylpicolinic acid, to provide the final product as a beige solid (33 mg, 96% yield). MS (apci) m/z = 435.2 (M+H).

Example 64

\[(^\circlearrowleft-N-fS-fl-fl\circlearrowleft$-$difluorophenyo$p$yrrolidin-1-yl)pyrazolo[1,5-alpyrimidin-3-yl)-1-hydroxy-2,2-dimethylpropanamide\]

Prepared by the method as described in Example 57, substituting pyrazine-2-carboxylic acid with 3-hydroxy-2,2-dimethylpropanoic acid, to provide the final product as a pale-yellowish solid (22 mg, 66% yield). MS (apci) m/z = 416.2 (M+H).

Example 65

\[(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-alpyrimidin-3-yl)-1-hydroxycyclopropanecarboxamide\]

Prepared by the method as described in Example 57, substituting pyrazine-2-carboxylic acid with 1-hydroxycyclopropanecarboxylic acid, to provide the final product as a beige solid (6 mg, 16% yield). MS (apci) m/z = 400.2 (M+H).

Example 66

\[(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-alpyrimidin-3-yl)-2-methyl-2-(methylamino)propanamide\]
Prepared by the method as described in Example 57, substituting pyrazine-2-carboxylic acid with 2-methyl-2-(methylamino)propanoic acid hydrochloride, to provide the final product as a solid (2 mg, 6% yield). MS (apci) m/z = 415.1 (M+H).

**Example 67**

![Chemical structure](image)

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-alpyrimidin-3-yl)pyrimidine-2-carboxamide)

To a mixture of (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-l-yl)pyrazolo[1,5-a]pyrimidin-3-amine (Preparation B; 25 mg, 0.079 mmol), pyrimidine-2-carboxylic acid (12 mg, 0.095 mmol), and HATU (36 mg, 0.095 mmol) was added 0.6 mL DMF. A few drops of DMSO were added to obtain a solution. After cooling in an ice bath for 10 minutes, DIEA (0.041 mL, 0.24 mmol) was added to the reaction drop-wise. The reaction was allowed to warm up to ambient temperature and stirred for one hour, then at 80 °C for 16 hours. Reaction did not reach completion before workup. The reaction mixture was diluted with EtOAc (15 mL), washed with water and brine (5 mL each), concentrated, and purified by reverse-phase column chromatography, eluting with 5 to 60% acetonitrile/water to yield the final product as a light yellowish solid (3 mg, 9% yield). MS (apci) m/z = 422.2 (M+H).

**Example 68**

![Chemical structure](image)

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-vDpicolinamide)

To a mixture of (R)-5-(2-(3-fluorophenyl)pyrrolidin-l-yl)pyrazolo[1,5-a]pyrimidin-3-amine (Example 6, Step A; 30 mg, 0.1 mmol), picolinic acid (15 mg, 0.12 mmol), and HATU (46 mg, 0.12 mmol) was added 0.7 mL DMF to make a solution. After cooling in an ice bath for 10 minutes, DIEA (0.053 mL, 0.3 mmol) was added to the reaction drop-wise. The reaction was allowed to warm up to ambient temperature and stirred for 10
minutes. The reaction mixture was diluted with EtOAc (15 mL), washed with water and brine (5 mL each), concentrated, and purified by reverse-phase column chromatography, eluting with 5 to 70% acetonitrile/water to yield the final product as a yellowish solid (35 mg, 86% yield). MS (apci) m/z = 403.2 (M+H).

Example 69

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-alpyrimidin-3-yl)-3-methylpicolinamide

[00485] Prepared by the method as described in Example 68, substituting picolinic acid with 3-methylpicolinic acid, to provide the final product as a solid (35 mg, 83% yield). MS (apci) m/z = 417.2 (M+H).

Example 70

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolino,5-alpyrimidin-3-yl)-1-methyl-2-oxo-1,2-dihydropyridine-4-carboxamide

[00486] Prepared by the method as described in Example 68, substituting picolinic acid with 1-methyl-2-oxo-1,2-dihydropyridine-4-carboxylic acid, to provide the final product as a yellowish solid (18 mg, 41% yield). MS (apci) m/z = 433.2 (M+H).

Example 71

(R)-6-chloro-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo,5-alpyrimidin-3-vDpicolinamide
Prepared by the method as described in Example 68, substituting (R)-5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine with (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine (Preparation B), and substituting picolinic acid with 6-chloropicolinic acid, to provide the final product as a yellowish solid (9.1 mg, 31% yield). MS (apci) m/z = 455.2 (M+H).

Example 72

(R)-4-(ethylsulfonamido)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)benzamide

Prepared by the method as described in Example 68, substituting picolinic acid with 4-(ethylsulfonamido)benzoic acid, to provide the final product as a yellowish solid (32 mg, 62% yield). MS (apci) m/z = 509.2 (M+H).

Example 73

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1-methyl-1H-pyrazole-3-carboxamide

Prepared by the method as described in Example 68, substituting picolinic acid with 1-methyl-1H-pyrazole-3-carboxylic acid, to provide the final product as a yellowish solid (32 mg, 78% yield). MS (apci) m/z = 406.3 (M+H).

Example 74
(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-lH-pyrazole-3-carboxamide

[00490] Prepared by the method as described in Example 68, substituting picolinic acid with lH-pyrazole-3-carboxylic acid, to provide the final product as a yellowish solid (14 mg, 35% yield). MS (apci) m/z = 392.2 (M+H).

Example 75

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-6-methoxypicolinamide

[00491] Prepared by the method as described in Example 68, substituting picolinic acid with 6-methoxypicolinic acid, to provide the final product as a yellowish solid (28 mg, 64% yield). MS (apci) m/z = 433.2 (M+H).

Example 75A

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-6-methoxypicolinamide hydrochloride

[00492] To a methanol (1 mL) solution of (R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-6-methoxypicolinamide (10.1 mg, 0.0234 mmol) was added HCl as a solution is dioxane (30 µL). After 30 minutes, the reaction was concentrated to provide (R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-6-methoxypicolinamide hydrochloride as a yellow solid.

Example 76
(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)nicotinamide

To a mixture of (R)-5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine (Example 6, Step A; 30 mg, 0.1 mmol), nicotinic acid (25 mg, 0.2 mmol), and HATU (77 mg, 0.2 mmol) was added 0.7 mL DMF to make a solution. After cooling in an ice bath for 10 minutes, DIEA (0.053 mL, 0.3 mmol) was added to the reaction drop-wise. The reaction was allowed to warm up to ambient temperature and stirred for 3 hours. The reaction mixture was diluted with EtOAc (15 mL), washed with water and brine (5 mL each), concentrated, and purified by reverse-phase column chromatography, eluting with 5 to 57% acetonitrile/water to yield the final product as a yellowish solid (30 mg, 74% yield). MS (apci) m/z = 403.2 (M+H).

Example 77

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)isonicotinamide

Prepared by the method as described in Example 76, substituting nicotinic acid with isonicotinic acid, to provide the final product as a yellowish solid (20 mg, 49% yield). MS (apci) m/z = 403.2 (M+H).

Example 78

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-6-methylnicotinamide

Prepared by the method as described in Example 76, substituting nicotinic acid with 6-methylnicotinic acid, to provide the final product as a yellowish solid (27 mg, 64% yield). MS (apci) m/z = 417.2 (M+H).
Example 79

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-l-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-2-methoxycytinic acid

Prepared by the method as described in Example 76, substituting nicotinic acid with 2-methoxycytinic acid, to provide the final product as a yellowish solid (32 mg, 73% yield). MS (apci) m/z = 433.2 (M+H).

Example 80

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-l-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-methylisocytinic acid

Prepared by the method as described in Example 76, substituting nicotinic acid with 3-methylisocytinic acid, to provide the final product as a yellowish solid (22 mg, 52% yield). MS (apci) m/z = 417.2 (M+H).

Example 81

(S)-N-(5-((R)-2-(2-chloro-5-fluorophenyl)pyrrolidin-l-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide

To a DCM (0.8 mL) solution of (R)-5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine (Example 8, Step A; 30 mg, 0.09 mmol) was added CDI (29 mg, 0.18 mmol) at ambient temperature in one portion. After stirring two hours, (S)-pyrrolidin-3-ol (15.8 mg, 0.181 mmol) was added in one portion. The reaction was stirred
for 5 minutes before it was concentrated and directly purified by reverse-phase column chromatography, eluting with 5 to 53% acetonitrile/water to yield the final product as a yellowish foamy powder (33 mg, 81% yield). MS (apci) m/z = 445.2 (M+H).

**Example 82**

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-5-methylpyrazine-2-carboxamide

[00499] To a mixture of (R)-5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine (Example 6, Step A; 50 mg, 0.17 mmol, prepared as described in a previous example), 5-methylpyrazine-2-carboxylic acid (46 mg, 0.34 mmol), and HATU (128 mg, 0.34 mmol) was added 0.7 mL DMF to make a solution. After cooling in an ice bath for 10 minutes, DIEA (0.088 mL, 0.5 mmol) was added to the reaction drop-wise. The reaction was allowed to warm up to ambient temperature and stirred for 2 hours. The reaction mixture was directly filtered, rinsing with acetonitrile and then with ether, to provide the final product as a beige solid (44 mg, 63% yield). MS (apci) m/z = 418.2 (M+H).

**Example 83**

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-ylD-1-methyl-1H-imidazole-2-carboxamide

[00500] To a mixture of (R)-5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine (Example 6, Step A; 40 mg, 0.13 mmol, prepared as described in a previous example), 1-methyl-1H-imidazole-2-carboxylic acid (34 mg, 0.27 mmol), and HATU (102 mg, 0.27 mmol) was added 1.0 mL DMF to make a solution. After cooling in an ice bath for 10 minutes, DIEA (0.07 mL, 0.4 mmol) was added to the reaction drop-wise. The reaction was allowed to warm up to ambient temperature and stirred for 10 minutes. The reaction mixture was diluted with EtOAc (15 mL), washed with water and brine (5 mL each),
concentrated, and purified by reverse-phase column chromatography, eluting with 5 to 65% acetonitrile/water to yield the final product as a yellowish solid (37 mg, 68% yield). MS (apci) m/z = 406.2 (M+H).

Example 84

(SVN-(5-((Ry2-(5-fluoro-2-(trifluoromethyl)phenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyprrolidine-1-carboxamide

[00501] Step A: Preparation of (R)-5-(2-(5-fluoro-2-(trifluoromethyl)phenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine: Prepared according to Preparation B, substituting (R)-2-(2,5-difluorophenyl)pyrrolidine in Step 1 with (R)-2-(5-fluoro-2-(trifluoromethyl)phenyl)pyrrolidine.

[00502] Step B: Preparation of (RV2-5-fluoro-2-(trifluoromethyl)phenylpyrrolidine): Prepared by the method of Preparation A, substituting 2-bromo-1,4-difluorobenzene with 2-bromo-4-fluoro-1-(trifluoromethyl)benzene in Step A.

[00503] Step C: Preparation of (SVN-(5-(YR)-2-(5-fluoro-2-(trifluoromethyl)phenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyprrolidine-1-carboxamide: To a DCM (1 mL) solution of (R)-5-(2-(5-fluoro-2-(trifluoromethyl)phenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine (25 mg, 0.068 mmol) was added CDI (22 mg, 0.14 mmol) at ambient temperature in one portion. After stirring for two hours, (S)-pyrrolidin-3-ol (18 mg, 0.21 mmol) was added in one portion. The reaction was stirred overnight before it was concentrated and directly purified by reverse-phase column chromatography, eluting with 0 to 60% acetonitrile/water to yield the final product as a yellowish solid (28 mg, 86% yield). MS (apci) m/z = 479.2 (M+H).

Example 85

(RVN-(5-(YRV2-(5-fluoro-2-(trifluoromethyl)phenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyprrolidine-1-carboxamide
Prepared by the method as described in Example 84, substituting (S)-pyrrolidin-3-ol in Step C with (R)-pyrrolidin-3-ol, giving the final product as a yellowish solid (26 mg, 79%). MS (apci) m/z = 479.2 (M+H).

Example 86

(RVN-(5-(YRV2-(5-fluoro-2-(trifluoromethv0phenyl)pyrrolidin-1-yl)-3-hydroxypiperidine-1-carboxamide

Prepared by the method as described in Example 84, substituting (S)-pyrrolidin-3-ol in Step C with (R)-piperidin-3-ol, giving the final product as a yellowish solid (37 mg, 91%). MS (apci) m/z = 493.2 (M+H).

Example 87

(S)-N-(5-((R)-2-(5-fluoro-2-(trifluoromethyl)phenyl)pyrrolidin-1-yl)pyrazolo[1,5-alpyrimidin-3-yl]-3-hydroxypiperidine-1-carboxamide

Prepared by the method as described in Example 84, substituting (S)-pyrrolidin-3-ol in Step C with (S)-piperidin-3-ol, giving the final product as a yellowish solid (39 mg, 97%). MS (apci) m/z = 493.2 (M+H).

Example 88

(S)-N-(5-((R)-2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-alpyrimidin-3-y]-3-hydroxypyrrolidine-1-carboxamide
Step A: Preparation of (R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine: Prepared according to Preparation B, substituting (R)-2-(2,5-difluorophenyl)pyrrolidine in Step 1 with (R)-3-fluoro-5-(pyrrolidin-2-yl)pyridine.

Step B: Preparation of (R)-3-fluoro-5-(pyrrolidin-2-yl)pyridine: Prepared by the method of Preparation A, substituting 2-bromo-1,4-difluorobenzene with 3-bromo-5-fluoropyridine in Step A.

Step C: Preparation of (S)-N-(5-((R)-2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide: To a DCM (1 mL) solution of (R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine (25 mg, 0.084 mmol) was added CDI (27 mg, 0.17 mmol) at ambient temperature in one portion. After stirring for two hours, (S)-pyrrolidin-3-ol (15 mg, 0.17 mmol) was added in one portion. The reaction was stirred overnight before it was concentrated and directly purified by reverse-phase column chromatography, eluting with 0 to 40% acetonitrile/water to yield the final product as a solid (27 mg, 78% yield). MS (apci) m/z = 412.2 (M+H).

Example 89

(R)-N-(5-((R)-2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxy-1-carboxamide

Prepared by the method as described in Example 88, substituting (S)-pyrrolidin-3-ol in Step C with (R)-pyrrolidin-3-ol, giving the final product as a solid (28 mg, 81%). MS (apci) m/z = 412.2 (M+H).

Example 90

(S)-N-(5-((R)-2-(5-fluoro-2-methoxyphenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide
Step A: Preparation of (R)-5-(2-(5-fluoro-2-methoxyphenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine: Prepared according to Preparation B, substituting (R)-2-(2,5-difluorophenyl)pyrrolidine in Step 1 with (R)-2-(5-fluoro-2-methoxyphenyl)pyrrolidine.

Step B: Preparation of (R)-2-(5-fluoro-2-methoxyphenyl)pyrrolidine: Prepared by the method of Preparation A, substituting 2-bromo-1,4-difluorobenzene with 2-bromo-4-fluoro-1-methoxybenzene in Step A.

Step C: Preparation of (SVN-(5-(YR)-2-(5-fluoro-2-methoxyphenyl)pyrrolidin-1-yl)pyrazolo[1,5-alpyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide: To a DCM (5 mL) solution of (R)-5-(2-(5-fluoro-2-methoxyphenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine (25 mg, 0.076 mmol) and DIEA (0.04 mL, 0.23 mmol) was added CDI (25 mg, 0.15 mmol) at ambient temperature in one portion. After stirring for one hour, (S)-pyrrolidin-3-ol (20 mg, 0.23 mmol) was added in one portion. The reaction was stirred overnight before it was concentrated and directly purified by reverse-phase column chromatography, eluting with 0 to 60% acetonitrile/water to yield the final product as a yellowish solid (28 mg, 83% yield). MS (apci) m/z = 441.2 (M+H).

Example 91

(S)-N-(5-((R)-2-(5-fluoro-2-methoxyphenyl)pyrrolidin-1-yl)pyrazolo[1,5-alpyrimidin-3-yl)-3-hydroxypiperidine-1-carboxamide

Prepared according to the method as described in Example 90, substituting (S)-pyrrolidin-3-ol in Step C with (S)-piperidin-3-ol, giving the final product as a yellowish solid. MS (apci) m/z = 455.2 (M+H).

Example 92
To a DCM (1.0 mL) solution of (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine (Preparation B; 50 mg, 0.16 mmol) was added CDI (51 mg, 0.32 mmol) at ambient temperature in one portion. After stirring 90 minutes, (1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptane hydrochloride (43 mg, 0.32 mmol) was added in one portion, followed by DIEA (0.083 mL, 0.48 mmol). The reaction was stirred for 5 minutes before it was concentrated and directly purified by reverse-phase column chromatography, eluting with 0 to 60% acetonitrile/water to yield the final product as a pale-yellowish powder (60 mg, 86% yield). MS (apci) m/z = 441.2 (M+H).

**Example 93**

(R)-N-(5-(R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-alpyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide

Prepared by the method as described in Example 92, substituting (1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptane hydrochloride with (R)-pyrrolidin-3-ol. The crude material was purified by reverse-phase column chromatography with 5 to 50% acetonitrile/water eluent, giving the final product as a solid (89 mg, 66% yield). MS (apci) m/z = 429.2 (M+H).

**Example 94**

(IS,3R)-N-(5-(R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-alpyrimidin-3-yl)-3-hydroxycyclopentane-3-carboxamide

A DMA (1 mL) solution of (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine (Preparation B; 50 mg, 0.16 mmol), (IS,3R)-3-hydroxycyclopentanecarboxylic acid (23 mg, 0.17 mmol) [purchased from AFID Therapeutics Inc.] and 2-(lH-benzo[d][1,2,3]triazol-1-yl)-1,1,3,3-tetramethyluronium...
tetrafluoroborate (TBTU) (56 mg, 0.17 mmol) was first cooled in an ice-water bath, then
DIEA (0.083 mL, 0.48 mmol) was added to reaction drop-wise. Ice bath was then removed
and the reaction was stirred at ambient temperature for 1 hour to reach completion. The
reaction mixture was diluted with water (10 mL) and vacuum-filtered, yielding the crude
product as a beige solid. The crude was purified by reverse phase column chromatography,
eluting with 5 to 57% acetonitrile/water to yield the final product as a solid (20 mg, 30% yield). MS (apci) m/z = 428.2 (M+H).

Example 95

(IS,3S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-alpyrimidin-3-yl)-3-
hydroxycyclopentanecarboxamide

[00518] Prepared by the same method as described in Example 94, substituting
(IS,3R)-3-hydroxycyclopentanecarboxylic acid with (IS,3S)-3-
hydroxycyclopentanecarboxylic acid (23 mg, 0.17 mmol) [purchased from AFID
Therapeutics Inc.] The crude product was purified by reverse phase column chromatography,
eluting with 5 to 53% acetonitrile/water to yield the final product as a solid (35 mg, 52% yield). MS (apci) m/z = 428.2 (M+H).

Example 96

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-alpyrimidin-3-yl)-3-
hydroxycyclobutanecarboxamide

[00519] Prepared by the same method as described in Example 94, substituting
(IS,3R)-3-hydroxycyclopentanecarboxylic acid with 3-hydroxyeyelobutanecarboxylic acid
(20 mg, 0.17 mmol) [purchased from Parkway Scientific]. The crude product was purified by
reverse phase column chromatography, eluting with 5 to 53% acetonitrile/water to yield the final product as a solid (8 mg, 12% yield). MS (apci) m/z = 414.2 (M+H).

**Example 97**

![Chemical Structure](image)

(R)-N^1-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-N^2-dimethylxalamide

[00520] To a DCM (1 mL) solution of (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine (Preparation B; 50 mg, 0.16 mmol) was drop-wise added methyl 2-chloro-2-oxoacetate (19.4 mg, 0.159 mmol), followed by DIEA (0.0829 mL, 0.476 mmol). After the mild exothermal subsided and the reaction cooled back to ambient temperature, dimethylamine (0.8 mL, 1.6 mmol) [2M, THF] was added. The reaction was heated to gentle reflux for a few minutes, allowed to cool back to ambient temperature and stirred for 1 hour to reach completion. The reaction was concentrated and directly purified by reverse phase column chromatography, eluting with 5 to 60% acetonitrile/water to yield the final product as a pale-yellowish solid (48 mg, 73% yield). MS (apci) m/z = 415.1 (M+H).

**Example 98**

![Chemical Structure](image)

(R)-N^1-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolol 1.5-a1pyrimidin-3-vD-N^2-methylxalamide

[00521] Prepared by the same method as described in Example 97, substituting dimethylamine with methanaline (2M, THF), and the reaction was carried out at room temperature instead of at reflux. The crude product was purified by reverse phase column chromatography, eluting with 5 to 60% acetonitrile/water to yield the final product as a white solid (50 mg, 79% yield). MS (apci) m/z = 401.1 (M+H).
Example 99

(RVN^-S^-S-difluorophenyOprrridin-1-yl)pyrazolo[1,5-a1pyrimidin-3-yl)oxalamide

[00522] Prepared by the same method as described in Example 97, substituting dimethylamine with ammonia (7 M, methanol), and the reaction was carried out at 50 °C overnight. The crude product was purified by reverse phase column chromatography, eluting with 5 to 55% acetonitrile/water to yield the final product as a white solid (50 mg, 82% yield). MS (apci) m/z = 387.1 (M+H).

Example 100

(^-N^-cyclopropyl-Nl-fS-fl-fl^-difluoropheny ppyrrolidin-1-ylpyrazolofl^-alpyrimidin-3-yDoxalamide

[00523] Prepared by the same method as described in Example 97, substituting dimethylamine with cyclopropanamine, and the reaction was carried out at ambient temperature instead of reflux. The crude product was purified by reverse phase column chromatography, eluting with 5 to 65% acetonitrile/water to yield the final product as a white solid (50 mg, 74% yield). MS (apci) m/z = 427.2 (M+H).

Example 101

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolori,5-alpyrimidin-3-yl)-2-(3-hydroxyazetidin-1-yl)-2-oxoacetamide

[00524] Prepared by the same method as described in Example 97, substituting dimethylamine with azetidin-3-ol, and the reaction was carried out at 50 °C overnight. The
crude product was purified by reverse phase column chromatography, eluting with 5 to 55% acetonitrile/water to yield the final product as a pale-yellowish solid (53 mg, 75% yield). MS (apci) m/z = 443.1 (M+H).

**Example 102**

![Chemical Structure](image)

N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[3,5-][1,5]alpyrimidin-3-yl)-2-((S)-3-hydroxyprrolidin-1-yl)-2-oxoacetamide

[00525] Prepared by the same method as described in Example 97, substituting dimethylamine with (S)-pyrrolidin-3-ol, and the reaction was carried out at ambient temperature for 1 hour instead of at reflux. The crude product was purified by reverse phase column chromatography, eluting with 5 to 55% acetonitrile/water to yield the final product as a pale-yellowish solid (54 mg, 75% yield). MS (apci) m/z = 457.2 (M+H).

**Example 103**

![Chemical Structure](image)

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazoloro,5-alpyrimidin-3-yl)-2-morpholino-2-oxoacetamide

[00526] Prepared by the same method as described in Example 97, substituting dimethylamine with morpholine, and the reaction was carried out at 50 °C for 1 hour. The crude product was purified by reverse phase column chromatography, eluting with 5 to 60% acetonitrile/water to yield the final product as a pale-yellowish solid (52 mg, 72% yield). MS (apci) m/z = 457.1 (M+H).
(R)-methyl 2-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-alpyrimidin-3-yldiamino)-2-oxoacetate

[00527] A DCM (5 mL, 0.7928 mmol) solution of (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine (Preparation B; 250 mg, 0.7928 mmol) and DIEA (0.2071 mL, 1.189 mmol) was first cooled in an ice-water bath, then methyl 2-chloro-2-oxoacetate (0.07657 mL, 0.8325 mmol) was added to reaction drop-wise. Ice bath was removed and the reaction was stirred at ambient temperature for approx. 10 minutes to reach completion. The reaction was washed with 10% citric acid (aqueous). The aqueous layer was back-washed with DCM. The combined organic layer was washed with 1:1 water/brine, dried (Na$_2$SO$_4$) and concentrated. The crude oil residue was directly purified by silica chromatography, eluting with EtOAc/hexanes 1:1 to 2:1, yielding the final product as a pale-yellowish foamy powder (270 mg, 85% yield). MS (apci) m/z = 402.2 (M+H).

Example 105

(R)-2-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yldiamino)-2-oxoacetic acid

[00528] (R)-methyl 2-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yldiamino)-2-oxoacetate (Example 104; 100 mg, 0.249 mmol) was dissolved in a mixture solvent of THF:MeOH:water (2:2:1, 1 mL), followed by addition OfLiOH-H$_2$O (31.4 mg, 0.747 mmol). The reaction was stirred at ambient temperature for 10 minutes to reach completion. The reaction was concentrated, re-dissolved in water (20 mL) and acidified with 6 N HCl. The precipitate was vacuum-filtered, rinsed with water, heptane, and dried on high vacuum, giving the final product as a fine pale-yellowish powder (50 mg, 52% yield). MS (apci negative) m/z = 386.1 (M-H).
What is claimed is:

1. A compound having the general formula I

\[
\begin{array}{c}
\text{R}^1 \\
\text{R}^2 \\
\text{R}^3 \\
\text{R}^4 \\
\text{X}
\end{array}
\]

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is H or (1-OC alkyl);

R^2 is NR^bR^c, (1-4C)alkyl, (1-4C)fluoroalkyl, CF_3, (1-4C)hydroxyalkyl, -(1-4C alkyl)hetAr\^1 -(1-4C alkyl)NH_2, -(1-4C alkyl)NH(1-4C alkyl), -(1-4C alkyl)N(1-4C alkyl), phenyl which is optionally substituted with NHSO_2(1-4C alkyl), or (3-6C)cycloalkyl which is optionally substituted with (1-4C alkyl), CN, OH, OMe, NH_2, NHMe, N(CH_3)_2, F, CF_3, CO_2(1-4C alkyl), CO_2H, C(=0)NR^eR^f or C(=O)OR^g;

R^b is H or (1-6C alkyl);

R^c is H, (1-4C)alkyl, (1-4C)hydroxyalkyl, hetAr^3, or phenyl, wherein said phenyl is optionally substituted with one or more substituents independently selected from halogen, CN, CF_3 and -0(1-4C alkyl),

or NR^bR^c forms a 4 membered heterocyclic ring having a ring nitrogen atom, wherein said heterocyclic ring is optionally substituted with one or more substituents independently selected from halogen, OH, (1-4C alkyl), (1-4 Qalkoxy, -OC(=O)(1-4C alkyl), NH_2, -NHC(=O)O(1-4C alkyl) and (1-4C)hydroxyalkyl,

or NR^bR^c forms a 5-6 membered heterocyclic ring having a ring heteroatom which is nitrogen and optionally having a second ring heteroatom or group selected from N, O and SO_2, wherein the heterocyclic ring is optionally substituted with one or more substituents independently selected from OH, halogen, CF_3, (1-4C)alkyl, CO_2(1-4C alkyl), CO_2H, NH_2, NHC(=0)(1-4C alkyl) and oxo,

or NR^bR^c forms a 7-8 membered bridged heterocyclic ring having a ring nitrogen atom and optionally having a second ring heteroatom selected from N and O, wherein said ring is optionally substituted with CO_2(1-4C alkyl);

hetAr^1 is a 5-membered heteroaryl ring having 1-3 ring nitrogen atoms;
hetAr² is 5-6 membered heteroaryl ring having at least one nitrogen ring atom and optionally having a second ring heteroatom independently selected from N and S, wherein said heteroaryl ring is optionally substituted with one or more substituents independently selected from (1-4C alkyl), halogen, -(1-4 Qalkoxy andNH(l-4C alkyl);

hetCyc¹ is a carbon-linked 4-6 membered azacyclic ring optionally substituted with one or more substituents independently selected from (1-4C alkyl), and CO2(l-4C alkyl);

hetCyc² is a pyridinone or pyrazatinone ring which is optionally substituted with a substituent selected from (l-4C)alkyl;

cyc² is a 5-6 membered heteroaryl ring having 1-2 ring heteroatoms independently selected from N and O and optionally substituted with one or more substituents independently selected from (l-4C)alkyl;

Rᵅ is H or (l-4C)alkyl;

Rᵦ is H, (l-4C)alkyl, or (3-6)cycloalkyl;

or NRᵅRᵦ forms a 4-6-membered azacyclic ring optionally having an additional ring heteroatom selected from N and O, wherein the azacyclic ring is optionally substituted with OH;

Rᵦ is H or (l-4C)alkyl;

Y is (i) phenyl optionally substituted with one or more substituents independently selected from halogen, (l-4C)alkoxy, CF₃ and CHF₂, or (ii) a 5-6 membered heteroaryl ring having a ring heteroatom selected from N and S, wherein said heteroaryl ring is optionally substituted with one or more halogen atoms;

X is null, -CH₂-, -CH₂CH₂-, -CH₂O-, or -CH₂NRᵦ;

Rᵦ is H or (l-4C alkyl);

Rᵦ is H or (l-4C alkyl);

each Rᵦ is independently selected from halogen, (l-4C)alkyl, OH, (1-4 Qalkoxy, NH₂, NH(l-4C alkyl) and CH₂OH; and

n is o, 1, 2, 3, 4, 5 or 6.

2. A compound of claim 1, wherein R² is NRᵅRᵦ, (l-4C)alkyl, (1-4C)fluoroalkyl, CF₃, (1-4C)hydroxyalkyl, -(1-4C alkyfhetAr¹, -(1-4C alkyl)NH₂, -(1-4C alkyl)NH(l-4C alkyl), -(1-4C alkyl)N(l-4C alkyl)₂, hetAr², hetCyc¹, hetCyc², phenyl which is optionally substituted with NHSO₂(l-4C alkyl), or (3-6)cycloalkyl which is
optionally substituted with (1-4C alkyl), CN, OH, OMe, NH₂, NHMe, N(CH₃)₂, F, CF₃, CO₂(1-4C alkyl) or CO₂H.

3. A compound of claim 1 or 2, wherein R² is NR⁵R⁶.

4. A compound according to any of claims 1-3, wherein:

NR⁵R⁶ forms a 4 membered heterocyclic ring having a ring nitrogen atom, wherein said ring is optionally substituted with one or more substituents independently selected from halogen, OH, (1-4C alkyl), (1-4 Qalkoxy, -OC(=O)(1-4C alkyl), NH₂, -NHC(=O)O(1-4C alkyl) and (1-4C)hydroxy alkyl,

or NR⁵R⁶ forms a 5-6 membered heterocyclic ring having a ring heteroatom which is nitrogen and optionally having a second ring heteroatom or group selected from N, O and SO₂, wherein the heterocyclic ring is optionally substituted with one or more substituents independently selected from OH, halogen, CF₃, (1-4C)alkyl, CO₂(1-4C alkyl), CO₂H, NH₂, NHC(=O)O(1-4C alkyl) and oxo,

or NR⁵R⁶ forms a 7-8 membered bridged heterocyclic ring having a ring nitrogen atom and optionally having a second ring heteroatom selected from N and O, wherein said ring is optionally substituted with CO₂(1-4C alkyl).

5. A compound according to any of claims 1-3, wherein:

R⁶ is H, (1-4C)alkyl, (1-4C)hydroxyalkyl, hetAr², or phenyl, wherein said phenyl is optionally substituted with one or more substituents independently selected from halogen, CN, CF₃ and -O(1-4C alkyl).

6. A compound of claim 1 or 2, wherein R² is (1-4C)alkyl, (1-4C)fluoroalkyl, CF₃, -(1-4C alkyOhetAr¹) or -(1-4C alkyl)NH(l-4C alkyl).

7. A compound of claim 1 or 2, wherein R² is hetAr², hetCyc¹ or hetCyc².

8. A compound of claim 1 or 2, wherein R² is phenyl optionally substituted with NHSO₂(1-4C alkyl).

9. A compound of claim 1 or 2, wherein R² is (3-6C)cycloalkyl which is optionally substituted with (1-4C alkyl), CN, OH, CF₃, CO₂(1-4C alkyl) or CO₂H.

10. A compound of claim 1, wherein R² is C(=0)NR ᵄR⁵ or C(=O)OR⁷.

11. A compound according to any of claims 1-10, wherein X is null, -CH₂⁻ or -CH₂CH₂⁻.

12. A compound according to claim 11, wherein X is -CH⁻.

13. A compound according to any of claims 1-10, wherein X is CH₂O⁻.

14. A compound according to any of claims 1-10, wherein X is -CH₂NR⁴⁻.
15. A compound according to any of claims 1-14, wherein Y is phenyl optionally substituted with one or more substituents independently selected from halogen, (1-4C)alkoxy, CF₃ and CHF₂.

16. A compound according to claim 15, wherein Y is phenyl, 3-fluorophenyl, 2,5-difluorophenyl, 2-chloro-5-fluorophenyl, 2-methoxyphenyl, 2-methoxy-5-fluorophenyl, 2-trifluoromethyl-5-fluorophenyl, 2-difluoromethyl-5-fluorophenyl or 3-chloro-5-fluorophenyl.

17. A compound according to any of claims 1-14, wherein Y is a 5-6 membered heteroaryl ring having a ring heteroatom selected from N and S, wherein said ring is optionally substituted with one or more halogen atoms.

18. A compound according to any of claims 1-17, wherein Y has the absolute configuration of Figure Ia:

![Chemical Structure](image)

19. A compound according to any of claims 1-18, wherein R³ is H.

20. A compound according to claim 1, wherein:

   R¹ is H or (1-OC alkyl);
   R² is NR²R⁵;

   NR²R⁵ forms a 4 membered heterocyclic ring having a ring nitrogen atom, wherein said heterocyclic ring is optionally substituted with one or more substituents independently selected from halogen, OH, (1-4C alkyl), (1-4 Qalkoxy, -OC(=O)(1-4C alkyl), NH₂, -NHC(=O)O(1-4C alkyl) and (1-4C)hydroxyalkyl,

   or NR²R⁵ forms a 5-6 membered heterocyclic ring having a ring heteroatom which is nitrogen and optionally having a second ring heteroatom or group selected from N, O and SO₂, wherein the heterocyclic ring is optionally substituted with one or more substituents independently selected from OH, halogen, CF₃, (1-4C)alkyl, CO₂(1-4C alkyl), CO₂H, NH₂, NHC(=O)(1-4C alkyl) and oxo;

   Y is phenyl optionally substituted with one or more substituents independently selected from halogen, (1-4C)alkoxy, CF₃ and CHF₂;
X is null, -CH₂⁻, or -CH₂CH₂⁻;
R³ is H or (1-4C alkyl);
each R⁴ is independently selected from halogen, (1-4C alkyl), OH, (1-4 Qalkoxy, 
NH₂, NH(I -4C alkyl) and CH₂OH; and

n is 0, 1, or 2.

21. A compound according to claim 20, wherein:
R¹ is H or (1-OC alkyl);
R² is NRᵇRᶜ;

NRᵇRᶜ forms a 5-6 membered heterocyclic ring having a ring heteroatom which is 
nitrogen and optionally having a second ring heteroatom or group selected from N, O and 
SO₂, wherein the heterocyclic ring is optionally substituted with one or more substituents 
independently selected from OH, halogen, CF₃, (1-4C alkyl), CO₂(1-4C alkyl), CO₂H, 
NH₂, NHC(O)O(1-4C alkyl) and oxo;

Y is phenyl optionally substituted with one or more substituents independently 
selected from halogen, (1-4C)alkoxy, CF₃ and CHF₂;

X is -CH₂⁻;
R³ is H or (1-4C alkyl);
each R⁴ is independently selected from halogen, (1-4C alkyl), OH, (1-4 Qalkoxy, 
NH₂, NH(I -4C alkyl) and CH₂OH; and

n is 0, 1, or 2.

22. A compound according to claim 21, wherein the heterocyclic ring formed 
by NRᵇRᶜ is optionally substituted with one or two substituents independently selected 
from OH, F, NH₂, CO₂H, CO₂Et, NHCO₂C(CH₃)₃, CF₃, methyl, ethyl, isopropyl, 
CO₂C(CH₂)₃ and oxo.

23. A compound according to claim 22, wherein Y is phenyl optionally 
substituted with one or more halogen atoms.

24. A compound according to claim 23, wherein Y is phenyl optionally 
substituted with one or two fluorine atoms.

25. A compound according to claim 20, wherein:
R¹ is H or (1-OC alkyl);
R² is NRᵇRᶜ;

NRᵇRᶜ forms a 4 membered heterocyclic ring having a ring nitrogen atom, 
wherein said ring is optionally substituted with one or more substituents independently
selected from halogen, OH, (1-4C alkyl), (1-4 Qalkoxy, -OC(=O)(1-4C alkyl), NH₂, -NHC(=O)O(1-4C alkyl) and (l-4C)hydroxyalkyl;

Y is phenyl optionally substituted with one or more substituents independently selected from halogen, (l-4C)alkoxy, CF₃ and CHF₂;

X is -CH₂⁻;

R³ is H or (l-4C alkyl);

each R⁴ is independently selected from halogen, (l-4C)alkyl, OH, (1-4 Qalkoxy, NH₂, NH(l-4C alkyl) and CH₂OH; and

n is 0, 1, or 2.

26. A compound according to claim 25, wherein the heterocyclic ring formed by NR³R⁴ is optionally substituted with one or two substituents independently selected from F, OH, methyl, OMe, OC(=O)C(CH₃)₂, NH₂, -NHC(=O)OC(CH₃)₃ and CH₂OH.

27. A compound according to claim 26, wherein Y is phenyl optionally substituted with one or more halogen atoms.

28. A compound according to claim 27, wherein Y is phenyl optionally substituted with one or two fluorine atoms.

29. A compound according to any of claims 20-28, wherein n is zero or one.

30. A compound according to claim 29, wherein R³ is hydrogen.

31. A compound according to claim 30, wherein R¹ is hydrogen.

32. A compound according to claim 1, which is a trifluoroacetate salt, a sulfate salt or a hydrochloride salt.

33. A pharmaceutical composition, which comprises a compound of Formula I as defined in any one of claims 1 to 32, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable diluent or carrier.

34. A method for treating pain, cancer, inflammation, neurodegenerative disease or Typanosoma cruzi infection in a mammal, which comprises administering to said mammal a therapeutically effective amount of a compound of Formula I as defined in any one of claims 1 to 32, or a pharmaceutically acceptable salt thereof.

35. A method for treating osteolytic disease in a mammal, which comprises administering to said mammal a therapeutically effective amount of a compound of Formula I as defined in any one of claims 1 to 32, or a pharmaceutically acceptable salt thereof.
36. A compound of Formula I as defined in any one of claims 1 to 32, or a pharmaceutically acceptable salt thereof, for use in the treatment of pain, cancer, inflammation, neurodegenerative disease or *Trypanosoma cruzi* infection in a mammal.

37. A compound of Formula I as defined in any one of claims 1 to 32, or a pharmaceutically acceptable salt thereof, for use in the treatment of osteolytic disease in a mammal.

38. A process for the preparation of a compound of claim 1, which comprises:

(a) for a compound of Formula I wherein \( R^2 \) is \( NR^bR^c \), reacting a corresponding compound of formula II

\[
\text{II}
\]

with a compound having the formula \( \text{FINR}^bR^c \) in the presence of a coupling reagent; or

(b) for a compound of Formula I wherein \( R^2 \) is \( NR^bR^c \) and \( R^b \) is \( H \), reacting a corresponding compound of formula II with a compound having the formula \( O=C=N-R^0 \); or

(c) for a compound of Formula I wherein \( R^2 \) is \( \text{hetAr}^2 \) or a phenyl ring which is optionally substituted with NH\( \text{SO}_2 \)(1-4C alkyl), reacting a corresponding compound of Formula II with a corresponding compound having the formula \( HOC(=O)R^2 \) in the presence of a coupling reagent and a base; or

(d) for a compound of Formula I wherein \( R^2 \) is (1-4C)alkyl, (1-4C)fluoroalkyl, CF\(_3\), (1-4C)hydroxyalkyl, or (3-6C)cycloalkyl which is optionally substituted with (1-4C alkyl), CN, OH, CF\(_3\), CO\(_2\)(1-4C alkyl) or CO\(_2\)H, reacting a corresponding compound of Formula II with a corresponding compound having the formula \( (R^2\text{CO})_2O \) in the presence of a base; or

(e) for a compound of Formula I wherein \( R^2 \) is (1-4C)alkyl, (1-4C)fluoroalkyl, CF\(_3\), (1-4C)hydroxyalkyl, or (3-6C)cycloalkyl which is optionally substituted with (1-4C alkyl), CN, OH, CF\(_3\), CO\(_2\)(1-4C alkyl) or CO\(_2\)H, reacting a corresponding compound of Formula II with a corresponding compound having the formula \( HOC(=O)R^2 \) in the presence of a coupling reagent and a base;
(f) for a compound of Formula I wherein R² is C(=O)NRᵉRᶠ, reacting a
compound of formula VII

![Formula VII]

with a compound having the formula HNRᵉRᶠ in the presence of a base; or
(g) for a compound of Formula I wherein R² is C(=O)ORᵍ, reacting a
compound of Formula II with methyl 2-chloro-2-oxoacetate, and treating with an alkali
hydroxide to prepare a compound of formula I where Rᵍ is H; and

- removing or adding any protecting groups if desired, and forming a salt if desire
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

INV. C07D471/04 A61K31/519 A61P29/00

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 practical, search terms used)

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

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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<th>Category</th>
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<th>Relevant to claim No</th>
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Further documents are listed in the continuation of Box C

See patent family annex

Date of the actual completion of the international search

21 January 2010

Date of mailing of the international search report

02/02/2010

Name and mailing address of the ISA/

European Patent Office, P B 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel (+31-70) 340-2040
Fax (+31-70) 340-3016

Authorized officer

Bakboord, Joan
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