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(57) Abstract: Compounds of Formula (I) and salts thereof in which $R^{1}, R^{2}, R^{3}, R^{4}, X, Y$ 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 such as pain, cancer, inflammation, neurodegenerative diseases and certain infectious diseases.


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

[0001] The present invention relates to novel compounds, to pharmaceutical compositions comprising the compounds, to processes 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, cancer, inflammation, neurodegenerative diseases and certain infectious diseases.
[0002] 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. Nonsteroidal anti-inflammatory analgesics (NSAIDs, such as COX-1 or COX-2 types) also have drawbacks including insufficient efficacy in treating severe pain. In addition, COX-1 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.
[0003] 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).
[0004] Inhibitors of the Trk/neurotrophin pathway have been demonstrated to be effective in numerous pre-clinical animal models of pain. For example, antagonistic NGF and TrkA antibodies such as RN-624 have been shown to be efficacious in inflammatory and neuropathic pain animal models (Woolf, C.J. et al. (1994) Neuroscience 62,327-331; Zahn, P.K. et al. (2004) J. Pain 5, 157-163; McMahon, S. B. et al., (1995) Nat. Med. 1, 774-780; Ma, Q. P. and Woolf, C. J. (1997) Neuroreport 8, 807-810; Shelton, D. L. et al. (2005) Pain 116, 8-16; Delafoy, L. et al. (2003) Pain 105, 489-497; Lamb, K. et al. (2003) Neurogastroenterol. Motil. 15, 355-361; Jaggar, S. I. et al. (1999) Br. J. Anaesth. 83, 442448) and neuropathic pain animal models (Ramer, M. S. and Bisby, M. A. (1999) Eur. J. Neurosci. 11, 837-846; Ro, L. S. et al. (1999); Pain 79, 265-274 Herzberg, U. et al. (1997) Neuroreport 8, 1613-1618; Theodosiou, M. et al. (1999) Pain 81, 245-255; Li, L. et al.
(2003) Mol. Cell. Neurosci. 23, 232-250; Gwak, Y. S. et al. (2003) Neurosci. Lett. 336, 117120). Additionally, recent literature indicates after inflammation, BDNF levels and TrkB signaling is increased in the dorsal root ganglion (Cho, L. et al. Brain Research 1997, 749, 358) and several studies have show antibodies that decrease signaling through the BDNF/TrkB pathway inhibit neuronal hypersensitization and the associated pain (Chang-Qi, Let al. Molecular Pain 2008, 4:27).
[0005] It has also been shown that NGF secreted by tumor cells and 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.
[0006] Recent literature has also shown that overexpression, activation, amplification and/or mutation of Trk kinases are associated with many cancers including neuroblastoma (Brodeur, G. M., Nat. Rev. Cancer 2003, 3, 203-216), ovarian (Davidson. B., et al., Clin. Cancer Res. 2003, 9, 2248-2259) and colorectal cancer (Bardelli, A., Science 2003, 300, 949). In preclinical models of cancer, non-selective small molecule inhibitors of Trk A, B and C were efficacious in both inhibiting tumor growth and stopping tumor metastasis (Nakagawara, A. (2001) Cancer Letters 169:107-114; Meyer, J. et al. (2007) Leukemia, 110; Pierottia, M.A. and Greco A., (2006) Cancer Letters 232:90-98; Eric Adriaenssens, E. et al. Cancer Res (2008) 68:(2) 346-351).
[0007] In addition, inhibition of the neurotrophin/Trk pathway has been shown to be effective in treatment of pre-clinical models of inflammatory diseases with NGF antibodies or non-selective small molecule inhibitors of Trk A, B and C. 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 Mola, 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., J. 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).
[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).
[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 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, lifethreatening 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) 625633). 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.
[0011] 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), 305-319).
[0012] Pyrazolo[1,5-a]pyrimidine compounds are known. For example, International patent application publication WO 2004/089415 discloses certain pyrazolo[1,5-a]pyrimidine3 -carboxamide compounds having a phenyl, thienyl or furyl group in the 5 -position which
are said to be 11-beta-hydroxysteroid dehydrogenase type 1 inhibitors useful in combination therapies.
[0013] European patent application publication No. EP 1948633A2 describes 5-phenyl-7-hydroxy-substituted pyrazolo[1,5-a]pyrimidine-3-carboxamide compounds as casein kinase II modulators for treating cancer.
[0014] PCT publication WO 2010/051549 describes pyrazolopyrimidine compounds having the general structure:

[0015] said to be inhibitors of Jak kinases.
[0016] It has now been found that certain pyrazolo[1,5-a]pyrimidine compounds bearing an aryl-substituted or heteroaryl-substituted heterocyclic group at the 5-position and a group having the formula $C(=O) N R^{1} R^{2}$ at the 3-position, wherein $R^{1}$ and $R^{2}$ are as defined herein, are inhibitors of Trk kinases, in particular inhibitors of TrkA and/or TrkB and/or TrkC, and are useful for treating disorders and diseases such as cancer and pain, including chronic and acute pain. 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. In addition, compounds of the invention may be useful for treating cancer, inflammation, neurodegenerative diseases and certain infectious diseases.
[0017] In addition, compounds of the invention have been shown to be selective for the Trk family of kinases over closely related kinases. In particular, compounds of the invention are more selective for inhibiting TrkA kinase activity over inhibiting the activity of one or more members of the Jak kinase family (Jak1, Jak2, Jak3 and Tyk2). Inhibition of the Jak family of kinases has been postulated or demonstrated to result in several unwanted side effects including CD8 T and NK cell depletion (which can result in loss of tumor surveillance and increased infections), elevated cholesterol, neutropenia, thrombocytopenia, decreased reticulocytes (resulting in anemia) and bone marrow suppression (Igaz P. et al., Inflamm. Res., 2001, 50:435-441; O'Shea J.J., Immunity, 1997, 7:1-11; Ihle J.N. et al., Canc. J. Sci. Am., 1998, 4 suppl 1 S84-91; Gupta P. et al., J. Clin. Pharm. 2009; Kremer J.M. et al., Arth. \& Rheum., 2009, 60:1895-1905 and van Gurp E., et al., Am. J. Transpl, 2008, 8:1711-18).

Accordingly, compounds of the invention may be more suitable as therapeutic treatments owing to their ability to inhibit the Trk family of kinases in preference over closely related kinases such as the Jak family of kinases, and therefore may avoid unwanted side effects in a mammal being treated with a compound of the invention.
[0018] Accordingly, one embodiment of this invention provides a compound of the general Formula I:


I
[0019] or a salt thereof, wherein:
[0020] $\quad \mathrm{R}^{1}$ is H or (1-6C alkyl);
[0021] $\quad \mathrm{R}^{2}$ is $\mathrm{H}, \quad(1-6 \mathrm{C})$ alkyl, $\quad-(1-6 \mathrm{C}) f l u o r o a l k y l, \quad-(1-6 \mathrm{C})$ difluoroalkyl, $\quad-(1-$ $6 \mathrm{C})$ trifluoroalkyl, -(1-6C)chloroalkyl, -(2-6C)chlorofluoroalkyl, -(2-6C)difluorochloroalkyl, -(2-6C)chlorohydroxyalkyl, -(1-6C)hydroxyalkyl, -(2-6C)dihydroxyalkyl, -(1-6C alkyl)CN, $-\left(1-6 \mathrm{C}\right.$ alkyl) $\mathrm{SO}_{2} \mathrm{NH}_{2}$, -(1-6C alkyl) $\mathrm{NHSO}_{2}\left(1-3 \mathrm{C}\right.$ alkyl), $-\left(1-6 \mathrm{C}\right.$ alkyl) $\mathrm{NH}_{2}$, $-(1-6 \mathrm{C}$ alkyl)NH(1-4C alkyl), -(1-6C alkyl)N(1-4C alkyl) $)_{2}$, $-(1-6 \mathrm{C}$ alkyl)NHC(=O)O(1-4C alkyl), -(1-6C alkyl)hetCyc ${ }^{1}$, $-\left(1-6 \mathrm{C}\right.$ alkyl)het $\mathrm{Ar}^{1}$, het $\mathrm{Ar}^{2}$, hetCyc ${ }^{2},-\mathrm{O}(1-6 \mathrm{C}$ alkyl) which is optionally substituted with halogen, OH or (1-4C)alkoxy, $-\mathrm{O}\left(3-6 \mathrm{C}\right.$ cycloalkyl), $\mathrm{Cyc}^{1},-(1-6 \mathrm{C}$ alkyl)(3-6C cycloalkyl), -(1-6Calkyl)(1-4C alkoxy), -(1-6C hydroxyalkyl)(1-4C alkoxy), a bridged 7-membered cycloalkyl ring optionally substituted with (1-6C)hydroxyalkyl, or a bridged 7-8 membered heterocyclic ring having 1-2 ring nitrogen atoms;
[0022] or $N R^{1} R^{2}$ forms a 4-6 membered azacyclic ring optionally substituted with one or more substituents independently selected from (1-6C)alkyl, $\mathrm{OH}, \mathrm{CO}_{2} \mathrm{H},(1-3 \mathrm{C}$ alkyl) $\mathrm{CO}_{2} \mathrm{H},-\mathrm{O}(1-6 \mathrm{C}$ alkyl) and (1-6C)hydroxyalkyl;
[0023] hetCyc ${ }^{1}$ is a $5-6$ membered heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O , wherein hetCyc ${ }^{1}$ is optionally substituted with oxo, OH , halogen or (1-6C)alkyl;
[0024] hetCyc ${ }^{2}$ is a 6 membered carbon-linked heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O , wherein het $\mathrm{Cyc}^{2}$ is optionally substituted with $\mathrm{F}, \mathrm{SO}_{2} \mathrm{NH}_{2}, \mathrm{SO}_{2}(1-3 \mathrm{C}$ alkyl) or halogen;
[0025] het $\mathrm{Ar}^{1}$ is a 5-membered heteroaryl ring having 1-2 ring heteroatoms independently selected from N and O and optionally substituted with (1-4C)alkyl;
[0026] het $\mathrm{Ar}^{2}$ is a 5-6 membered heteroaryl ring having 1-2 ring nitrogen atoms and optionally substituted with one or more substituents independently selected from (1-4C)alkyl, (3-6C)cycloalkyl, halogen and OH;
[0027] $\mathrm{Cyc}^{1}$ is a $3-6$ membered cycloalkyl ring which is optionally substituted with one or more substituents independently selected from -( $1-4 \mathrm{C}$ alkyl), $-\mathrm{OH},-\mathrm{OMe},-\mathrm{CO}_{2} \mathrm{H},-$ (1-4C alkyl) OH , halogen and $\mathrm{CF}_{3}$;
[0028] $\quad \mathrm{Y}$ is (i) phenyl optionally substituted with one or more substituents independently selected from halogen, (1-4C)alkoxy, $-\mathrm{CF}_{3}-\mathrm{CHF}_{2},-\mathrm{O}\left(1-4 \mathrm{C}\right.$ alkyl)hetCyc ${ }^{3}$, $-(1-$ 4 C alkyl)hetCyc ${ }^{3},-\mathrm{O}(1-4 \mathrm{C}$ alkyl $) \mathrm{O}(1-3 \mathrm{C}$ alkyl) and $-\mathrm{O}(3-6 \mathrm{C}$ dihydroxyalkyl), 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 substituents independently selected from halogen, $-\mathrm{O}\left(1-4 \mathrm{C}\right.$ alkyl), (1-4C)alkyl and $\mathrm{NH}_{2}$, or (iii) a pyrid-2-on-3-yl ring optionally substituted with one or more substituents independently selected from halogen and (14C)alkyl;
[0029] hetCyc ${ }^{3}$ is a 5-6 membered heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O and optionally substituted with (1-6C)alkyl;
[0030] X is null, $-\mathrm{CH}_{2}-,-\mathrm{CH}_{2} \mathrm{CH}_{2}-,-\mathrm{CH}_{2} \mathrm{O}$ - or $-\mathrm{CH}_{2} \mathrm{NR}^{\mathrm{d}}$-;
[0031] $\quad \mathrm{R}^{\mathrm{d}}$ is H or -(1-4C alkyl);
[0032] $\quad \mathrm{R}^{3}$ is H or $-(1-4 \mathrm{C}$ alkyl);
[0033] each $\mathrm{R}^{4}$ is independently selected from halogen, -(1-4C)alkyl, -OH, -(14C)alkoxy, $-\mathrm{NH}_{2},-\mathrm{NH}\left(1-4 \mathrm{C}\right.$ alkyl) and $-\mathrm{CH}_{2} \mathrm{OH}$; and
[0034] n is $0,1,2,3,4,5$ or 6 .
[0035] In one embodiment of Formula $\mathbf{I}, \mathrm{X}$ is selected from any of the values described above, other than null.
[0036] In one embodiment of Formula $\mathbf{I}, \mathrm{X}$ is $\mathrm{CH}_{2}$.
[0037] Compounds of Formula I include compounds of the general Formula Ia:


Ia
[0038] or a salt thereof, wherein:
[0039]

$$
\mathrm{R}^{1} \text { is } \mathrm{H} \text { or ( } 1-6 \mathrm{C} \text { alkyl); }
$$

[0040] $\quad \mathrm{R}^{2}$ is $\mathrm{H}, \quad(1-6 \mathrm{C})$ alkyl, $-(1-6 \mathrm{C})$ fluoroalkyl, $\quad-(1-6 \mathrm{C})$ hydroxyalkyl, -(2$6 \mathrm{C})$ dihydroxyalkyl, $-\left(1-6 \mathrm{C}\right.$ alkyl) CN , -(1-6C alkyl) $\mathrm{SO}_{2} \mathrm{NH}_{2}$, -(1-6C alkyl) $\mathrm{NHSO}_{2}(1-3 \mathrm{C}$ alkyl), -(1-6C alkyl) $\mathrm{NH}_{2}$, -(1-6C alkyl)NH(1-4C alkyl), $-(1-6 \mathrm{C}$ alkyl $) \mathrm{N}(1-4 \mathrm{C} \text { alkyl })_{2}$, $-(1-$ 6C alkyl)hetCyc ${ }^{1}$, -(1-6C alkyl)het $\mathrm{Ar}^{1}$, het $\mathrm{Ar}^{2}$, hetCyc ${ }^{2}$, -O(1-6C alkyl), -O(3-6C cycloalkyl), $\mathrm{Cyc}^{1}$, or a bridged 7 -membered cycloalkyl ring,
[0041] or $N R^{1} R^{2}$ forms a 4-6 membered azacyclic ring optionally substituted with one or more substituents independently selected from (1-6C)alkyl, $\mathrm{OH}, \mathrm{CO}_{2} \mathrm{H}$ and $(1-3 \mathrm{C}$ alkyl) $\mathrm{CO}_{2} \mathrm{H}$;
[0042] hetCyc ${ }^{1}$ is a $5-6$ membered heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O , wherein hetCyc ${ }^{1}$ is optionally substituted with oxo;
[0043] hetCyc ${ }^{2}$ is a 6 membered carbon-linked heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O , wherein hetCyc ${ }^{2}$ is optionally substituted with $\mathrm{F}, \mathrm{SO}_{2} \mathrm{NH}_{2}$, or $\mathrm{SO}_{2}$ (1-3C alkyl);
[0044] het $\mathrm{Ar}^{1}$ is a 5-membered heteroaryl ring having 1-2 ring heteroatoms independently selected from N and O and optionally substituted with (1-4C)alkyl;
[0045] het $\mathrm{Ar}^{2}$ is a 5-6 membered heteroaryl ring having 1-2 ring nitrogen atoms and optionally substituted with one or more substituents independently selected from (1-4C)alkyl; $\mathrm{Cyc}^{1}$ is a 3-6 membered cycloalkyl ring which is optionally substituted with one or more substituents independently selected from -(1-4C alkyl), $-\mathrm{OH},-\mathrm{OMe},-\mathrm{CO}_{2} \mathrm{H}$ and -(1-4C alkyl)OH;
[0047] $Y$ is (i) phenyl optionally substituted with one or more substituents independently selected from halogen, (1-4C)alkoxy, $-\mathrm{CF}_{3}-\mathrm{CHF}_{2},-\mathrm{O}\left(1-4 \mathrm{C}\right.$ alkyl)hetCyc ${ }^{3}$ and $-\mathrm{O}(1-4 \mathrm{C}$ alkyl) $\mathrm{O}(1-3 \mathrm{C}$ alkyl), 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 substituents independently selected from halogen, $-\mathrm{O}(1-4 \mathrm{C}$ alkyl) and (14C)alkyl;
[0048] hetCyc ${ }^{3}$ is a 5-6 membered heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O ;
[0049]
X is null, $-\mathrm{CH}_{2}-,-\mathrm{CH}_{2} \mathrm{CH}_{2}-,-\mathrm{CH}_{2} \mathrm{O}$ - or $-\mathrm{CH}_{2} \mathrm{NR}^{\mathrm{d}}$-;
[0050]
$\mathrm{R}^{\mathrm{d}}$ is H or -(1-4C alkyl);
[0051]
$\mathrm{R}^{3}$ is H or -(1-4C alkyl);
[0052] each $\mathrm{R}^{4}$ is independently selected from halogen, -(1-4C)alkyl, -OH, -(14C)alkoxy, $-\mathrm{NH}_{2},-\mathrm{NH}\left(1-4 \mathrm{C}\right.$ alkyl) and $-\mathrm{CH}_{2} \mathrm{OH}$; and
[0053] n is $0,1,2,3,4,5$ or 6 .
[0054] In one embodiment of Formula Ia, X is selected from any of the values described above, other than null.
[0055] In one embodiment of Formula Ia, X is $\mathrm{CH}_{2}$.
[0056] In certain embodiments of Formula $\mathbf{I}, \mathrm{R}^{1}$ is hydrogen.
[0057] In certain embodiments of Formula $\mathbf{I}, \mathrm{R}^{1}$ is $-(1-6 \mathrm{C})$ alkyl. Examples include methyl, ethyl, propyl and isopropyl. A particular example is methyl.
[0058] In certain embodiments of Formula $\mathbf{I}, \mathrm{R}^{2}$ is H or -(1-6C)alkyl.
[0059] In certain embodiments, $R^{2}$ is hydrogen. In one embodiment, $R^{2}$ and $R^{1}$ are both hydrogen. In one embodiment, $\mathrm{R}^{2}$ is hydrogen and $\mathrm{R}^{1}$ is -( $1-6 \mathrm{C}$ alkyl).
[0060] In certain embodiments, $\mathrm{R}^{2}$ is selected from -(1-6C)alkyl, -(1-6C)fluoroalkyl, -(1-6C)difluoroalkyl, -(1-6C)trifluoroalkyl, -(1-6C)chloroalkyl, --(2-6C)chlorofluoroalkyl, $-(2-6 \mathrm{C})$ chlorohydroxyalkyl, $\quad-\left(1-6 \mathrm{C}\right.$ alkyl) $\mathrm{CN}, \quad-(1-6 \mathrm{C}$ alkyl $) \mathrm{SO}_{2} \mathrm{NH}_{2}$, and $-(1-6 \mathrm{C}$ alkyl) $\mathrm{NHSO}_{2}(1-3 \mathrm{C}$ alkyl).
[0061] In certain embodiments, $R^{2}$ is $-(1-6 C)$ alkyl. In certain embodiments $R^{2}$ is selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl and tert-butyl. Particular examples include methyl, ethyl, isopropyl and tert-butyl. In one embodiment, $\mathrm{R}^{2}$ is $-(1-$ $6 C$ )alkyl and $R^{1}$ is hydrogen. In one embodiment, $R^{2}$ is -( $1-6 C$ )alkyl and $R^{1}$ is ( $1-6 C$ alkyl).
[0062] In certain embodiments, $\mathrm{R}^{2}$ is selected from -(1-6C)fluoroalkyl, -(16C)difluoroalkyl, -(1-6C)trifluoroalkyl, -(1-6C)chloroalkyl, --(2-6C)chlorofluoroalkyl, $-(2-6 \mathrm{C})$ chlorohydroxyalkyl, $\quad-\left(1-6 \mathrm{C}\right.$ alkyl) $\mathrm{CN}, \quad-\left(1-6 \mathrm{C}\right.$ alkyl) $\mathrm{SO}_{2} \mathrm{NH}_{2}$, and $-(1-6 \mathrm{C}$ alkyl) $\mathrm{NHSO}_{2}(1-3 \mathrm{C}$ alkyl).
[0063] In certain embodiments, $\mathrm{R}^{2}$ is selected from -(1-6C)fluoroalkyl, -(1-6C alkyl) $\mathrm{CN},-\left(1-6 \mathrm{C}\right.$ alkyl) $\mathrm{SO}_{2} \mathrm{NH}_{2}$, and -(1-6C alkyl) $\mathrm{NHSO}_{2}(1-3 \mathrm{C}$ alkyl).
[0064] In certain embodiments, $\mathrm{R}^{2}$ is $-(1-6 \mathrm{C})$ fluoroalkyl. A particular example is $\mathrm{C}\left(\mathrm{CH}_{3}\right)_{2} \mathrm{CH}_{2} \mathrm{~F}$. In one embodiment, $\mathrm{R}^{2}$ is $-(1-6 \mathrm{C})$ fluoroalkyl and $\mathrm{R}^{1}$ is hydrogen. In one embodiment, $\mathrm{R}^{2}$ is $-(1-6 \mathrm{C})$ fluoroalkyl and $\mathrm{R}^{1}$ is (1-6C alkyl).
[0065] In certain embodiments, $\mathrm{R}^{2}$ is -(1-6C)difluoroalkyl. Examples include - $\mathrm{CHF}_{2}$ and $-\mathrm{CH}_{2} \mathrm{CHF}_{2}$. In one embodiment, $\mathrm{R}^{2}$ is $-(1-6 \mathrm{C})$ difluoroalkyl and $\mathrm{R}^{1}$ is hydrogen. In one embodiment, $\mathrm{R}^{2}$ is $-(1-6 \mathrm{C})$ difluoroalkyl and $\mathrm{R}^{1}$ is (1-6C alkyl).
[0066] In certain embodiments, $\mathrm{R}^{2}$ is -(1-6C)trifluoroalkyl. Examples include $\mathrm{CF}_{3}$, $\mathrm{CH}_{2} \mathrm{CF}_{3}$ and $\mathrm{CH}\left(\mathrm{CH}_{3}\right) \mathrm{CF}_{3}$. In one embodiment, $\mathrm{R}^{2}$ is $-(1-6 \mathrm{C})$ trifluoroalkyl and $\mathrm{R}^{1}$ is hydrogen. In one embodiment, $\mathrm{R}^{2}$ is -( $1-6 \mathrm{C}$ )trifluoroalkyl and $\mathrm{R}^{1}$ is ( $1-6 \mathrm{C}$ alkyl).
[0067] In certain embodiments, $\mathrm{R}^{2}$ is $-(1-6 \mathrm{C})$ chloroalkyl. An example includes $\mathrm{CH}_{2} \mathrm{CH}_{2} \mathrm{Cl}$. In one embodiment, $\mathrm{R}^{2}$ is $-(1-6 \mathrm{C})$ chloroalkyl and $\mathrm{R}^{1}$ is hydrogen. In one embodiment, $\mathrm{R}^{2}$ is $-(1-6 \mathrm{C})$ chloroalkyl and $\mathrm{R}^{1}$ is ( $1-6 \mathrm{C}$ alkyl).
[0068] In certain embodiments, $\mathrm{R}^{2}$ is $-(1-6 \mathrm{C})$ chlorofluoroalkyl. An example includes $\mathrm{CH}_{2} \mathrm{CHFCH}_{2} \mathrm{Cl}$. In one embodiment, $\mathrm{R}^{2}$ is $-(1-6 \mathrm{C})$ chlorofluoroalkyl and $\mathrm{R}^{1}$ is hydrogen. In one embodiment, $R^{2}$ is $-(1-6 C)$ chlorofluoroalkyl and $R^{1}$ is (1-6C alkyl).
[0069] In certain embodiments, $\mathrm{R}^{2}$ is $-(1-6 \mathrm{C})$ difluorochloroalkyl. An example includes $-\mathrm{CH}_{2} \mathrm{CF}_{2} \mathrm{CH}_{2} \mathrm{Cl}$. In one embodiment, $\mathrm{R}^{2}$ is $-(1-6 \mathrm{C})$ difluorochloroalkyl and $\mathrm{R}^{1}$ is H . In one embodiment, $\mathrm{R}^{2}$ is $-(1-6 \mathrm{C})$ difluorochloroalkyl and $\mathrm{R}^{1}$ is ( $1-6 \mathrm{C}$ alkyl).
[0070] In certain embodiments, $\mathrm{R}^{2}$ is $-(2-6 \mathrm{C})$ chlorohydroxyalkyl. An example includes $-\mathrm{CH}_{2} \mathrm{CH}(\mathrm{OH}) \mathrm{CH}_{2} \mathrm{Cl}$. In one embodiment, $\mathrm{R}^{2}$ is $-(2-6 \mathrm{C})$ chlorohydroxyalkyl and $\mathrm{R}^{1}$ is hydrogen. In one embodiment, $R^{2}$ is $-(2-6 C)$ chlorohydroxyalkyl and $R^{1}$ is ( $1-6 \mathrm{C}$ alkyl).
[0071] In certain embodiments, $\mathrm{R}^{2}$ is selected from methyl, ethyl, propyl, isopropyl, isobutyl, tert-butyl, $-\mathrm{C}\left(\mathrm{CH}_{3}\right)_{2} \mathrm{CH}_{2} \mathrm{~F},-\mathrm{CHF}_{2},-\mathrm{CH}_{2} \mathrm{CHF}_{2}, \mathrm{CF}_{3}, \mathrm{CH}_{2} \mathrm{CF}_{3}, \mathrm{CH}\left(\mathrm{CH}_{3}\right) \mathrm{CF}_{3}$, $\mathrm{CH}_{2} \mathrm{CH}_{2} \mathrm{Cl}, \mathrm{CH}_{2} \mathrm{CHFCH}_{2} \mathrm{Cl}$, and $-\mathrm{CH}_{2} \mathrm{CF}_{2} \mathrm{CH}_{2} \mathrm{Cl}$.
[0072] In certain embodiments, $\mathrm{R}^{2}$ is selected from methyl, ethyl, propyl, isopropyl, $-\mathrm{CF}_{3}$ and $-\mathrm{CH}_{2} \mathrm{CF}_{3}$.
[0073] In certain embodiments, $\mathrm{R}^{2}$ is -(1-6C)hydroxyalkyl or -(2-6C)dihydroxyalkyl.
[0074] In certain embodiments, $\mathrm{R}^{2}$ is -(1-6C)hydroxyalkyl. Examples include $-\mathrm{CH}_{2} \mathrm{CH}_{2} \mathrm{OH},-\mathrm{CH}_{2} \mathrm{CH}_{2} \mathrm{CH}_{2} \mathrm{OH},-\mathrm{CH}_{2} \mathrm{CH}_{2} \mathrm{CH}_{2} \mathrm{CH}_{2} \mathrm{OH},-\mathrm{CH}_{2} \mathrm{CH}(\mathrm{OH}) \mathrm{CH}_{3},-\mathrm{C}\left(\mathrm{CH}_{3}\right)_{2} \mathrm{CH}_{2} \mathrm{OH}$, $-\mathrm{CH}_{2} \mathrm{C}\left(\mathrm{CH}_{3}\right)_{2} \mathrm{OH}, \quad-\mathrm{CH}\left(\mathrm{CH}_{3}\right) \mathrm{CH}_{2} \mathrm{OH}, \quad-\mathrm{CH}_{2} \mathrm{C}\left(\mathrm{CH}_{3}\right)_{2} \mathrm{CH}_{2} \mathrm{OH}, \quad-\mathrm{CH}\left(\mathrm{CH}_{2} \mathrm{OH}\right) \mathrm{CH}\left(\mathrm{CH}_{3}\right)_{2}$, $-\mathrm{CH}\left(\mathrm{CH}_{2} \mathrm{CH}_{3}\right) \mathrm{CH}_{2} \mathrm{OH}$, and $-\mathrm{CH}\left(\mathrm{CH}_{2} \mathrm{OH}\right) \mathrm{C}\left(\mathrm{CH}_{3}\right)_{3}$. A particular example is $-\mathrm{CH}_{2} \mathrm{CH}_{2} \mathrm{OH}$. In one embodiment, $\mathrm{R}^{2}$ is $-(1-6 \mathrm{C})$ hydroxyalkyl and $\mathrm{R}^{1}$ is hydrogen. In one embodiment, $\mathrm{R}^{2}$ is $-(1-6 \mathrm{C})$ hydroxyalkyl and $\mathrm{R}^{1}$ is -(1-6C alkyl).
[0075] In certain embodiments, $\mathrm{R}^{2}$ is -(2-6C)dihydroxyalkyl. Examples include $-\mathrm{CH}_{2} \mathrm{CH}(\mathrm{OH}) \mathrm{CH}_{2} \mathrm{OH}, \quad-\mathrm{C}\left(\mathrm{CH}_{3}\right)\left(\mathrm{CH}_{2} \mathrm{OH}\right)_{2},-\mathrm{CH}\left(\mathrm{CH}_{2} \mathrm{OH}\right)_{2}$ and $-\mathrm{CH}\left(\mathrm{CH}_{2} \mathrm{OH}\right)\left(\mathrm{CHOHCH}_{3}\right)$. Particular examples include $-\mathrm{CH}_{2} \mathrm{CH}(\mathrm{OH}) \mathrm{CH}_{2} \mathrm{OH}$ and $-\mathrm{C}\left(\mathrm{CH}_{3}\right)\left(\mathrm{CH}_{2} \mathrm{OH}\right)_{2}$. In one embodiment, $\mathrm{R}^{2}$ is -(2-6C)dihydroxyalkyl and $\mathrm{R}^{1}$ is hydrogen. In one embodiment, $\mathrm{R}^{2}$ is -(26 C )dihydroxyalkyl and $\mathrm{R}^{1}$ is -(1-6C alkyl).
[0076] In certain embodiments, $\mathrm{R}^{2}$ is $-(1-6 \mathrm{C}$ alkyl)CN. Particular examples include $-\mathrm{CH}_{2} \mathrm{CN}$ and $-\mathrm{C}\left(\mathrm{CH}_{3}\right)_{2} \mathrm{CN}$. In one embodiment, $\mathrm{R}^{2}$ is $-\left(1-6 \mathrm{C}\right.$ alkyl) CN and $\mathrm{R}^{1}$ is hydrogen. In one embodiment, $\mathrm{R}^{2}$ is $-\left(1-6 \mathrm{C}\right.$ alkyl) CN and $\mathrm{R}^{1}$ is ( $1-6 \mathrm{C}$ alkyl).
[0077] In certain embodiments, $\mathrm{R}^{2}$ is $-\left(1-6 \mathrm{C}\right.$ alkyl) $\mathrm{SO}_{2} \mathrm{NH}_{2}$. A particular example is $\mathrm{CH}_{2} \mathrm{CH}_{2} \mathrm{SO}_{2} \mathrm{NH}_{2}$. In one embodiment, $\mathrm{R}^{2}$ is $-(1-6 \mathrm{C}$ alkyl $) \mathrm{SO}_{2} \mathrm{NH}_{2}$ and $\mathrm{R}^{1}$ is hydrogen. In one embodiment, $\mathrm{R}^{2}$ is $-\left(1-6 \mathrm{C}\right.$ alkyl) $\mathrm{SO}_{2} \mathrm{NH}_{2}$ and $\mathrm{R}^{1}$ is ( $1-6 \mathrm{C}$ alkyl).
[0078] In certain embodiments, $\mathrm{R}^{2}$ is $-\left(1-6 \mathrm{C}\right.$ alkyl) $\mathrm{NHSO}_{2}(1-3 \mathrm{C}$ alkyl). Particular examples include $-\mathrm{CH}_{2} \mathrm{CH}_{2} \mathrm{NHSO}_{2} \mathrm{CH}_{3}$ and $-\mathrm{C}\left(\mathrm{CH}_{3}\right)_{2} \mathrm{CH}_{2} \mathrm{NHSO}_{2} \mathrm{CH}_{3}$. In one embodiment, $R^{2}$ is $-(1-6 \mathrm{C}$ alkyl $) \mathrm{NHSO}_{2}\left(1-3 \mathrm{C}\right.$ alkyl) and $\mathrm{R}^{1}$ is hydrogen. In one embodiment, $\mathrm{R}^{2}$ is $-(1-6 \mathrm{C}$ alkyl) $\mathrm{NHSO}_{2}\left(1-3 \mathrm{C}\right.$ alkyl) and $\mathrm{R}^{1}$ is ( $1-6 \mathrm{C}$ alkyl).
[0079] In certain embodiments, $\mathrm{R}^{2}$ is selected from -(1-6C alkyl) $\mathrm{NH}_{2}$, $-(1-6 \mathrm{C}$ alkyl) $\mathrm{NH}\left(1-4 \mathrm{C}\right.$ alkyl) and $-(1-6 \mathrm{C}$ alkyl $) \mathrm{N}(1-4 \mathrm{C} \text { alkyl })_{2}$.
[0080] In certain embodiments, $\mathrm{R}^{2}$ is $-\left(1-6 \mathrm{C}\right.$ alkyl) $\mathrm{NH}_{2}$. Examples include $-\mathrm{CH}_{2} \mathrm{C}\left(\mathrm{CH}_{3}\right)_{2} \mathrm{NH}_{2}$ and $-\mathrm{CH}_{2} \mathrm{CH}_{2} \mathrm{CH}_{2} \mathrm{NH}_{2}$. A particular example is $-\mathrm{CH}_{2} \mathrm{C}\left(\mathrm{CH}_{3}\right)_{2} \mathrm{NH}_{2}$. In one embodiment, $\mathrm{R}^{2}$ is $-\left(1-6 \mathrm{C}\right.$ alkyl) $\mathrm{NH}_{2}$ and $\mathrm{R}^{1}$ is hydrogen. In one embodiment, $\mathrm{R}^{2}$ is $-(1-6 \mathrm{C}$ alkyl) $\mathrm{NH}_{2}$ and $\mathrm{R}^{1}$ is ( $1-6 \mathrm{C}$ alkyl).
[0081] In certain embodiments, $\mathrm{R}^{2}$ is $-(1-6 \mathrm{C}$ alkyl) $\mathrm{NH}(1-4 \mathrm{C}$ alkyl). Examples include groups having the formula $-(1-4 \mathrm{C}$ alkyl $) \mathrm{NHCH}_{3}$. A particular value is $-\mathrm{C}\left(\mathrm{CH}_{3}\right)_{2} \mathrm{NHCH}_{3}$. In one embodiment, $\mathrm{R}^{2}$ is $-(1-6 \mathrm{C}$ alkyl $) \mathrm{NH}\left(1-4 \mathrm{C}\right.$ alkyl) and $\mathrm{R}^{1}$ is hydrogen. In one embodiment, $\mathrm{R}^{2}$ is -( $1-6 \mathrm{C}$ alkyl) $\mathrm{NH}\left(1-4 \mathrm{C}\right.$ alkyl) and $\mathrm{R}^{1}$ is ( $1-6 \mathrm{C}$ alkyl).
[0082] In certain embodiments, $\mathrm{R}^{2}$ is $-(1-6 \mathrm{C}$ alkyl $) \mathrm{N}(1-4 \mathrm{C} \text { alkyl })_{2}$. Examples include groups having the formula $-(1-4 \mathrm{C}$ alkyl $) \mathrm{N}\left(\mathrm{CH}_{3}\right)_{2}$. A particular value is $-(1-6 \mathrm{C}$ alkyl $) \mathrm{NMe}_{2}$. In one embodiment, $\mathrm{R}^{2}$ is $-(1-6 \mathrm{C}$ alkyl $) \mathrm{N}(1-4 \mathrm{C} \text { alkyl })_{2}$ and $\mathrm{R}^{1}$ is hydrogen. In one embodiment, $\mathrm{R}^{2}$ is $-(1-6 \mathrm{C}$ alkyl $) \mathrm{N}(1-4 \mathrm{C} \text { alkyl })_{2}$ and $\mathrm{R}^{1}$ is ( $1-6 \mathrm{C}$ alkyl).
[0083] In certain embodiments, $\mathrm{R}^{2}$ is -(1-6C alkyl)NHC(=O)O(1-4C alkyl). An example includes $\mathrm{CH}_{2} \mathrm{CH}_{2} \mathrm{CH}_{2} \mathrm{NHC}(=\mathrm{O}) \mathrm{OC}\left(\mathrm{CH}_{3}\right)_{3}$. In one embodiment, $\mathrm{R}^{2}$ is $-(1-6 \mathrm{C}$ alkyl $) \mathrm{NHC}(=\mathrm{O}) \mathrm{O}\left(1-4 \mathrm{C}\right.$ alkyl) and $\mathrm{R}^{1}$ is hydrogen. In one embodiment, $\mathrm{R}^{2}$ is $-(1-6 \mathrm{C}$ alkyl) $\mathrm{NHC}(=\mathrm{O}) \mathrm{O}\left(1-4 \mathrm{C}\right.$ alkyl) and $\mathrm{R}^{1}$ is (1-6C alkyl).
[0084] In certain embodiments, $\mathrm{R}^{2}$ is selected from -(1-6C alkyl)hetCyc ${ }^{1}$ and -(1-6C alkyl)hetAr ${ }^{1}$.
[0085]
In certain embodiments, $\mathrm{R}^{2}$ is $-\left(1-6 \mathrm{C}\right.$ alkyl)hetCyc ${ }^{1}$. Examples of hetCyc ${ }^{1}$ rings include morpholinyl, piperidinyl, piperazinyl and imidazolidinyl, each of which is optionally substituted with a substituent selected from oxo, OH , halogen, and (1-6C)alkyl. In certain embodiments hetCyc ${ }^{1}$ is morpholinyl, piperidinyl, piperazinyl or imidazolidin-2-one optionally substituted with OH , halogen or (1-6C)alkyl. Examples of the $-(1-6 \mathrm{C})$ alkyl portion include methylene, ethylene, dimethylethylene, and the like.
[0086] Examples of $\mathrm{R}^{2}$ when represented by $-\left(1-6 \mathrm{C}\right.$ alkyl)hetCyc ${ }^{1}$ include the structures:





[0087] In certain embodiments, $\mathrm{R}^{2}$ when represented by $-\left(1-6 \mathrm{C}\right.$ alkyl)hetCyc ${ }^{1}$ includes the structures:



[0088] In certain embodiments hetCyc ${ }^{1}$ is morpholinyl or imidazolidin-2-one.
[0089] In one embodiment, $R^{2}$ is $-\left(1-6 C\right.$ alkyl)hetCyc ${ }^{1}$ and $R^{1}$ is hydrogen. In one embodiment, $\mathrm{R}^{2}$ is-( $1-6 \mathrm{C}$ alkyl)hetCyc ${ }^{1}$ and $\mathrm{R}^{1}$ is ( $1-6 \mathrm{C}$ alkyl).
[0090] In certain embodiments, $\mathrm{R}^{2}$ is $-\left(1-6 \mathrm{C}\right.$ alkyl)hetAr ${ }^{1}$. Examples of hetAr ${ }^{1}$ include furanyl, pyrazolyl, and imidazolyl rings which are optionally substituted with -(1-4C alkyl), for example methyl. Examples of the -(1-6C)alkyl portion include methylene, ethylene, dimethylmethylene, and the like. Examples of $\mathrm{R}^{2}$ when represented by $-(1-6 \mathrm{C}$ alkyl)hetAr ${ }^{1}$ include the structures:




Particular values for $\mathrm{R}^{2}$ when represented by -(1-6C alkyl)hetAr ${ }^{1}$ include the structures:

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[0092] In one embodiment, $R^{2}$ is $-\left(1-6 C\right.$ alkyl)het $A r^{1}$ and $R^{1}$ is hydrogen. In one embodiment, $\mathrm{R}^{2}$ is -( $1-6 \mathrm{C}$ alkyl)het $\mathrm{Ar}^{1}$ and $\mathrm{R}^{1}$ is ( $1-6 \mathrm{C}$ alkyl).
[0093] In certain embodiments, $\mathrm{R}^{2}$ is het $\mathrm{Ar}^{2}$. Examples of het $\mathrm{Ar}^{2}$ include pyridyl, pyrazolyl and imidazolyl rings optionally substituted with one or more substituents independently selected from (1-4C)alkyl, (3-6C)cycloalkyl, halogen and OH. Particular examples of hetAr ${ }^{2}$ substituents include methyl, ethyl, isopropyl, cyclopropyl, fluoro and hydroxy. Particular examples of het $\mathrm{Ar}^{2}$ include the structures:













[0094] In certain embodiments het $\mathrm{Ar}^{2}$ is a pyridyl or pyrazolyl ring optionally substituted with one or more substituents independently selected from -(1-4C)alkyl, for example one or more methyl groups, for example 1 or 2 methyl groups. Particular examples of hetAr ${ }^{2}$ include the structures:



[0095] In one embodiment, $\mathrm{R}^{2}$ is het $\mathrm{Ar}^{2}$ and $\mathrm{R}^{1}$ is hydrogen. In one embodiment, $\mathrm{R}^{2}$ is het $\mathrm{Ar}^{2}$ and $\mathrm{R}^{1}$ is ( $1-6 \mathrm{C}$ alkyl).
[0096]
In certain embodiments, $\mathrm{R}^{2}$ is hetCyc ${ }^{2}$. Examples of hetCyc ${ }^{2}$ include piperidinyl and tetrahydropyranyl rings optionally substituted with $\mathrm{F}, \mathrm{SO}_{2} \mathrm{NH}_{2}$ or $\mathrm{SO}_{2}(1-3 \mathrm{C}$ alkyl). Particular examples of $\mathrm{R}^{2}$ when represented by hetCyc ${ }^{2}$ include the structures:




[0097]
In one embodiment, $\mathrm{R}^{2}$ is het $\mathrm{Cyc}^{2}$ and $\mathrm{R}^{1}$ is hydrogen. In one embodiment, $\mathrm{R}^{2}$ is hetCyc ${ }^{2}$ and $R^{1}$ is ( $1-6 \mathrm{C}$ alkyl).
[0098] In certain embodiments, $\mathrm{R}^{2}$ is $-\mathrm{O}(1-6 \mathrm{C}$ alkyl) which is optionally substituted with halogen, OH or (1-4C)alkoxy. Examples include -OMe, $-\mathrm{OEt},-\mathrm{OCH}_{2} \mathrm{CH}_{2} \mathrm{OC}\left(\mathrm{CH}_{3}\right)_{3}$, $\mathrm{OCH}_{2} \mathrm{CH}_{2} \mathrm{Br}$, $-\mathrm{OCH}_{2} \mathrm{CH}_{2} \mathrm{Cl}$ and $-\mathrm{OCH}_{2} \mathrm{CH}_{2} \mathrm{OH}$. In one embodiment, $\mathrm{R}^{2}$ is $-\mathrm{O}(1-6 \mathrm{C}$ alkyl) which is optionally substituted with halogen, OH or (1-4C)alkoxy, and $\mathrm{R}^{1}$ is hydrogen. In one embodiment, $\mathrm{R}^{2}$ is $-\mathrm{O}(1-6 \mathrm{C}$ alkyl) which is optionally substituted with halogen, OH or (1-4C)alkoxy, and $\mathrm{R}^{1}$ is ( $1-6 \mathrm{C}$ alkyl).
[0099] In certain embodiments, $\mathrm{R}^{2}$ is $-\mathrm{O}(1-6 \mathrm{C}$ alkyl). Particular examples include OMe and OEt.
[00100] In certain embodiments, $\mathrm{R}^{2}$ is $-\mathrm{O}(3-6 \mathrm{C}$ cycloalkyl). A particular example is cyclopropoxy. In one embodiment, $\mathrm{R}^{2}$ is $-\mathrm{O}\left(3-6 \mathrm{C}\right.$ cycloalkyl) and $\mathrm{R}^{1}$ is hydrogen. In one embodiment, $\mathrm{R}^{2}$ is $-\mathrm{O}\left(3-6 \mathrm{C}\right.$ cycloalkyl) and $\mathrm{R}^{1}$ is ( $1-6 \mathrm{C}$ alkyl).
[00101] In certain embodiments, $\mathrm{R}^{2}$ is $-\mathrm{O}(1-6 \mathrm{C}$ alkyl) or $-\mathrm{O}(3-6 \mathrm{C}$ cycloalkyl)
[00102] In certain embodiments, $\mathrm{R}^{2}$ is Cyc ${ }^{1}$ or a bridged 7 -membered cycloalkyl ring.
[00103] In certain embodiments, $\mathrm{R}^{2}$ is $\mathrm{Cyc}^{1}$, wherein $\mathrm{Cyc}^{1}$ is a $3-6$ membered cycloalkyl ring optionally substituted with one or more substituents independently selected from -(1-4C alkyl), $-\mathrm{OH},-\mathrm{OMe},-\mathrm{CO}_{2} \mathrm{H},-(1-4 \mathrm{C}$ alkyl $) \mathrm{OH}$, halogen and $\mathrm{CF}_{3}$. In one embodiment, $\mathrm{Cyc}^{1}$ is optionally substituted with one or more substituents independently selected from methyl, $-\mathrm{OH},-\mathrm{OMe},-\mathrm{CO}_{2} \mathrm{H}, \mathrm{CH}_{2} \mathrm{OH}, \mathrm{CH}_{2} \mathrm{CH}_{2} \mathrm{OH}$ and $\mathrm{CF}_{3}$. In certain
embodiments, $\mathrm{R}^{2}$ is $\mathrm{Cyc}^{1}$, wherein the cycloalkyl ring is optionally substituted with one or more substituents independently selected from $-(1-4 \mathrm{C}$ alkyl $),-\mathrm{OH},-\mathrm{OMe},-\mathrm{CO}_{2} \mathrm{H}$ and $-(1-$ 4 C alkyl $) \mathrm{OH}$, such as one or more substituents independently selected from methyl, $-\mathrm{OH},-$ $\mathrm{CH}_{2} \mathrm{OH}$ and $-\mathrm{CO}_{2} \mathrm{H}$. In one embodiment, $\mathrm{Cyc}^{1}$ is optionally substituted with one or more substituents independently selected from methyl, $-\mathrm{OH},-\mathrm{CH}_{2} \mathrm{OH}$ and $-\mathrm{CO}_{2} \mathrm{H}$. In one embodiment, $\mathrm{Cyc}^{1}$ is optionally substituted with one or two of said substituents.
[00104] Examples of $\mathrm{R}^{2}$ when represented by Cyc ${ }^{1}$ include the structures:











Particular examples of $\mathrm{R}^{2}$ when represented by $\mathrm{Cyc}^{1}$ include the structures:
[00105]



[00106]


In one embodiment of Formula $\mathbf{I}$, Cyc $^{1}$ is a 3,4 or 5 membered cycloalkyl ring which is optionally substituted with one or more substituents independently selected from -(1-4C alkyl), $-\mathrm{OH},-\mathrm{OMe},-\mathrm{CO}_{2} \mathrm{H},-(1-4 \mathrm{C}$ alkyl $) \mathrm{OH}$, halogen and $\mathrm{CF}_{3}$.
[00107] In one embodiment of Formula $\mathbf{I}, \mathrm{Cyc}^{1}$ is a 3,4 or 5 membered cycloalkyl ring which is optionally substituted with one or more substituents independently selected from -( $1-4 \mathrm{C}$ alkyl), $-\mathrm{OH}, \mathrm{OMe},-\mathrm{CO}_{2} \mathrm{H}$ and $-(1-4 \mathrm{C}$ alkyl $) \mathrm{OH}$.
[00108] In one embodiment, $\mathrm{R}^{2}$ is cyclopropyl.
[00109] In one embodiment $\mathrm{R}_{2}$ is selected from the structures:






In one embodiment, $\mathrm{R}^{2}$ is $\mathrm{Cyc}^{1}$ and $\mathrm{R}^{1}$ is hydrogen. In one embodiment, $\mathrm{R}^{2}$ is Cyc ${ }^{1}$ and $\mathrm{R}^{1}$ is ( $1-6 \mathrm{C}$ alkyl).
[00111] In one embodiment, $\mathrm{R}^{2}$ is a 3,4 or 5 membered cycloalkyl ring which is optionally substituted with one or more substituents independently selected from -(1-4C alkyl $),-\mathrm{OH},-\mathrm{OMe},-\mathrm{CO}_{2} \mathrm{H},-(1-4 \mathrm{C}$ alkyl $) \mathrm{OH}$, halogen and $\mathrm{CF}_{3}$.
[00112] In one embodiment, $\mathrm{R}^{2}$ is a 3,4 or 5 membered cycloalkyl ring which is optionally substituted with one or more substituents independently selected from -(1-4C alkyl), $-\mathrm{OH}, \mathrm{OMe},-\mathrm{CO}_{2} \mathrm{H}$ and $-(1-4 \mathrm{C}$ alkyl $) \mathrm{OH}$.
[00113] In one embodiment, $\mathrm{R}^{2}$ is a 3,4 or 5 membered cycloalkyl ring which is optionally substituted with one or more substituents independently selected from methyl, $\mathrm{CO}_{2} \mathrm{H}$, and $\mathrm{CH}_{2} \mathrm{OH}$.
[00114] In certain embodiments, $\mathrm{R}^{2}$ is cyclopropyl optionally substituted with one or more substituents independently selected from -(1-4C alkyl), $-\mathrm{OH},-\mathrm{OMe},-\mathrm{CO}_{2} \mathrm{H},-(1-4 \mathrm{C}$ alkyl) OH , halogen and $\mathrm{CF}_{3}$.
[00115] In certain embodiments, $\mathrm{R}^{2}$ is cyclopropyl optionally substituted with one or more substituents independently selected from methyl, $-\mathrm{CO}_{2} \mathrm{H}$, and $\mathrm{CH}_{2} \mathrm{OH}$.
[00116] In certain embodiments, $\mathrm{R}^{2}$ is cyclobutyl optionally substituted with one or more substituents independently selected from $-(1-4 \mathrm{C}$ alkyl $),-\mathrm{OH},-\mathrm{OMe},-\mathrm{CO}_{2} \mathrm{H},-(1-4 \mathrm{C}$ alkyl) OH , halogen and $\mathrm{CF}_{3}$. In certain embodiments, $\mathrm{R}^{2}$ is cyclobutyl optionally substituted with one or more substituents independently selected from methyl, $-\mathrm{OH},-\mathrm{OMe},-\mathrm{CO}_{2} \mathrm{H}$, $\mathrm{CH}_{2} \mathrm{OH}, \mathrm{CH}_{2} \mathrm{CH}_{2} \mathrm{OH}$ and $\mathrm{CF}_{3}$.
[00117] In certain embodiments, $\mathrm{R}^{2}$ is cyclopentyl optionally substituted with one or more substituents independently selected from $-(1-4 \mathrm{C}$ alkyl $),-\mathrm{OH},-\mathrm{OMe},-\mathrm{CO}_{2} \mathrm{H},-(1-4 \mathrm{C}$
alkyl) OH , halogen and $\mathrm{CF}_{3}$. In certain embodiments, $\mathrm{R}^{2}$ is cyclopentyl optionally substituted with one or more substituents independently selected from methyl, $-\mathrm{OH},-\mathrm{OMe},-\mathrm{CO}_{2} \mathrm{H}$, $\mathrm{CH}_{2} \mathrm{OH}, \mathrm{CH}_{2} \mathrm{CH}_{2} \mathrm{OH}$ and $\mathrm{CF}_{3}$.
[00118] In certain embodiments, $\mathrm{R}^{2}$ is cyclohexyl optionally substituted with one or more substituents independently selected from -(1-4C alkyl), $-\mathrm{OH},-\mathrm{OMe},-\mathrm{CO}_{2} \mathrm{H},-(1-4 \mathrm{C}$ alkyl) OH , halogen and $\mathrm{CF}_{3}$. In certain embodiments, $\mathrm{R}^{2}$ is cyclohexyl optionally substituted with one or more substituents independently selected from methyl, $-\mathrm{OH},-\mathrm{OMe},-\mathrm{CO}_{2} \mathrm{H}$, $\mathrm{CH}_{2} \mathrm{OH}, \mathrm{CH}_{2} \mathrm{CH}_{2} \mathrm{OH}$ and $\mathrm{CF}_{3}$.
[00119] In certain embodiments, $\mathrm{R}^{2}$ is -(1-6C alkyl)(3-6C cycloalkyl). Examples of the ( $1-6 \mathrm{C}$ alkyl) portion include methyl, ethyl, propyl and butyl. Examples of the cycloalkyl portion include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. In one embodiment, the cycloalkyl portion is cyclopropyl. Particular examples include the structures:


[00120] In one embodiment, $\mathrm{R}^{2}$ is -(1-6C alkyl)(3-6C cycloalkyl) and $\mathrm{R}^{1}$ is hydrogen. In one embodiment, $\mathrm{R}^{2}$ is $-\left(1-6 \mathrm{C}\right.$ alkyl)(3-6C cycloalkyl) and $\mathrm{R}^{1}$ is ( $1-6 \mathrm{C}$ alkyl).
[00121] In certain embodiments, $\mathrm{R}^{2}$ is $-(1-6 \mathrm{Calkyl})(1-4 \mathrm{C}$ alkoxy $)$. Examples include $\mathrm{CH}_{2} \mathrm{CH}_{2} \mathrm{OCH}_{3}$ and $\mathrm{CH}\left(\mathrm{CH}_{3}\right) \mathrm{CH}_{2} \mathrm{OCH}_{3}$. In one embodiment, $\mathrm{R}^{2}$ is -( $\left.1-6 \mathrm{Calkyl}\right)(1-4 \mathrm{C}$ alkoxy $)$ and $R^{1}$ is hydrogen. In one embodiment, $R^{2}$ is -( $1-6$ Calkyl) ( $1-4 C$ alkoxy) and $R^{1}$ is ( $1-6 C$ alkyl).
[00122] In certain embodiments, $\mathrm{R}^{2}$ is -(1-6C hydroxyalkyl)(1-4C alkoxy). An example includes $-\mathrm{CH}_{2} \mathrm{CH}(\mathrm{OH}) \mathrm{CH}_{2} \mathrm{OCH}_{3}$. In one embodiment, $\mathrm{R}^{2}$ is $-(1-6 \mathrm{C}$ hydroxyalkyl)(1-4C alkoxy) and $\mathrm{R}^{1}$ is hydrogen. In one embodiment, $\mathrm{R}^{2}$ is $-(1-6 \mathrm{C}$ hydroxyalkyl)(1-4C alkoxy) and $\mathrm{R}^{1}$ is ( $1-6 \mathrm{C}$ alkyl).
[00123] In certain embodiments, $\mathrm{R}^{2}$ is a bridged 7-membered cycloalkyl ring. In certain embodiments, $\mathrm{R}^{2}$ is a bridged 7 -membered cycloalkyl ring optionally substituted with (1-6C)hydroxyalkyl. In certain embodiments, $R^{2}$ is a bridged 7-membered cycloalkyl ring optionally substituted with hydroxymethyl. Examples of $\mathrm{R}^{2}$ include the structures:


[00124] A particular example or $\mathrm{R}^{2}$ is the structure:

[00125] In one embodiment, $\mathrm{R}^{2}$ is a bridged 7-membered cycloalkyl ring optionally substituted with ( $1-6 \mathrm{C}$ )hydroxyalkyl and $\mathrm{R}^{1}$ is hydrogen. In one embodiment, $\mathrm{R}^{2}$ is a bridged 7-membered cycloalkyl ring and $\mathrm{R}^{1}$ is ( $1-6 \mathrm{C}$ alkyl).
[00126] In certain embodiments, $\mathrm{R}^{2}$ is a bridged 7-8 membered heterocyclic ring having 1-2 ring nitrogen atoms. A particular example is the structure:

[00127] In one embodiment, $\mathrm{R}^{2}$ is a bridged 7-8 membered heterocyclic ring having 12 ring nitrogen atoms and $\mathrm{R}^{1}$ is hydrogen. In one embodiment, $\mathrm{R}^{2}$ is a bridged 7-8 membered heterocyclic ring having 1-2 ring nitrogen atoms and $\mathrm{R}^{1}$ is (1-6C alkyl).
[00128] In certain embodiments, $N R{ }^{1} \mathrm{R}^{2}$ forms a 4-6 membered azacyclic ring optionally substituted with one or more substituents independently selected from (1-6C)alkyl, $\mathrm{OH}, \mathrm{CO}_{2} \mathrm{H},(1-3 \mathrm{C}$ alkyl $) \mathrm{CO}_{2} \mathrm{H},-\mathrm{O}(1-6 \mathrm{C}$ alkyl) and (1-6C)hydroxyalkyl. Examples include 4-6 membered azacyclic rings optionally substituted with one or more groups independently selected from methyl, $\mathrm{OH},-\mathrm{C}(=\mathrm{O}) \mathrm{OH},-\mathrm{CH}_{2} \mathrm{COOH}, \mathrm{OMe}$, and $-\mathrm{CH}_{2} \mathrm{OH}$. In certain embodiments, the azacyclic ring is optionally substituted with one or two of said substituents. Particular examples include the structures:










[00129] In certain embodiments, $N R{ }^{1} R^{2}$ forms a 4-6 membered azacyclic ring optionally substituted with one or more substituents independently selected from -(1$6 \mathrm{C})$ alkyl, $-\mathrm{OH},-\mathrm{CO}_{2} \mathrm{H}$ and $-(1-3 \mathrm{C}$ alkyl $) \mathrm{CO}_{2} \mathrm{H}$. Examples include 4-6 membered azacyclic rings optionally substituted with one or two groups independently selected from methyl, OH , $-\mathrm{C}(=\mathrm{O}) \mathrm{OH}$ and $-\mathrm{CH}_{2} \mathrm{COOH}$. Particular examples include the structures:





[00130] Compounds of Formula I also include compounds wherein:
[00131] $\quad R^{1}$ is H or -(1-6C alkyl);
[00132] $\mathrm{R}^{2}$ is $\mathrm{H}, \quad-(1-6 \mathrm{C})$ alkyl, $-(1-6 \mathrm{C}) f l u o r o a l k y l, ~-(1-6 \mathrm{C})$ hydroxyalkyl, -(2$6 \mathrm{C})$ dihydroxyalkyl, $-\left(1-6 \mathrm{C}\right.$ alkyl) CN , -(1-6C alkyl) $\mathrm{SO}_{2} \mathrm{NH}_{2}$, -(1-6C alkyl) $\mathrm{NHSO}_{2}(1-3 \mathrm{C}$ alkyl), -(1-6C alkyl) $\mathrm{NH}_{2}$, -(1-6C alkyl)NH(1-4C alkyl), -(1-6C alkyl)N(1-4C alkyl) $)_{2}$, -(16 C alkyl)hetCyc ${ }^{1},-\left(1-6 \mathrm{C}\right.$ alkyl)hetAr ${ }^{1}$, het $\mathrm{Ar}^{2}$, $-\mathrm{O}(1-6 \mathrm{C}$ alkyl), $-\mathrm{O}(3-6 \mathrm{C}$ cycloalkyl), or a 3, 4 or 5 membered cycloalkyl ring optionally substituted with one or more substituents independently selected from -(1-4C alkyl), -OH, OMe, $-\mathrm{CO}_{2} \mathrm{H}$ and -(1-4C alkyl)OH;
[00133] or $N R^{1} R^{2}$ forms a 4-6 membered azacyclic ring optionally substituted with one or more substituents independently selected from -(1-6C)alkyl, $-\mathrm{OH},-\mathrm{CO}_{2} \mathrm{H}$ and $-(1-3 \mathrm{C}$ alkyl) $\mathrm{CO}_{2} \mathrm{H}$;
[00134] and $\mathrm{X}, \mathrm{Y}, \mathrm{R}^{3}, \mathrm{R}^{4}$ and n are as defined for Formula $\mathbf{I}$.
[00135] Compounds of Formula $I$ also include compounds wherein:
[00136] $\quad \mathrm{R}^{1}$ is H or -( $1-6 \mathrm{C}$ alkyl);
[00137] $\quad \mathrm{R}^{2}$ is $\mathrm{H}, \quad-(1-6 \mathrm{C})$ alkyl, $\quad-(1-6 \mathrm{C})$ fluoroalkyl, $\quad-(1-6 \mathrm{C})$ hydroxyalkyl, $\quad$-(2$6 \mathrm{C})$ dihydroxyalkyl, -(1-6C alkyl)CN, -(1-6C alkyl) $\mathrm{SO}_{2} \mathrm{NH}_{2}$, -(1-6C alkyl) $\mathrm{NHSO}_{2}(1-3 \mathrm{C}$ alkyl), -(1-6C alkyl) $\mathrm{NH}_{2}$, -(1-6C alkyl) $\mathrm{NH}\left(1-4 \mathrm{C}\right.$ alkyl), $-\left(1-6 \mathrm{C}\right.$ alkyl) $\mathrm{N}(1-4 \mathrm{C} \text { alkyl })_{2}$, -(16 C alkyl)hetCyc ${ }^{1},-\left(1-6 \mathrm{C}\right.$ alkyl)hetAr ${ }^{1}$, hetAr ${ }^{2}$, hetCyc ${ }^{2},-\mathrm{O}(1-6 \mathrm{C}$ alkyl), $-\mathrm{O}(3-6 \mathrm{C}$ cycloalkyl), or a bridged 7-membered cycloalkyl ring,
[00138] or $N R^{1} R^{2}$ forms a 4-6 membered azacyclic ring optionally substituted with one or more substituents independently selected from -(1-6C)alkyl, $-\mathrm{OH},-\mathrm{CO}_{2} \mathrm{H}$ and $-(1-3 \mathrm{C}$ alkyl) $\mathrm{CO}_{2} \mathrm{H}$; and
[00139] and $\mathrm{X}, \mathrm{Y}, \mathrm{R}^{3}, \mathrm{R}^{4}$ and n are as defined for Formula $\mathbf{I}$.
[00140] Referring now to the substituents on the ring at the 5-position of Formula $\mathbf{I}$, wherein the 5 -position is identified in the following structure:

[00141] in one embodiment Y is phenyl optionally substituted with one or more substituents independently selected from halogen, (1-4C)alkoxy, $-\mathrm{CF}_{3}-\mathrm{CHF}_{2},-\mathrm{O}(1-4 \mathrm{C}$ alkyl)hetCyc ${ }^{3}$, -(1-4C alkyl)hetCyc ${ }^{3}$, $-\mathrm{O}(1-4 \mathrm{C}$ alkyl $) \mathrm{O}(1-3 \mathrm{C}$ alkyl) and $-\mathrm{O}(3-6 \mathrm{C}$ dihydroxyalkyl).
[00142] In one embodiment, Y is phenyl optionally substituted with one or two of said substituents. In one embodiment Y is phenyl optionally substituted with one or more substituents independently selected from halogen, (1-4C)alkoxy, $-\mathrm{O}\left(1-4 \mathrm{C}\right.$ alkyl)hetCyc ${ }^{3}$, -(14 C alkyl)hetCyc ${ }^{3}$, $-\mathrm{O}(1-4 \mathrm{C}$ alkyl $) \mathrm{O}(1-3 \mathrm{C}$ alkyl) and $-\mathrm{O}(3-6 \mathrm{C}$ dihydroxyalkyl). In one embodiment, Y is phenyl optionally substituted with one or two of said substituents.
[00143] In one embodiment, Y is phenyl optionally substituted with one or more substituents independently selected from $-\mathrm{F},-\mathrm{Cl},-\mathrm{OMe},-\mathrm{CF}_{3},-\mathrm{CHF}_{2}$, morpholinylethoxy, morpholinylethyl, $-\mathrm{OCH}_{2} \mathrm{CH}_{2} \mathrm{OMe}$, 2,3-dihydroxypropoxy and 2,2-dimethyl-1,3-dioxolanyl. In one embodiment, Y is phenyl optionally substituted with one or two of said substituents.
[00144] The term "morpholinylethoxy" as used herein refers to a morpholinyl ring substituted at the nitrogen ring atom with an ethoxy group and can be represented by the structure:

[00145] The term "morpholinylethyl" as used herein refers to a morpholinyl ring substituted at the nitrogen ring atom with an ethyl group and can be represented by the structure:

[00146] Example of Y include phenyl, 3-fluorophenyl, 2,5-difluorophenyl, 2-chloro-5fluorophenyl, 2-methoxyphenyl, 2-methoxy-5-fluorophenyl, 2-trifluoromethyl-5-fluorophenyl, 2-difluoromethyl-5-fluorophenyl, 3-chloro-5-fluorophenyl, 3-fluoro-5-(2-morpholinylethoxy)phenyl, 3-fluoro-5-(2-morpholinylethyl)phenyl, 5-fluoro-2-(2-morpholinylethyl)phenyl, 3-fluoro-5-methoxyethoxyphenyl, 5-fluoro-2-methoxyethoxyphenyl, 3-fluoro-5-(2,3-dihydroxypropoxy)phenyl, 2-(2,3-dihydroxypropoxy)-5-fluorophenyl,


[00147] The terms "3-fluoro-5-(2-morpholinylethoxy)phenyl", "3-fluoro-5-(2morpholinylethyl)phenyl" and "5-fluoro-2-(2-morpholinylethyl)phenyl" can be represented by the structures:



respectively.
[00148] In one embodiment, Y is fluorophenyl optionally substituted with a substituent selected from - $\mathrm{O}\left(1-4 \mathrm{C}\right.$ alkyl)hetCyc ${ }^{3}$, -(1-4C alkyl)hetCyc ${ }^{3},-\mathrm{O}(1-4 \mathrm{C}$ alkyl $) \mathrm{O}(1-3 \mathrm{C}$ alkyl) and - O (3-6C dihydroxyalkyl).
[00149] In one embodiment, Y is fluorophenyl substituted with a substituent selected from morpholinylethoxy, morpholinylethyl, $-\mathrm{OCH}_{2} \mathrm{CH}_{2} \mathrm{OMe}, 2,3$-dihydroxypropoxy and 2,2-dimethyl-1,3-dioxolanyl.
[00150] In one embodiment, Y is selected from 3-fluoro-5-(2morpholinylethoxy)phenyl, $\quad$ 5-fluoro-2-(2-morpholinoethoxy)phenyl, 3-fluoro-5methoxyethoxyphenyl, 3-fluoro-5-(2-morpholinylethyl)phenyl, 5-fluoro-2-(2morpholinylethyl)phenyl, 3-fluoro-5-(2,3-dihydroxypropoxy)phenyl, 2-(2,3-dihydroxypropoxy)-5-fluorophenyl,

and

[00151] In one embodiment Y is phenyl optionally substituted with one or more substituents independently selected from halogen, $-(1-4 \mathrm{C})$ alkoxy, $-\mathrm{CF}_{3},-\mathrm{CHF}_{2},-\mathrm{O}(1-4 \mathrm{C}$ alkyl)hetCyc ${ }^{3}$ and - $\mathrm{O}(1-4 \mathrm{C}$ alkyl) $\mathrm{O}(1-3 \mathrm{C}$ alkyl).
[00152] In one embodiment, Y is phenyl optionally substituted with one or more substituents independently selected from $-\mathrm{F},-\mathrm{Cl},-\mathrm{OMe},-\mathrm{CF}_{3},-\mathrm{CHF}_{2}$, morpholinylethoxy and $-\mathrm{OCH}_{2} \mathrm{CH}_{2} \mathrm{OMe}$. In certain embodiments, Y is phenyl optionally substituted with one or two
of said substituents. Particular values for Y include phenyl, 3-fluorophenyl, 2,5difluorophenyl, 2-chloro-5-fluorophenyl, 2-methoxyphenyl, 2-methoxy-5-fluorophenyl, 2-trifluoromethyl-5-fluorophenyl, 2-difluoromethyl-5-fluorophenyl, 3-chloro-5-fluorophenyl, 3-fluoro-5-(2-morpholinylethoxy)phenyl, 5-fluoro-2-(2-morpholinoethoxy)phenyl, 3-fluoro-5-methoxyethoxyphenyl and 5-fluoro-2-methoxyethoxyphenyl.
[00153] 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 substituents independently selected from halogen, $-\mathrm{O}(1-4 \mathrm{C}$ alkyl), (1-4C)alkyl and $\mathrm{NH}_{2}$. Examples include pyridyl and thienyl groups optionally substituted with one or more substituents independently selected from halogen, -O (1-4C alkyl), (1-4C)alkyl and $\mathrm{NH}_{2}$.
[00154] In certain embodiments, Y is pyridyl optionally substituted with one or more substituents independently selected from fluoro, chloro, methoxy, methyl, ethyl, and amino.
[00155] In certain embodiments Y is pyrid-2-yl, pyrid-3-yl, 5-fluoropyrid-3-yl, 2-methoxy-5-fluoropyridy-3-yl, 2-chloro-5-fluoropyridy-3-yl, 2-methyl-5-fluoropyrid-3-yl, 2-ethyl-5-fluoropyrid-3-yl or 2-amino-5-fluoropyrid-3-yl.
[00156] In certain embodiments, Y is pyridyl substituted with one or more substituents independently selected from halogen, (1-4C)alkyl and amino.
[00157] In certain embodiments, Y is pyridyl substituted with one or more substituents independently selected from halogen and (1-4C)alkyl.
[00158] In certain embodiments, Y is pyridyl substituted with one or more substituents independently selected from fluoro, chloro, methyl and ethyl.
[00159] In certain embodiments, Y is pyridyl substituted with one or more substituents independently selected from F , methyl and ethyl.
[00160] In certain embodiments, Y is 5-fluoropyrid-3-yl, 2-methyl-5-fluoropyrid-3-yl or 2-ethyl-5-fluoropyrid-3-yl.
[00161] In certain embodiments, Y is 5-fluoropyrid-3-yl.
[00162] 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 substituents independently selected from halogen, $-\mathrm{O}(1-4 \mathrm{C}$ alkyl) and (14C)alkyl. Examples include pyridyl and thienyl groups optionally substituted with one or more substituents independently selected from halogen, $-\mathrm{O}(1-4 \mathrm{C}$ alkyl) and (1-4C)alkyl, for example one or more substituents independently selected from fluoro, methoxy and methyl.

Particular values for Y include pyrid-2-yl, pyrid-3-yl, 5-fluoropyrid-3-yl, 2-methoxy-5-fluoropyridy-3-yl and 2-methyl-5-fluoropyridy-3-yl.
[00163] In one embodiment, Y is a pyrid-2-on-3-yl ring optionally substituted with one or more substituents independently selected from halogen and (1-4C)alkyl. Examples include pyrid-2-on-3-yl rings optionally substituted with one or more substituents independently selected from fluoro and methyl. In certain embodiments the pyrid-2-on-3-yl ring is optionally substituted with one or two of said substituents. In one embodiment, Y is 5 -fluoropyridin-2(1H)-one optionally substituted with (1-4C)alkyl, for example methyl. Particular values for Y include the structures:


[00164] In one embodiment, the Y group has the absolute configuration shown in Figure Ia:


Ia
[00165] wherein $R^{1}, R^{2}, R^{3}, R^{4}, X, Y$ and $n$ are as defined herein.
[00166] With reference to the $R^{3}$ substituent, in one embodiment $R^{3}$ is $H$.
[00167] In one embodiment, $\mathrm{R}^{3}$ is -(1-4C)alkyl, for example, methyl, ethyl, propyl, isopropyl or butyl. In one embodiment, $\mathrm{R}^{3}$ is methyl.
[00168] With reference to the $R^{4}$ substituent, in one embodiment $R^{4}$ is halogen. Particular examples are fluoro and chloro.
[00169] In one embodiment, $\mathrm{R}^{4}$ is -(1-4C)alkyl, such as methyl, ethyl, propyl, isopropyl, or butyl. A particular example is methyl.
[00170] In one embodiment, $\mathrm{R}^{4}$ is -OH .
In one embodiment, $\mathrm{R}^{4}$ is (1-4 C)alkoxy, for example -OMe and -OEt.
[00172]
In one embodiment, $\mathrm{R}^{4}$ is $-\mathrm{NH}_{2}$.
[00173] In one embodiment, $\mathrm{R}^{4}$ is $-\mathrm{NH}(1-4 \mathrm{C}$ alkyl), for example -NHMe, -NHEt, NHPr, -NHiPr or -NHBu. A particular example is -NHMe.
[00174] In one embodiment, $\mathrm{R}^{4}$ is $\mathrm{CH}_{2} \mathrm{OH}$.
[00175] In one embodiment, each $\mathrm{R}^{4}$ is independently selected from $-\mathrm{F},-\mathrm{Cl},-\mathrm{OH}$, -$\mathrm{OMe},-\mathrm{NH}_{2},-\mathrm{Me},-\mathrm{CH}_{2} \mathrm{OH}$ and -NHMe .
[00176] 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 .
[00177] In one embodiment, n is 0 .
[00178] In one embodiment, n is 1.
[00179] In one embodiment, n is 2.
[00180] With reference to the heterocyclic ring directly attached to the 5-position of Formula $\mathbf{I}$, in certain embodiments, X is null, $-\mathrm{CH}_{2}$ - or $-\mathrm{CH}_{2} \mathrm{CH}_{2}$ -
[00181] In one embodiment X is null, such that the heterocyclic ring at the 5-position of Formula I has the structure:

[00182] 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, $-\mathrm{CF}_{3}$ and $-\mathrm{CHF}_{2}$. In one embodiment, Y is phenyl, 3-fluorophenyl and 2,5difluorophenyl. In one embodiment, Y is 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 substituents independently selected from halogen, -O (1-4C alkyl) and (14 C )alkyl, for example one or more halogen atoms. In one embodiment, Y is pyridyl. In one embodiment, $\mathrm{R}^{3}$ is hydrogen. In another embodiment, $\mathrm{R}^{3}$ is methyl. In one embodiment, n is 0 . A particular example of the ring at the 5 -position of Formula $\mathbf{I}$ when X is null includes the structures:



[00183] In one embodiment, X is $\mathrm{CH}_{2}$, such that the heterocyclic ring at the 5-position of Formula $\mathbf{I}$ has the structure:

[00184] where $R^{3}, R^{4}, Y$ and $n$ are as defined herein. In one embodiment, $X$ is $\mathrm{CH}_{2}$, $R^{3}, R^{4}$ and $n$ are as defined herein, and $Y$ is phenyl optionally substituted with one or more substituents independently selected from $-\mathrm{F},-\mathrm{Cl},-\mathrm{OMe},-\mathrm{CF}_{3},-\mathrm{CHF}_{2}$, morpholinylethoxy, morpholinylethyl, $-\mathrm{OCH}_{2} \mathrm{CH}_{2} \mathrm{OMe}$, 2,3-dihydroxypropoxy and 2,2-dimethyl-1,3-dioxolanyl.
[00185] In one embodiment, X is $\mathrm{CH}_{2}, \mathrm{R}^{3}, \mathrm{R}^{4}$ and n are as defined herein, and 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, 3-chloro-5-fluorophenyl, 3-fluoro-5-(2-morpholinylethoxy)phenyl, 3-fluoro-5-(2morpholinylethyl)phenyl, methoxyethoxyphenyl,

5-fluoro-2-(2-morpholinylethyl)phenyl, 3-fluoro-5-
5-fluoro-2-methoxyethoxyphenyl, 3-fluoro-5-(2,3dihydroxypropoxy)phenyl, 2-(2,3-dihydroxypropoxy)-5-fluorophenyl,

or


In one embodiment, X is $\mathrm{CH}_{2}, \mathrm{R}^{3}, \mathrm{R}^{4}$ and n are as defined herein, and Y is fluorophenyl substituted with a substituent selected from morpholinylethoxy, $\mathrm{OCH}_{2} \mathrm{CH}_{2} \mathrm{OMe}$, 2,3-dihydroxypropoxy and 2,2-dimethyl-1,3-dioxolanyl.
[00187] In one embodiment, X is $\mathrm{CH}_{2}, \mathrm{Y}$ and $\mathrm{R}^{4}$ are as defined herein, and $\mathrm{R}^{3}$ is hydrogen. In another embodiment, X is $\mathrm{CH}_{2}, \mathrm{Y}$ and $\mathrm{R}^{4}$ are as defined herein, and $\mathrm{R}^{3}$ is methyl. In one embodiment, each $\mathrm{R}^{4}$ is independently selected from $\mathrm{F}, \mathrm{Cl}, \mathrm{Me}, \mathrm{OH}, \mathrm{OMe}$, $\mathrm{NH}_{2}, \mathrm{NHMe}, \mathrm{CH}_{2} \mathrm{OH}, \mathrm{CHF}_{2}$ and $\mathrm{CF}_{3}$. In one embodiment, n is 0 . In one embodiment, n is 1 . In one embodiment, n is 2 .
[00188] In one embodiment X is $\mathrm{CH}_{2}, \mathrm{R}^{3}, \mathrm{R}^{4}$ and n are as defined herein, and Y is a 56 membered heteroaryl ring having a ring heteroatom selected from N and S , wherein said heteroaryl ring is optionally substituted with one or more substituents independently selected from halogen, $-\mathrm{O}\left(1-4 \mathrm{C}\right.$ alkyl), (1-4C)alkyl and $\mathrm{NH}_{2}$.
[00189] In one embodiment, X is $\mathrm{CH}_{2}, \mathrm{R}^{3}, \mathrm{R}^{4}$ and n are as defined herein, and Y is pyrid-2-yl, pyrid-3-yl, 5 -fluoropyrid-3-yl, 2-chloro-5-fluoropyridy-3-yl, 2-methyl-5-
fluoropyrid-3-yl, or 2-ethyl-5-fluoropyrid-3-yl. In one embodiment, $\mathrm{R}^{3}$ is hydrogen. In another embodiment, $\mathrm{R}^{3}$ is methyl. In one embodiment, each $\mathrm{R}^{4}$ is independently selected from $\mathrm{F}, \mathrm{Cl}, \mathrm{Me}, \mathrm{OH}, \mathrm{OMe}, \mathrm{NH}_{2}, \mathrm{NHMe}, \mathrm{CH}_{2} \mathrm{OH}, \mathrm{CHF}_{2}$ and $\mathrm{CF}_{3}$. In one embodiment, n is 0 . In one embodiment, n is 1 . In one embodiment, n is 2 .
[00190] In one embodiment, X is $\mathrm{CH}_{2}, \mathrm{R}^{3}, \mathrm{R}^{4}$ and n are as defined herein, and Y is pyridyl optionally substituted with one or more substituents independently selected from halogen and ( $1-4 \mathrm{C}$ )alkyl.
[00191] In one embodiment, X is $\mathrm{CH}_{2}, \mathrm{R}^{3}, \mathrm{R}^{4}$ and n are as defined herein, and Y is pyridyl optionally substituted with one or more substituents independently selected from fluoro, methyl and ethyl.
[00192] In one embodiment, X is $\mathrm{CH}_{2}, \mathrm{R}^{3}, \mathrm{R}^{4}$ and n are as defined herein, and Y is 5-fluoropyrid-3-yl, 2-methyl-5-fluoropyrid-3-yl, or 2-ethyl-5-fluoropyrid-3-yl. In one embodiment, $\mathrm{R}^{3}$ is hydrogen.
[00193] In one embodiment, X is $\mathrm{CH}_{2}, \mathrm{R}^{3}, \mathrm{R}^{4}$ and n are as defined herein, and Y is a pyrid-2-on-3-yl ring optionally substituted with one or more substituents independently selected from halogen and (1-4C)alkyl.
[00194] In one embodiment, X is $\mathrm{CH}_{2}, \mathrm{R}^{3}, \mathrm{R}^{4}$ and n are as defined herein, and Y is a pyrid-2-on-3-yl ring optionally substituted with one or more groups selected from methyl and fluoro. In one embodiment, Y is 5 -fluoropyridin- $2(1 \mathrm{H})$-one optionally substituted with methyl. In one embodiment, $\mathrm{R}^{3}$ is hydrogen. In another embodiment, $\mathrm{R}^{3}$ is methyl. In one embodiment, each $\mathrm{R}^{4}$ is independently selected from $\mathrm{F}, \mathrm{Cl}, \mathrm{Me}, \mathrm{OH}, \mathrm{OMe}, \mathrm{NH}_{2}, \mathrm{NHMe}$, $\mathrm{CH}_{2} \mathrm{OH}, \mathrm{CHF}_{2}$ and $\mathrm{CF}_{3}$. In one embodiment, n is 0 . In one embodiment, n is 1 . In one embodiment, n is 2 .
[00195] In one embodiment the ring at the 5-position of Formula I when X is $\mathrm{CH}_{2}$ include the structures:





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[00196]
In one embodiment, X is $\mathrm{CH}_{2}$, such that the heterocyclic ring at the 5 -position of Formula I has the structure:

[00197] where $\mathrm{R}^{3}, \mathrm{R}^{4}, \mathrm{Y}$ 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, $-\mathrm{CF}_{3}-\mathrm{CHF}_{2},-\mathrm{O}\left(1-4 \mathrm{C}\right.$ alkyl)hetCyc ${ }^{3}$ or $-\mathrm{O}(1-4 \mathrm{C}$ alkyl) $\mathrm{O}(1-3 \mathrm{C}$ alkyl). In one embodiment, Y is phenyl, 3-fluorophenyl, 2,5-difluorophenyl, 2-difluoromethyl-5fluorophenyl, 2-trifluoromethyl-5-fluorophenyl, 2-chloro-5-fluorophenyl, 3-chloro-5fluorophenyl, 2-methoxy-5-fluorophenyl, 3-fluoro-5-methoxyethoxyphenyl, 3-fluoro-5-(2morpholinylethoxy)phenyl, 5-fluoro-2-(2-morpholinoethoxy)phenyl, or 5-fluoro-2methoxyethoxyphenyl. 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 substituents independently selected from halogen, $-\mathrm{O}(1-4 \mathrm{C}$ alkyl) and (14 C )alkyl. In one embodiment, $\mathrm{R}^{3}$ is hydrogen. In another embodiment, $\mathrm{R}^{3}$ is methyl. In one embodiment, each $\mathrm{R}^{4}$ is independently selected from $\mathrm{F}, \mathrm{Cl}, \mathrm{Me}, \mathrm{OH}, \mathrm{OMe}, \mathrm{NH}_{2}$, NHMe , $\mathrm{CH}_{2} \mathrm{OH}, \mathrm{CHF}_{2}$ and $\mathrm{CF}_{3}$. In one embodiment, Y is pyrid-2-yl, 5-fluoropyrid-3-yl or 2-methoxy-5-fluoropyridy-3-yl. In one embodiment, n is 0,1 or 2 .
[00198] Particular examples of the ring at the 5-position of Formula $\mathbf{I}$ when X is $\mathrm{CH}_{2}$ include the structures:















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[00199] In one embodiment, X is $-\mathrm{CH}_{2} \mathrm{CH}_{2}$-, such that the heterocyclic ring at the 5position of Formula I has the structure:

[00200] 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, $-\mathrm{CF}_{3}$ and $-\mathrm{CHF}_{2}$. In one embodiment, Y is phenyl or 3 -fluorophenyl. 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 substituents independently selected from halogen, $-\mathrm{O}(1-4 \mathrm{C}$ alkyl) and (1-4C)alkyl. In one embodiment, Y is pyridyl optionally substituted with one or more F atoms. In one embodiment, $\mathrm{R}^{3}$ is hydrogen. In another embodiment, $\mathrm{R}^{3}$ 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 $\mathbf{I}$ when X is $-\mathrm{CH}_{2} \mathrm{CH}_{2}$ - include the structures:


[00201] In one embodiment, X is $-\mathrm{CH}_{2} \mathrm{O}$-. In one embodiment, the heterocyclic ring at the 5-position of Formula I has the structure:

[00202] 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, $-\mathrm{CF}_{3}$ and $-\mathrm{CHF}_{2}$. 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 phenyl, 3-fluorophenyl, 2,5-difluorophenyl, or 2-methoxyphenyl. 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 substituents independently selected from halogen, $-\mathrm{O}(1-4 \mathrm{C}$ alkyl) and (1-4C)alkyl, for example one or more halogen atoms. In one embodiment, Y is pyrid-3-yl. In one embodiment, $\mathrm{R}^{3}$ is hydrogen. In another embodiment, $\mathrm{R}^{3}$ is methyl. In one embodiment, n is 0,1 or 2 . Particular examples of the ring at the 5-position of Formula $\mathbf{I}$ when X is $-\mathrm{CH}_{2} \mathrm{O}$ - include the structures:






[00203]
In one embodiment, X is $-\mathrm{CH}_{2} \mathrm{NR}^{\mathrm{d}}$-. In one embodiment, the heterocyclic ring at the 5-position of Formula $\mathbf{I}$ has the structure:

[00204]
where $R^{3}, R^{4}, Y, R^{d}$ and $n$ are as defined herein. In one embodiment, $R^{d}$ is $H$. In one embodiment, $\mathrm{R}^{\mathrm{d}}$ is $-(1-4 \mathrm{C}$ 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, -(14C)alkoxy, $-\mathrm{CF}_{3}$ and $-\mathrm{CHF}_{2}$. 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 substituents independently selected from halogen, $-\mathrm{O}(1-4 \mathrm{C}$ alkyl) and (1-4C)alkyl. In one embodiment, Y is pyridyl optionally substituted with one or more F atoms. In one embodiment, n is 0 . Particular examples of the ring at the 5 -position of Formula I when X is $-\mathrm{CH}_{2} \mathrm{NR}^{\mathrm{d}}$ - include the structures:




[00205] 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 as a mixture of isomers such as a racemic or diastereomeric mixture, or in an enantiomerically or diastereomerically pure form.
[00206] The compounds of Formula I also include compounds of Formula Ib


Ib
[00207] and salts thereof, wherein:
[00208] $\quad \mathrm{R}^{1}$ is H ;
[00209] $\mathrm{R}^{2}$ is H , (1-6C)alkyl, (1-6C)fluoroalkyl, -(1-6C)hydroxyalkyl or -(2-6C)dihydroxyalkyl;
[00210] Y is (i) phenyl optionally substituted with one or more substituents independently selected from halogen, $-(1-4 \mathrm{C})$ alkoxy, $-\mathrm{CF}_{3}-\mathrm{CHF}_{2},-\mathrm{O}\left(1-4 \mathrm{C}\right.$ alkyl)hetCyc ${ }^{3}$ and $-\mathrm{O}(1-4 \mathrm{C}$ alkyl) $\mathrm{O}(1-3 \mathrm{C}$ alkyl) 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 substituents independently selected from halogen, -O (1-4C alkyl) and (14C)alkyl;
[00211] hetCyc ${ }^{3}$ is a 5-6 membered heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O ;
[00212] X is $\mathrm{CH}_{2}$ or $\mathrm{CH}_{2} \mathrm{CH}_{2}$;
[00213] $\mathrm{R}^{3}$ is H ;
[00214] each $\mathrm{R}^{4}$ is independently selected from halogen, -(1-4C)alkyl, -OH, -(14 C )alkoxy, $-\mathrm{NH}_{2},-\mathrm{NH}\left(1-4 \mathrm{C}\right.$ alkyl) and $-\mathrm{CH}_{2} \mathrm{OH}$; and
[00215] $n$ is 0,1 , or 2 .
[00216] In certain embodiments of Formula Ib, $\mathrm{R}^{2}$ is H , (1-6C)alkyl, -(16C)hydroxyalkyl or -(2-6C)dihydroxyalkyl; Y is phenyl optionally substituted with one or more substituents independently selected from $-\mathrm{F},-\mathrm{Cl},-\mathrm{OMe},-\mathrm{CF}_{3}, \quad-\mathrm{CHF}_{2}$, morpholinylethoxy and $-\mathrm{OCH}_{2} \mathrm{CH}_{2} \mathrm{OMe}$; X is $\mathrm{CH}_{2}$ and n is 0 .
[00217] In certain embodiments of Formula $\mathbf{I b}, \mathrm{R}^{2}$ is H , methyl, ethyl, isopropyl, tertbutyl, $\mathrm{CH}_{2} \mathrm{CH}_{2} \mathrm{OH}$, or $\mathrm{CH}_{2} \mathrm{CH}(\mathrm{OH}) \mathrm{CH}_{2} \mathrm{OH}$; Y is phenyl, 3-fluorophenyl, 2,5-difluorophenyl, 2-chloro-5-fluorophenyl, 2-methoxyphenyl, 2-methoxy-5-fluorophenyl, 2-trifluoromethyl-5fluorophenyl, 2-difluoromethyl-5-fluorophenyl, 3-chloro-5-fluorophenyl, 3-fluoro-5-(2morpholinylethoxy) phenyl, 5-fluoro-2-(2-morpholinoethoxy)phenyl, 3-fluoro-5methoxyethoxyphenyl or 5-fluoro-2-methoxyethoxyphenyl; X is $\mathrm{CH}_{2}$; and n is 0 .
[00218] In certain embodiments of Formula Ib, $R^{2}$ is $H$, (1-6C)alkyl, -(16C)hydroxyalkyl or -(2-6C)dihydroxyalkyl; Y is pyridyl optionally substituted with one or more substituents independently selected from $\mathrm{F}, \mathrm{OMe}$ and $\mathrm{Me} ; \mathrm{X}$ is $\mathrm{CH}_{2}$; and n is 0 .
[00219] In certain embodiments of Formula $\mathbf{I b}, \mathrm{R}^{2}$ is H , methyl, ethyl, isopropyl, tertbutyl, $\mathrm{CH}_{2} \mathrm{CH}_{2} \mathrm{OH}$, or $\mathrm{CH}_{2} \mathrm{CH}(\mathrm{OH}) \mathrm{CH}_{2} \mathrm{OH}$; Y is pyrid-2-yl, pyrid-3-yl, 5-fluoropyrid-3-yl, 2-methoxy-5-fluoropyridy-3-yl or 2-methyl-5-fluoropyridy-3-yl; X is $\mathrm{CH}_{2}$; and n is 0 .
[00220] Compounds of Formula I also include compounds of Formula Ic,


Ic
[00221] and salts thereof, wherein:
[00222]
$N R{ }^{1} R^{2}$ forms a 4-6 membered azacyclic ring optionally substituted with one or more substituents independently selected from (1-6C)alkyl, $\mathrm{OH}, \mathrm{CO}_{2} \mathrm{H}$ and (1-3C alkyl) $\mathrm{CO}_{2} \mathrm{H}$;
[00223] X is $\mathrm{CH}_{2}$ or $\mathrm{CH}_{2} \mathrm{CH}_{2}$;
[00224] $Y$ is (i) phenyl optionally substituted with one or more substituents independently selected from halogen, (1-4C)alkoxy, $-\mathrm{CF}_{3}-\mathrm{CHF}_{2},-\mathrm{O}\left(1-4 \mathrm{C}\right.$ alkyl)hetCyc ${ }^{3}$ and $-\mathrm{O}(1-4 \mathrm{C}$ alkyl $) \mathrm{O}(1-3 \mathrm{C}$ alkyl) 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 substituents independently selected from halogen, -O (1-4C alkyl) and (14C)alkyl;
[00225] hetCyc ${ }^{3}$ is a 5-6 membered heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O ;
[00226]
$\mathrm{R}^{3}$ is H ;
[00227]
each $\mathrm{R}^{4}$ is independently selected from halogen, -(1-4C)alkyl, -OH, -( $1-$ 4C)alkoxy, $-\mathrm{NH}_{2},-\mathrm{NH}\left(1-4 \mathrm{C}\right.$ alkyl) and $-\mathrm{CH}_{2} \mathrm{OH}$; and
[00228] n is 0,1 , or 2 .
[00229] In certain embodiments of Formula Ic, $\mathrm{NR}^{1} \mathrm{R}^{2}$ forms 4-6 membered azacyclic ring optionally substituted with one or two groups independently selected from methyl, OH , $\mathrm{C}(=\mathrm{O}) \mathrm{OH}$ or $\mathrm{CH}_{2} \mathrm{COOH} ; \mathrm{Y}$ is phenyl optionally substituted with one or more substituents independently selected from $-\mathrm{F},-\mathrm{Cl},-\mathrm{OMe},-\mathrm{CF}_{3},-\mathrm{CHF}_{2}$, morpholinylethoxy and $\mathrm{OCH}_{2} \mathrm{CH}_{2} \mathrm{OMe} ; \mathrm{X}$ is $\mathrm{CH}_{2}$; and n is 0 .
[00230] In certain embodiments of Formula Ic, Y is phenyl, 3-fluorophenyl, 2,5difluorophenyl, 2-chloro-5-fluorophenyl, 2-methoxyphenyl, 2-methoxy-5-fluorophenyl, 2-trifluoromethyl-5-fluorophenyl, 2-difluoromethyl-5-fluorophenyl, 3-chloro-5-fluorophenyl, 3-fluoro-5-(2-morpholinylethoxy) phenyl, 5-fluoro-2-(2-morpholinoethoxy)phenyl, 3-fluoro-5-methoxyethoxyphenyl or 5-fluoro-2-methoxyethoxyphenyl; X is $\mathrm{CH}_{2} ; \mathrm{n}$ is 0 ; and $\mathrm{NR}^{1} \mathrm{R}^{2}$ forms 4-6 membered azacyclic ring selected from one of the following structures:





[00231] In certain embodiments of Formula IC, $N R^{1} R^{2}$ forms 4-6 membered azacyclic ring optionally substituted with one or two groups independently selected from methyl, OH , $\mathrm{C}(=\mathrm{O}) \mathrm{OH}$ or $\mathrm{CH}_{2} \mathrm{COOH} ; \mathrm{Y}$ is pyridyl optionally substituted with one or more substituents independently selected from F , OMe and $\mathrm{Me} ; \mathrm{X}$ is $\mathrm{CH}_{2}$; and n is 0 .
[00232] In certain embodiments of Formula Ic, $Y$ is pyrid-2-yl, pyrid-3-yl, 5-fluoropyrid-3-yl, 2-methoxy-5-fluoropyridy-3-yl or 2-methyl-5-fluoropyridy-3-yl; X is $\mathrm{CH}_{2}$; n is 0 ; and $\mathrm{NR}^{1} \mathrm{R}^{2}$ forms 4-6 membered azacyclic ring selected from one of the following structures:





[00233] Compounds of Formula I also include compounds of Formula Id:


Id
[00234]
and salts thereof, wherein:
[00235]
[00236]
$R^{1}$ is $H$; membered cycloalkyl ring optionally substituted with one or more substituents independently selected from -(1-4C alkyl), - OH, -OMe, $-\mathrm{CO}_{2} \mathrm{H}$ and $-(1-4 \mathrm{C}$ alkyl) OH ;
[00237] $Y$ is (i) phenyl optionally substituted with one or more substituents independently selected from halogen, $-(1-4 \mathrm{C})$ alkoxy, $-\mathrm{CF}_{3}-\mathrm{CHF}_{2},-\mathrm{O}\left(1-4 \mathrm{C}\right.$ alkyl)hetCyc ${ }^{3}$ and $-\mathrm{O}(1-4 \mathrm{C}$ alkyl) $\mathrm{O}(1-3 \mathrm{C}$ alkyl) 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 substituents independently selected from halogen, $-\mathrm{O}(1-4 \mathrm{C}$ alkyl) and (14C)alkyl;
[00238] hetCyc ${ }^{3}$ is a 5-6 membered heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O ;
[00239] X is $\mathrm{CH}_{2}$ or $\mathrm{CH}_{2} \mathrm{CH}_{2}$;
[00240] $\mathrm{R}^{3}$ is H ;
[00241] each $\mathrm{R}^{4}$ is independently selected from halogen, -(1-4C)alkyl, -OH, -(14 C )alkoxy, $-\mathrm{NH}_{2},-\mathrm{NH}\left(1-4 \mathrm{C}\right.$ alkyl) and $-\mathrm{CH}_{2} \mathrm{OH}$; and
[00242] n is 0,1 , or 2 .
[00243] In certain embodiments of Formula Id, $\mathrm{R}^{2}$ is $\mathrm{Cyc}^{1}$ which is optionally substituted with one or more substituents independently selected from methyl, $-\mathrm{OH},-\mathrm{CH}_{2} \mathrm{OH}$ and $-\mathrm{CO}_{2} \mathrm{H} ; \mathrm{Y}$ is phenyl optionally substituted with one or more substituents independently selected from $-\mathrm{F},-\mathrm{Cl},-\mathrm{OMe},-\mathrm{CF}_{3},-\mathrm{CHF}_{2}$, morpholinylethoxy and $-\mathrm{OCH}_{2} \mathrm{CH}_{2} \mathrm{OMe}$; X is $\mathrm{CH}_{2}$; and n is 0 .
[00244] In certain embodiments of Formula Id, Y is phenyl, 3-fluorophenyl, 2,5difluorophenyl, 2-chloro-5-fluorophenyl, 2-methoxyphenyl, 2-methoxy-5-fluorophenyl, 2-trifluoromethyl-5-fluorophenyl, 2-difluoromethyl-5-fluorophenyl, 3-chloro-5-fluorophenyl, 3-fluoro-5-(2-morpholinylethoxy)phenyl, 5-fluoro-2-(2-morpholinoethoxy)phenyl, 3-fluoro-5-methoxyethoxyphenyl or 5-fluoro-2-methoxyethoxyphenyl; X is $\mathrm{CH}_{2}, \mathrm{n}$ is 0 ; and $\mathrm{R}^{2}$ is selected from the structures:






[00245] In certain embodiments of Formula Id, $\mathrm{R}^{2}$ is cyclopropyl optionally substituted with one or two substituents independently selected from methyl, $-\mathrm{OH},-\mathrm{CH}_{2} \mathrm{OH}$ and $-\mathrm{CO}_{2} \mathrm{H} ; \quad \mathrm{Y}$ is phenyl optionally substituted with one or more substituents independently selected from - $\mathrm{F},-\mathrm{Cl},-\mathrm{OMe},-\mathrm{CF}_{3},-\mathrm{CHF}_{2}$, morpholinylethoxy and $-\mathrm{OCH}_{2} \mathrm{CH}_{2} \mathrm{OMe}$; X is $\mathrm{CH}_{2}$; and n is 0 .
[00246] In certain embodiments of Formula Id, $\mathrm{R}^{2}$ is $\mathrm{Cyc}^{1}$ which is optionally substituted with one or more substituents independently selected from methyl, $-\mathrm{OH},-\mathrm{CH}_{2} \mathrm{OH}$ and $-\mathrm{CO}_{2} \mathrm{H} ; \mathrm{Y}$ is pyridyl optionally substituted with one or more substituents independently selected from $\mathrm{F}, \mathrm{OMe}$ and Me ; X is $\mathrm{CH}_{2}$; and n is 0 .
[00247] In certain embodiments of Formula Id, Y is pyrid-2-yl, pyrid-3-yl, 5-fluoropyrid-3-yl, 2-methoxy-5-fluoropyridy-3-yl or 2-methyl-5-fluoropyridy-3-yl; X is $\mathrm{CH}_{2}$; n is 0 ; and $\mathrm{R}^{2}$ is selected from the structures:

[00248] Compounds of Formula I also include compounds of Formula Ie


Ie
[00249] and salts thereof, wherein:
[00250] $\mathrm{R}^{1}$ is H ;
[00251] $\quad \mathrm{R}^{2}$ is $-\left(1-6 \mathrm{C}\right.$ alkyl) CN , $-(1-6 \mathrm{C}$ alkyl $) \mathrm{SO}_{2} \mathrm{NH}_{2}$, $-\left(1-6 \mathrm{C}\right.$ alkyl) $\mathrm{NHSO}_{2}(1-3 \mathrm{C}$
alkyl), -(1-6C alkyl) NH 2 , -(1-6C alkyl) $\mathrm{NH}(1-4 \mathrm{C}$ alkyl $)$, or $-\left(1-6 \mathrm{C}\right.$ alkyl) $\mathrm{N}(1-4 \mathrm{C} \text { alkyl })_{2}$;
[00252] $\quad \mathrm{Y}$ is (i) phenyl optionally substituted with one or more substituents independently selected from halogen, (1-4C)alkoxy, $-\mathrm{CF}_{3}-\mathrm{CHF}_{2},-\mathrm{O}\left(1-4 \mathrm{C}\right.$ alkyl)hetCyc ${ }^{3}$ and $-\mathrm{O}(1-4 \mathrm{C}$ alkyl) $\mathrm{O}(1-3 \mathrm{C}$ alkyl), 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 substituents independently selected from halogen and -O(1-4C alkyl);
[00253] hetCyc ${ }^{3}$ is a 5-6 membered heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O ;
[00254] X is $\mathrm{CH}_{2}$ or $\mathrm{CH}_{2} \mathrm{CH}_{2}$;
[00255] $\mathrm{R}^{3}$ is H ;
[00256] each $\mathrm{R}^{4}$ is independently selected from halogen, -(1-4C)alkyl, -OH, -(14 C )alkoxy, $-\mathrm{NH}_{2},-\mathrm{NH}\left(1-4 \mathrm{C}\right.$ alkyl) and $-\mathrm{CH}_{2} \mathrm{OH}$; and
[00257] n is 0,1 , or 2 .
[00258] In certain embodiments of Formula $\mathbf{I e}$, Y is phenyl optionally substituted with one or more substituents independently selected from halogen, (1-4C)alkoxy, $-\mathrm{CF}_{3}-\mathrm{CHF}_{2}$, -$\mathrm{O}\left(1-4 \mathrm{C}\right.$ alkyl)hetCyc ${ }^{3}$ and $-\mathrm{O}(1-4 \mathrm{C}$ alkyl $) \mathrm{O}(1-3 \mathrm{C}$ alkyl $) ; \mathrm{X}$ is $\mathrm{CH}_{2}$; and n is 0 .
[00259] In certain embodiments of Formula Ie, Y is phenyl, 3-fluorophenyl, 2,5difluorophenyl, 2-chloro-5-fluorophenyl, 2-methoxyphenyl, 2-methoxy-5-fluorophenyl, 2-trifluoromethyl-5-fluorophenyl, 2-difluoromethyl-5-fluorophenyl, 3-chloro-5-fluorophenyl, 3-fluoro-5-(2-morpholinylethoxy) phenyl, 5-fluoro-2-(2-morpholinoethoxy)phenyl, 3-fluoro-5-methoxyethoxyphenyl or 5-fluoro-2-methoxyethoxyphenyl; X is $\mathrm{CH}_{2}$; and n is 0 .
[00260] In certain embodiments of Formula Ie, 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 substituents independently selected from halogen and $-\mathrm{O}(1-4 \mathrm{C}$ alkyl); X is $\mathrm{CH}_{2}$; and n is 0 .
[00261] In certain embodiments of Formula Ie, Y is pyrid-2-yl, pyrid-3-yl, 5-fluoropyrid-3-yl, 2-methoxy-5-fluoropyridy-3-yl or 2-methyl-5-fluoropyridy-3-yl; X is $\mathrm{CH}_{2}$ and $n$ is 0 .
[00262] Compounds of Formula I also include compounds of Formula If


If
[00263] and salts thereof, wherein:
[00264]
[00265] $R^{1}$ is $H$; $R^{2}$ is -(1-6C alkyl)hetCyc ${ }^{1}$, ( $1-6 \mathrm{C}$ alkyl)hetAr ${ }^{1}$, het $\mathrm{Ar}^{2}$ or hetCyc ${ }^{2}$;
[00266] hetCyc ${ }^{1}$ is a $5-6$ membered heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O , wherein hetCyc ${ }^{1}$ is optionally substituted with oxo; [00267] hetCyc ${ }^{2}$ is a 6 membered carbon-linked heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O , wherein het $\mathrm{Cyc}^{2}$ is optionally substituted with $\mathrm{F}, \mathrm{SO}_{2} \mathrm{NH}_{2}$, or $\mathrm{SO}_{2}(1-3 \mathrm{C}$ alkyl);
[00268] het $\mathrm{Ar}^{1}$ is a 5 -membered heteroaryl ring having 1-2 ring heteroatoms independently selected from N and O and optionally substituted with (1-4C)alkyl;
[00269] het $\mathrm{rr}^{2}$ is a 5-6 membered heteroaryl ring having 1-2 ring nitrogen atoms and optionally substituted with one or more substituents independently selected from (1-4C)alkyl;
[00270] Y is (i) phenyl optionally substituted with one or more substituents independently selected from halogen, (1-4C)alkoxy, $-\mathrm{CF}_{3}-\mathrm{CHF}_{2},-\mathrm{O}\left(1-4 \mathrm{C}\right.$ alkyl)hetCyc ${ }^{3}$ and $-\mathrm{O}(1-4 \mathrm{C}$ alkyl) $\mathrm{O}(1-3 \mathrm{C}$ alkyl), 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 substituents independently selected from halogen and $-\mathrm{O}(1-4 \mathrm{C}$ alkyl);
[00271] X is $\mathrm{CH}_{2}$ or $\mathrm{CH}_{2} \mathrm{CH}_{2}$;
[00272] $\mathrm{R}^{3}$ is H ;
[00273] each $\mathrm{R}^{4}$ is independently selected from halogen, -(1-4C)alkyl, -OH, -(14C)alkoxy, $-\mathrm{NH}_{2},-\mathrm{NH}\left(1-4 \mathrm{C}\right.$ alkyl) and $-\mathrm{CH}_{2} \mathrm{OH}$; and
[00274] n is 0,1 , or 2 .
[00275] In certain embodiments of Formula If, $\mathrm{R}^{2}$ is -(1-6C alkyl)hetAr ${ }^{1}$ or hetAr ${ }^{2} ; \mathrm{Y}$ is (i) phenyl optionally substituted with one or more substituents independently selected from halogen, (1-4C)alkoxy, $-\mathrm{CF}_{3}-\mathrm{CHF}_{2},-\mathrm{O}\left(1-4 \mathrm{C}\right.$ alkyl)hetCyc ${ }^{3}$ and $-\mathrm{O}(1-4 \mathrm{C}$ alkyl) $\mathrm{O}(1-3 \mathrm{C}$ alkyl); X is $\mathrm{CH}_{2}$; and n is 0 .
[00276] In certain embodiments of Formula If, $\mathrm{R}^{2}$ is $-\left(1-6 \mathrm{C}\right.$ alkyl)hetAr ${ }^{1}$ or hetAr ${ }^{2}$; het $\mathrm{Ar}^{1}$ is a furanyl, pyrazolyl, or imidazolyl ring optionally substituted with -( $1-4 \mathrm{C}$ alkyl); het $\mathrm{Ar}^{2}$ is a pyridyl or pyrazolo ring optionally substituted with one or more methyl groups; Y is phenyl, 3-fluorophenyl, 2,5-difluorophenyl, 2-methoxyphenyl, 2-chloro-5-fluorophenyl, 2-methoxy-5-fluorophenyl, 2-trifluoromethyl-5-fluorophenyl, 2-difluoromethyl-5-fluorophenyl, 3-chloro-5-fluorophenyl, 3-fluoro-5-(2-morpholinylethoxy)phenyl, 5-fluoro-2-(2morpholinoethoxy)phenyl, 3-fluoro-5-methoxyethoxyphenyl or 5-fluoro-2methoxyethoxyphenyl; X is $\mathrm{CH}_{2}$ and n is 0 .
[00277] In certain embodiments of Formula If, $\mathrm{R}^{2}$ is -(1-6C alkyl)hetAr ${ }^{1}$ or het $\mathrm{Ar}^{2} ; \mathrm{Y}$ 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 substituents independently selected from halogen and $-\mathrm{O}(1-4 \mathrm{C}$ alkyl $) ; \mathrm{X}$ is $\mathrm{CH}_{2}$; and n is 0 .
[00278] In certain embodiments of Formula If, $\mathrm{R}^{2}$ is $-\left(1-6 \mathrm{C}\right.$ alkyl)hetAr ${ }^{1}$ or hetAr ${ }^{2}$; het $\mathrm{Ar}^{1}$ is a furanyl, pyrazolyl, or imidazolyl ring optionally substituted with -( $1-4 \mathrm{C}$ alkyl); het $\mathrm{Ar}^{2}$ is a pyridyl or pyrazolo ring optionally substituted with one or more methyl groups; Y is pyrid-2-yl, pyrid-3-yl, 5-fluoropyrid-3-yl, 2-methoxy-5-fluoropyridy-3-yl or 2-methyl5 -fluoropyridy- 3 -yl; X is $\mathrm{CH}_{2}$; and n is 0 .
[00279] In certain embodiments of Formula If, $\mathrm{R}^{2}$ is -(1-6C alkyl)hetCyc ${ }^{1}$ or hetCyc ${ }^{2}$; Y is (i) phenyl optionally substituted with one or more substituents independently selected
from halogen, (1-4C)alkoxy, $-\mathrm{CF}_{3}-\mathrm{CHF}_{2},-\mathrm{O}\left(1-4 \mathrm{C}\right.$ alkyl)hetCyc ${ }^{3}$ and $-\mathrm{O}(1-4 \mathrm{C}$ alkyl) $\mathrm{O}(1-3 \mathrm{C}$ alkyl); X is $\mathrm{CH}_{2}$; and n is 0 .
[00280] In certain embodiments of Formula If, $\mathrm{R}^{2}$ is -(1-6C alkyl)hetCyc ${ }^{1}$ or hetCyc ${ }^{2}$; hetCyc ${ }^{1}$ is a morpholinyl or imidazolidin-2-one ring; hetCyc ${ }^{2}$ is a piperidinyl or tetrahydropyranyl ring optionally substituted with $\mathrm{F}, \mathrm{SO}_{2} \mathrm{NH}_{2}$, or $\mathrm{SO}_{2}(1-3 \mathrm{C}$ alkyl); 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, 3-chloro-5-fluorophenyl, 3-fluoro-5-(2-morpholinylethoxy)phenyl, 5-fluoro-2-(2morpholinoethoxy)phenyl, 3-fluoro-5-methoxyethoxyphenyl or 5-fluoro-2methoxyethoxyphenyl; X is $\mathrm{CH}_{2}$; and n is 0 .
[00281] In certain embodiments of Formula If, $\mathrm{R}^{2}$ is hetCyc ${ }^{2}$; hetCyc ${ }^{2}$ is a piperidinyl or tetrahydropyranyl ring optionally substituted with $\mathrm{F}, \mathrm{SO}_{2} \mathrm{NH}_{2}$, or $\mathrm{SO}_{2}(1-3 \mathrm{C}$ alkyl); Y is pyrid-2-yl, pyrid-3-yl, 5-fluoropyrid-3-yl, 2-methoxy-5-fluoropyridy-3-yl or 2-methyl-5-fluoropyridy-3-yl; X is $\mathrm{CH}_{2}$; and n is 0 .
[00282] The compounds of Formula I also include compounds of Formula Ig


Ig
[00283] and salts thereof, wherein:
[00284] $\mathrm{R}^{1}$ is H ;
[00285] $\quad \mathrm{R}^{2}$ is $-\mathrm{O}(1-6 \mathrm{C}$ alkyl), $-\mathrm{O}(3-6 \mathrm{C}$ cycloalkyl);
[00286] $\quad \mathrm{Y}$ is (i) phenyl optionally substituted with one or more substituents independently selected from halogen, $-(1-4 \mathrm{C})$ alkoxy, $-\mathrm{CF}_{3}-\mathrm{CHF}_{2},-\mathrm{O}\left(1-4 \mathrm{C}\right.$ alkyl)hetCyc ${ }^{3}$ and $-\mathrm{O}(1-4 \mathrm{C}$ alkyl $) \mathrm{O}(1-3 \mathrm{C} \mathrm{alkyl})$ 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 substituents independently selected from halogen, -O (1-4C alkyl) and (1-4C)alkyl;
[00287] hetCyc ${ }^{3}$ is a 5-6 membered heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O ;
[00288] X is $\mathrm{CH}_{2}$ or $\mathrm{CH}_{2} \mathrm{CH}_{2}$;
[00289] $\mathrm{R}^{3}$ is H ;
[00290] each $\mathrm{R}^{4}$ is independently selected from halogen, -(1-4C)alkyl, -OH, -(14 C )alkoxy, $-\mathrm{NH}_{2},-\mathrm{NH}\left(1-4 \mathrm{C}\right.$ alkyl) and $-\mathrm{CH}_{2} \mathrm{OH}$; and
[00291] n is 0,1 , or 2 .
[00292] In certain embodiments of Formula $\mathbf{I g}, \mathrm{R}^{2}$ is $-\mathrm{O}(1-6 \mathrm{C}$ alkyl), $-\mathrm{O}(3-6 \mathrm{C}$ cycloalkyl); Y is phenyl optionally substituted with one or more substituents independently selected from - $\mathrm{F},-\mathrm{Cl}$, $-\mathrm{OMe},-\mathrm{CF}_{3},-\mathrm{CHF}_{2}$, morpholinylethoxy and $-\mathrm{OCH}_{2} \mathrm{CH}_{2} \mathrm{OMe}$; X is $\mathrm{CH}_{2}$ and n is 0 .
[00293] In certain embodiments of Formula $\mathbf{I g}, \mathrm{R}^{2}$ is OMe , OEt or cyclopropoxy; 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, 3-chloro-5-fluorophenyl, 3-fluoro-5-(2-morpholinylethoxy)phenyl, 5-fluoro-2-(2morpholinoethoxy)phenyl, 3-fluoro-5-methoxyethoxyphenyl or 5-fluoro-2methoxyethoxyphenyl; X is $\mathrm{CH}_{2}$; and n is 0 .
[00294] In certain embodiments of Formula $\mathbf{I g}, \mathrm{R}^{2}$ is $-\mathrm{O}(1-6 \mathrm{C}$ alkyl), $-\mathrm{O}(3-6 \mathrm{C}$ cycloalkyl); Y is pyridyl optionally substituted with one or more substituents independently selected from $\mathrm{F}, \mathrm{OMe}$ and $\mathrm{Me} ; \mathrm{X}$ is $\mathrm{CH}_{2}$; and n is 0 .
[00295] In certain embodiments of Formula $\mathbf{I g}, \mathrm{R}^{2}$ is $\mathrm{OMe}, \mathrm{OEt}$ or cyclopropoxy; Y is pyrid-2-yl, pyrid-3-yl, 5-fluoropyrid-3-yl, 2-methoxy-5-fluoropyridy-3-yl or 2-methyl-5-fluoropyridy-3-yl; X is $\mathrm{CH}_{2}$; and n is 0 .
[00296] The compounds of Formula I also include compounds of Formula Ih


Ih
[00297] and salts thereof, wherein:
[00298] $\mathrm{R}^{1}$ is H or $-(1-6 \mathrm{C}$ alkyl);
[00299] $\mathrm{R}^{2}$ is $\mathrm{H}, \quad-(1-6 \mathrm{C})$ alkyl, $-(1-6 \mathrm{C})$ fluoroalkyl, $\quad-(1-6 \mathrm{C})$ hydroxyalkyl, -(2$6 \mathrm{C})$ dihydroxyalkyl, $-\left(1-6 \mathrm{C}\right.$ alkyl) CN , -(1-6C alkyl) $\mathrm{SO}_{2} \mathrm{NH}_{2}$, -(1-6C alkyl) $\mathrm{NHSO}_{2}(1-3 \mathrm{C}$ alkyl), -(1-6C alkyl) $\mathrm{NH}_{2}$, -(1-6C alkyl)NH(1-4C alkyl), $-(1-6 \mathrm{C}$ alkyl $) \mathrm{N}(1-4 \mathrm{C} \text { alkyl })_{2},-(1-$ 6 C alkyl)hetCyc ${ }^{1},-\left(1-6 \mathrm{C}\right.$ alkyl)hetAr ${ }^{1}$, hetAr ${ }^{2}$, hetCyc ${ }^{2},-\mathrm{O}(1-6 \mathrm{C}$ alkyl), $-\mathrm{O}(3-6 \mathrm{C}$ cycloalkyl), or Cyc ${ }^{1}$;
[00300] or $N R^{1} R^{2}$ forms a 4-6 membered azacyclic ring optionally substituted with one or more substituents independently selected from -(1-6C)alkyl, $-\mathrm{OH},-\mathrm{CO}_{2} \mathrm{H}$ and $-(1-3 \mathrm{C}$ alkyl) $\mathrm{CO}_{2} \mathrm{H}$;
[00301] Cyc $^{1}$ is a 3,4 or 5 membered cycloalkyl ring which is optionally substituted with one or more substituents independently selected from -(1-4C alkyl), $-\mathrm{OH}, \mathrm{OMe},-\mathrm{CO}_{2} \mathrm{H}$ and -(1-4C alkyl)OH;
[00302] hetCyc ${ }^{1}$ is a $5-6$ membered heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O , wherein hetCyc ${ }^{1}$ is optionally substituted with oxo;
[00303] hetCyc ${ }^{2}$ is a 6 membered carbon-linked heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O , wherein het $\mathrm{Cyc}^{2}$ is optionally substituted with $\mathrm{F}, \mathrm{SO}_{2} \mathrm{NH}_{2}$, or $\mathrm{SO}_{2}(1-3 \mathrm{C}$ alkyl);
[00304] het $\mathrm{Ar}^{1}$ is a 5 -membered heteroaryl ring having 1-2 ring heteroatoms independently selected from N and O and optionally substituted with (1-4C)alkyl;
[00305] het $\mathrm{Ar}^{2}$ is a 5-6 membered heteroaryl ring having 1-2 ring nitrogen atoms and optionally substituted with one or more substituents independently selected from (1-4C)alkyl;
[00306] X is $\mathrm{CH}_{2}$;
[00307] $\quad \mathrm{Y}$ is (i) fluorophenyl optionally substituted with a substituent selected from -$\mathrm{O}\left(1-4 \mathrm{C}\right.$ alkyl)hetCyc ${ }^{3}$, $-\left(1-4 \mathrm{C}\right.$ alkyl)hetCyc ${ }^{3},-\mathrm{O}(1-4 \mathrm{C}$ alkyl) $\mathrm{O}(1-3 \mathrm{C}$ alkyl) and $-\mathrm{O}(3-6 \mathrm{C}$ dihydroxyalkyl), (ii) pyridyl substituted with one or more substituents independently selected from F, methyl and ethyl, or (iii) 5-fluoropyridin-2(1H)-one optionally substituted with (14C)alkyl;
[00308] $\mathrm{R}^{3}$ is H or $-(1-4 \mathrm{C}$ alkyl);
[00309] each $\mathrm{R}^{4}$ is independently selected from halogen, -(1-4C)alkyl, -OH, -(14C)alkoxy, $-\mathrm{NH}_{2},-\mathrm{NH}\left(1-4 \mathrm{C}\right.$ alkyl) and $-\mathrm{CH}_{2} \mathrm{OH}$; and
[00310] n is $0,1,2,3,4,5$ or 6 .
[00311] In one embodiment of Formula Ih, Y is fluorophenyl optionally substituted with a substituent selected from - $\mathrm{O}(1-4 \mathrm{C}$ alkyl $)$ hetCyc ${ }^{3}$, -( $1-4 \mathrm{C}$ alkyl)hetCyc ${ }^{3},-\mathrm{O}(1-4 \mathrm{C}$ alkyl) O (1-3C alkyl) and - O (3-6C dihydroxyalkyl).
[00312] In one embodiment of Formula Ih, Y is pyridyl substituted with one or more substituents independently selected from F , methyl and ethyl.
[00313] In one embodiment of Formula $\mathbf{I h}, \mathrm{Y}$ is 5-fluoropyridin-2(1H)-one optionally substituted with (1-4C)alkyl.
[00314] In one embodiment of Formula $\mathbf{I h}, \mathrm{R}^{2}$ is a 3,4 or 5 membered cycloalkyl ring which is optionally substituted with one or more substituents independently selected from -(1-4C alkyl), $-\mathrm{OH}, \mathrm{OMe},-\mathrm{CO}_{2} \mathrm{H}$ and $-(1-4 \mathrm{C}$ alkyl) OH .
[00315] In one embodiment of Formula $\mathbf{I h}, \mathrm{R}^{2}$ is cyclopropyl optionally substituted with methyl, $-\mathrm{CO}_{2} \mathrm{H}$ or $-\mathrm{CH}_{2} \mathrm{OH}$.
[00316] In one embodiment of Formula $\mathbf{I h}, \mathrm{R}^{4}$ is $\mathrm{OH}, \mathrm{F}$, methyl, or $\mathrm{CH}_{2} \mathrm{OH}$.
[00317] In one embodiment of Formula $\mathbf{I h}, \mathrm{n}$ is 0,1 or 2.
[00318] In one embodiment of Formula $\mathbf{I h}, \mathrm{R}^{3}$ is hydrogen.
[00319] In one embodiment of Formula $\mathbf{I h}, \mathrm{R}^{1}$ is $\mathrm{H} ; \mathrm{R}^{2}$ is a 3, 4 or 5 membered cycloalkyl ring which is optionally substituted with one or more substituents independently selected from -(1-4C alkyl), $-\mathrm{OH}, \mathrm{OMe},-\mathrm{CO}_{2} \mathrm{H}$ and $-(1-4 \mathrm{C}$ alkyl $) \mathrm{OH} ; \mathrm{X}$ is $\mathrm{CH}_{2} ; \mathrm{Y}$ is (i) fluorophenyl optionally substituted with a substituent selected from $-\mathrm{O}\left(1-4 \mathrm{C}\right.$ alkyl)hetCyc ${ }^{3}$, -$\mathrm{O}(1-4 \mathrm{C}$ alkyl) $\mathrm{O}(1-3 \mathrm{C}$ alkyl) and -O(3-6C dihydroxyalkyl), (ii) pyridyl substituted with one or more substituents independently selected from F, methyl and ethyl, or (iii) 5-fluoropyridin- $2\left(1 \mathrm{H}\right.$ )-one optionally substituted with ( $1-4 \mathrm{C}$ )alkyl; $\mathrm{R}^{3}$ is H , and n is 0 .
[00320] It will be appreciated that certain compounds of the invention may contain asymmetric or chiral centers, and therefore exist in different stereoisomeric forms. 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.
[00321] 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.
[00322] It will also be appreciated that certain compounds of Formula I may be used as intermediates for further compounds of Formula $\mathbf{I}$.
[00323] The compounds of Formula I include salts thereof. In certain embodiments, the salts are pharmaceutically acceptable salts. In addition, the compounds of Formula I 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 $\mathbf{I}$ and/or for separating enantiomers of compounds of Formula $\mathbf{I}$.
[00324] 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.
[00325] Compounds of the invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. That is, an atom, in
particular when mentioned in relation to a compound according to Formula I, comprises all isotopes and isotopic mixtures of that atom, either naturally occurring or synthetically produced, either with natural abundance or in an isotopically enriched form. For example, when hydrogen is mentioned, it is understood to refer to ${ }^{1} \mathrm{H},{ }^{2} \mathrm{H},{ }^{3} \mathrm{H}$ or mixtures thereof; when carbon is mentioned, it is understood to refer to ${ }^{11} \mathrm{C},{ }^{12} \mathrm{C},{ }^{13} \mathrm{C},{ }^{14} \mathrm{C}$ or mixtures thereof; when nitrogen is mentioned, it is understood to refer to ${ }^{13} \mathrm{~N},{ }^{14} \mathrm{~N},{ }^{15} \mathrm{~N}$ or mixtures thereof; when oxygen is mentioned, it is understood to refer to ${ }^{14} \mathrm{O},{ }^{15} \mathrm{O},{ }^{16} \mathrm{O},{ }^{17} \mathrm{O},{ }^{18} \mathrm{O}$ or mixtures thereof; and when fluoro is mentioned, it is understood to refer to ${ }^{18} \mathrm{~F},{ }^{19} \mathrm{~F}$ or mixtures thereof. The compounds according to the invention therefore also comprise compounds with one or more isotopes of one or more atom, and mixtures thereof, including radioactive compounds, wherein one or more non-radioactive atoms has been replaced by one of its radioactive enriched isotopes. Radiolabeled compounds are useful as therapeutics, research reagents, e.g., assay reagents, and diagnostic agents, e.g., in vivo imaging agents. All isotopic variations of the compounds of the present invention, whether radioactive or not, are intended to be encompassed within the scope of the present invention.
[00326] The term "(1-6C) alkyl" as used herein refers to saturated linear or branchedchain monovalent hydrocarbon radicals of one to six carbon atoms, respectively. Examples include, but are not limited to, methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-methyl-1-propyl, 2-butyl, 2-methyl-2-propyl, pentyl, and hexyl. The definition of "(1-6C) alkyl" likewise applies to the term "O-(1-6C alkyl)".
[00327] The terms "(1-6C)fluoroalkyl", "(1-6C alkyl)CN", "(1-6C alkyl) $\mathrm{SO}_{2} \mathrm{NH}_{2} "$, "(16 C alkyl $) \mathrm{NHSO}_{2}\left(1-3 \mathrm{C}\right.$ alkyl)", "(1-6C alkyl) $\mathrm{NH}_{2} "$, "(1-6C alkyl)NH(1-4C alkyl)", "(1-6C alkyl) $\mathrm{N}(1-4 \mathrm{C} \text { alkyl })_{2}$ ", "(1-6C alkyl)hetCyc ${ }^{10}$ and "(1-6C alkyl)hetAr ${ }^{1 "}$ as used herein refer to saturated linear or branched-chain monovalent hydrocarbon radicals of one to six carbon atoms, respectively, wherein one of the hydrogen atoms is replaced with a fluoro atom, or a $\mathrm{CN}, \mathrm{SO}_{2} \mathrm{NH}_{2}, \mathrm{NHSO}_{2}\left(1-3 \mathrm{C}\right.$ alkyl), $\mathrm{NH}_{2}, \mathrm{NH}(1-4 \mathrm{C}$ alkyl $), \mathrm{N}(1-4 \mathrm{C} \text { alkyl })_{2}$, hetCyc ${ }^{1}$ or hetAr ${ }^{1}$ group, respectively.
[00328] The term "(1-6C)chloroalkyl" as used herein refers to saturated linear or branched-chain monovalent hydrocarbon radicals of one to six carbon atoms, respectively, wherein one of the hydrogen atoms is replaced with a chloro atom.
[00329] The term "(1-6C)hydroxyalkyl" as used herein refers to saturated linear or branched-chain monovalent hydrocarbon radicals of one to six carbon atoms, respectively, wherein one of the hydrogen atoms are replaced with a OH group.
[00330] The term "(2-6C)dihydroxyalkyl" as used herein refers to saturated linear or branched-chain monovalent hydrocarbon radicals of two to six carbon atoms, respectively, wherein two of the hydrogen atoms are replaced with a OH group, provided that two OH groups are not on the same carbon.
[00331] The term "(1-6C)difluoroalkyl" as used herein refers to saturated linear or branched-chain monovalent hydrocarbon radicals of one to six carbon atoms, respectively, wherein two of the hydrogen atoms are replaced with a fluoro atom.
[00332] The term "(1-6C)trifluoroalkyl" as used herein refers to saturated linear or branched-chain monovalent hydrocarbon radicals of one to six carbon atoms, respectively, wherein three of the hydrogen atoms are replaced with a fluoro atom.
[00333] The term "(2-6C)chlorofluoroalkyl" as used herein refers to saturated linear or branched-chain monovalent hydrocarbon radicals of two to six carbon atoms, respectively, wherein one of the hydrogen atoms is replaced with a chloro atom and one of the hydrogen atoms is replaced with a fluoro atom.
[00334] The term "(2-6C)difluorochloroalkyl" as used herein refers to saturated linear or branched-chain monovalent hydrocarbon radicals of two to six carbon atoms, respectively, wherein one of the hydrogen atoms is replaced with a chloro and two of the hydrogen atoms are replaced with a fluoro atom.
[00335] The term "(2-6C)chlorohydroxyalkyl" as used herein refers to a saturated linear or branched-chain monovalent hydrocarbon radicals of two to six carbon atoms, respectively, wherein one of the hydrogen atoms is replaced with a chloro and one of the hydrogen atoms is replaced with OH .
[00336] The term "(1-6C alkyl)NHC $(=\mathrm{O}) \mathrm{O}(1-4 \mathrm{C}$ alkyl $)$ " as used herein refers to saturated linear or branched-chain monovalent hydrocarbon radicals of one to six carbon atoms, respectively, wherein one of the hydrogen atoms is replaced with a $-\mathrm{NHC}(=\mathrm{O}) \mathrm{O}(1-4 \mathrm{C}$ alkyl) group.
[00337] The phrase "O(1-6C alkyl) which is optionally substituted with halogen, OH or (1-4C)alkoxy" as used herein refers to a saturated linear or branched-chain monovalent alkyl ether radical of one to six carbon atoms wherein the term "alkyl" is as defined herein and the radical is on the oxygen atom, and one of the hydrogen atoms on the carbon chain is optionally replaced with halogen, OH or (1-4C)alkoxy. Examples include methoxy, ethoxy, propoxy, isopropoxy, and butoxy radicals optionally substituted with halogen, OH or (14C)alkoxy.
[00338] The term "O(3-6C cycloalkyl)" as used herein refers to a cycloalkyl ether radical wherein the term "cycloalkyl" is a a 3-6 membered carbocyclic ring and the radical is on the oxygen atom.
[00339] The term "-(1-6C alkyl)(3-6C cycloalkyl)" as used herein refers to a saturated linear or branched-chain monovalent hydrocarbon radical of one to six carbon atoms, respectively, wherein one of the hydrogen atoms is replaced with a 3-6 membered carbocyclic ring.
[00340] The term "-(1-6Calkyl)(1-4C alkoxy)" as used herein refers to a saturated linear or branched-chain monovalent hydrocarbon radical of one to six carbon atoms, respectively, wherein one of the hydrogen atoms is replaced with an (1-4C)alkoxy group.
[00341] The term "-(1-6C hydroxyalkyl)(1-4C alkoxy)" as used herein refers to a saturated linear or branched-chain monovalent hydrocarbon radical of one to six carbon atoms, respectively, wherein one of the hydrogen atoms is replaced with hydroxy $(\mathrm{OH})$ group and one of the hydrogen atoms is replaced with an (1-4C)alkoxy group.
[00342] The term "halogen" includes fluoro, chloro, bromo and iodo.
[00343] The term "pharmaceutically acceptable" indicates that the substance or composition is compatible chemically and/or toxicologically, with the other ingredients comprising a formulation, and/or the mammal being treated therewith.
[00344] The present invention also provides a process for the preparation of a compound of Formula I or a salt thereof as defined herein, which comprises:
[00345] (a) reacting a corresponding compound of Formula II


II
[00346] or a reactive derivative thereof with an amine having the formula $H N R{ }^{1} \mathrm{R}^{2}$; or
[00347] (b) for compounds of Formula I where $\mathrm{R}^{1}$ and $\mathrm{R}^{2}$ are each hydrogen, reacting a compound of Formula III


III
[00348] with an inorganic acid; or
[00349] (c) for a compound of Formula $\mathbf{I}$ where $\mathrm{R}^{2}$ is (alkyl) $\mathrm{NHSO}_{2}((1-3 \mathrm{C}$ alkyl), reacting a compound having the formula IV

[00350] with -(1-3C alkyl) $\mathrm{SO}_{2} \mathrm{Cl}$; or
[00351] (d) for compounds of Formula I wherein Y is 5 -fluoropyridin-2(1H)-one, treating a corresponding compound having the formula VIII

[00352] with an acid at elevated temperatures; or
[00353] (e) for a compound of Formula $\mathbf{I}$ wherein $\mathrm{R}^{2}$ is $\mathrm{CH}_{2} \mathrm{CH}(\mathrm{OH}) \mathrm{CH}_{2} \mathrm{OH}$, treating a corresponding compound having the formula IX


IX
[00354] with an acid; or
[00355] (f) for a compound of Formula I wherein Y is fluorophenyl substituted with $\mathrm{OCH}_{2} \mathrm{CH}(\mathrm{OH}) \mathrm{CH}_{2} \mathrm{OH}$, treating a corresponding compound having the formula $\mathbf{X}$

[00356] with an acid; and
[00357] removing or adding any protecting groups if desired, and forming a salt if desired.
[00358] Referring to method (a), the coupling of the compound of formula II with an amine having the formula $H N R^{1} \mathrm{R}^{2}$ may be performed using conventional amide bond formation conditions, for example by reacting an amine with a reactive derivative of a carboxylic acid, for example an acid halide, such as an acid chloride. When reacting the acid form of a compound of Formula II, the reaction may be performed in the presence of a suitable coupling agent such as 2 -( $1 \mathrm{H}-7-$ Azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate methanaminium (HATU), O-Benzotriazole-N,N,N',N'-tetramethyl-uronium-hexafluoro-phosphate (HBTU), O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU), $\mathrm{N}, \mathrm{N}$ '-dicyclohexylcarbodiimide (DCC), 1-(3-dimethylaminopropyl)-3-ethylcarboiimide (DIEC) 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 $\mathrm{CH}_{3} \mathrm{CN}$.
[00359] Referring to method (b), suitable acids include strong inorganic acids such as sulfuric acid.
[00360] Referring to methods (d), (e) and (f), suitable acids include inorganic acids such as hydrogen halides, for example HCl .
[00361] Compounds of formula II may be prepared by coupling a corresponding compound having formula IV

[00362] with a corresponding compound having formula $\mathbf{V}$

[00363] where $\mathrm{Z}^{1}$ is OH or a leaving group or atom and $\mathrm{P}^{1}$ is H or a carboxyl protecting group. The leaving atom represented by $Z^{1}$ may be, for example, a halogen atom such as a chlorine atom. In this instance, the reaction is performed in the presence of a base, such as an amine base, for example diisopropylethylamine. The reaction is conveniently performed at elevated temperatures, for example at $100{ }^{\circ} \mathrm{C}$. Convenient solvents include alcohols such as butanol. When $\mathrm{Z}^{1}$ is OH the reaction is performed in the presence of a coupling reagent. Suitable coupling reagents when $\mathrm{Z}^{1}$ is OH include benzotriazolyloxy tris [dimethyl-amino] phosphonium hexafluorophosphate (BOP), HATU, HBTU or TBTU. The carboxyl protecting group may be any convenient carboxyl protecting group, for example as described in Greene \& Wuts, eds., "Protecting Groups in Organic Synthesis", John Wiley \& Sons, Inc. Examples of carboxyl protecting groups include (1-6C)alkyl groups, such as methyl, ethyl and t-butyl.
[00364] A compound of Formula $\mathbf{V}$ can be prepared by cyclizing a corresponding compound of Formula VI

[00365] with (E)-ethyl 3-ethoxyacrylate to provide the compound of Formula $\mathbf{V}$ where $\mathrm{Z}^{1}$ is OH as shown

[00366] or when $Z^{1}$ is a leaving group or atom, converting the hydroxy group into a leaving atom or group, for example by treating the compound of Formula $\mathbf{V}$ where $\mathrm{Z}^{1}$ is OH with $\mathrm{POCl}_{3}$.
[00367] Compounds of Formula I where the Y group has the absolute configuration shown in Figure Ia:


Ia
[00368] are prepared by coupling a compound of Formula $\mathbf{V}$ with a corresponding compound having the formula IV-A


IV-A
[00369] The compound of Formula IV-A can be prepared by treating a compound of Formula VII

[0001] where $\mathrm{P}^{2}$ is an amine protecting group, with an alkyl lithium base (for example sec-butyl lithium) in the presence of a chiral complexing agent (for example (-)-sparteine), followed by coupling with a compound having $\mathrm{Y}-\mathrm{Z}^{2}$ where $\mathrm{Z}^{2}$ is a leaving group or atom, such as a halogen atom (for example bromine) in the presence of a palladium (II) catalyst and a ligand. Such enantioselective palladium-catalyzed reactions are described in Campos, et al., J. Am. Chem. Soc., 2006, 128:3538-3539. Suitable catalysts include $\operatorname{Pd}(\mathrm{OAc})_{2}$. Suitable ligands include phosphine ligands such as $\mathrm{t}-\mathrm{Bu}_{3} \mathrm{P}_{-}-\mathrm{HBF}_{4}$. The amine protecting group may be any convenient amine protecting group, for example as described in Greene \& Wuts, eds., "Protecting Groups in Organic Synthesis", John Wiley \& Sons, Inc. Examples of amine protecting groups include acyl and alkoxycarbonyl groups, such as t-butoxycarbonyl (BOC).
[0001] The compounds of the formulas II, III, and IV are also believed to be novel and are provided as further aspects of the invention.
[00370] The ability of compounds of the invention to act as TrkA inhibitors may be demonstrated by the assays described in Examples A and B. The ability of compounds of the invention to act as TrkB inhibitors may be demonstrated by the assay described in Example B.
[00371] The selectivity of compounds of Formula I for TrkA versus one or more JAK kinases was determined using the assays describes in Examples C, D, E and F.
[00372] It was unexpectedly discovered that compounds of Formula $\mathbf{I}$ wherein X is $\mathrm{CH}_{2}$ are particularly selective for inhibiting TrkA activity over inhibiting the activity of one or more JAK kinases, for example JAK2, as shown in Table 1. In one embodiment, compounds of Formula I are 10-30 fold more potent in inhibiting TrkA kinase activity over inhibiting Jak2 kinase activity. In one embodiment, compounds of Formula I are 30-100 fold more potent in inhibiting TrkA kinase activity over inhibiting Jak2 kinase activity. In one embodiment, compounds of Formula I are greater than 100 fold more potent in inhibiting TrkA kinase activity over inhibiting Jak2 kinase activity.
[00373] Additionally, it was unexpectedly discovered that compounds of Formula I wherein $R^{2}$ is a 3,4 or 5 membered cycloalkyl ring which is optionally substituted with one or more substituents independently selected from -(1-4C alkyl), $-\mathrm{OH}, \mathrm{OMe},-\mathrm{CO}_{2} \mathrm{H}$ and $-(1-$ 4C alkyl)OH are particularly selective for inhibiting TrkA activity over inhibiting the activity of one or more JAK kinases, for example JAK2, as shown in Table 1.
[00374] Additionally, it was unexpectedly discovered that compounds of Formula I wherein Y is (i) fluorophenyl optionally substituted with a substituent selected from - $\mathrm{O}(1-4 \mathrm{C}$ alkyl)hetCyc ${ }^{3},-\mathrm{O}(1-4 \mathrm{C}$ alkyl) $\mathrm{O}(1-3 \mathrm{C}$ alkyl) and $-\mathrm{O}(3-6 \mathrm{C}$ dihydroxyalkyl), (ii) pyridyl substituted with one or more substituents independently selected from F, methyl and ethyl, or (iii) 5 -fluoropyridin- $2(1 \mathrm{H}$ )-one optionally substituted with (1-4C)alkyl, are particularly selective for inhibiting TrkA activity over inhibiting the activity of one or more JAK kinases, for example JAK2, as shown in Table 1.
[00375] Compounds of Formula I are useful for treating pain, including chronic and acute pain. 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.
[00376] In one embodiment, compounds of Formula I are useful for treating acute pain. Acute pain, as defined by the International Association for the Study of Pain, results from disease, inflammation, or injury to tissues. This type of pain generally comes on suddenly, for example, after trauma or surgery, and may be accompanied by anxiety or stress. The cause can usually be diagnosed and treated, and the pain is confined to a given period of time and severity. In some instances, it can become chronic.
[00377] In one embodiment, compounds of Formula I are useful for treating chronic pain. Chronic pain, as defined by the International Association for the Study of Pain, is widely believed to represent disease itself. It can be made much worse by environmental and psychological factors. Chronic pain persists over a longer period than acute pain and is resistant to most medical treatments, generally over 3 months or more. It can and often does cause severe problems for patients.
[00378] Compounds of Formula I are also useful for treating cancer. Particular examples include neuroblastoma, ovarian, pancreatic, colorectal and prostate cancer.
[00379] Compounds of Formula I are also useful for treating inflammation and certain infectious diseases.
[00380] 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.
[00381] Compounds of Formula I are also useful for treating a neurodegenerative disease in a mammal, 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 neurodegenerative disease. In one embodiment, 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. In one embodiment, the neurodegenerative disease is multiple sclerosis. In one embodiment, the neurodegenerative disease is Parkinson's disease. In one embodiment, the neurodegenerative disease is Alzheimer's disease.
[00382] As used herein, the term treatment includes prophylaxis as well as treatment of a preexisting condition. Beneficial or desired clinical results include, but are not limited to, alleviation of symptoms, diminishment of extent of disease, stabilized (i.e., not worsening) state of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, and remission (whether partial or total), whether detectable or undetectable. "Treatment" can also mean prolonging survival as compared to expected survival if not receiving treatment. Those in need of treatment include those already with the condition or disorder, as well as those prone to have the condition or disorder or those in which the condition or disorder is to be prevented.
[00383] Accordingly, another embodiment of this invention provides a method of treating pain in a mammal, 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 pain.
[00384] Another embodiment of this invention provides a method of treating inflammation in a mammal, 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 inflammation.
[00385] Another embodiment of this invention provides a method of treating a neurodegenerative disease in a mammal, 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 neurodegenerative disease.
[00386] Another embodiment of this invention provides a method of treating Trypanosoma cruzi infection in a mammal, 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 Trypanosoma cruzi infection.
[00387] 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.
[00388] 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.
[00389] 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.
[00390] 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. 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.
[00391] 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.
[00392] 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, together with a pharmaceutically acceptable diluent or carrier.
[00393] According to another embodiment, the present invention provides a compound of Formula I or a pharmaceutically acceptable salt thereof, for use in the treatment of pain in a mammal.
[00394] In another embodiment, the present invention provides a compound of Formula I or a pharmaceutically acceptable salt thereof, for use in the treatment of inflammation in a mammal.
[00395] In another embodiment, the present invention provides a compound of Formula I or a pharmaceutically acceptable salt thereof, for use in the treatment of infectious diseases, for example Trypanosoma cruzi infection, in a mammal.
[00396] In another embodiment, the present invention provides a compound of Formula I or a pharmaceutically acceptable salt thereof, for use in the treatment of a neurodegenerative disease in a mammal.
[00397] 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 selected from pain, cancer, inflammation, neurodegenerative disease or Trypanosoma cruzi infection. In one embodiment, the condition is pain. In one embodiment, the condition is cancer. In one embodiment, the condition is inflammation. In one embodiment, the condition is a neurodegenerative disease. In one embodiment, the condition is Trypanosoma cruzi infection.

## Examples

[00398] 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, dimethyl formamide (DMF) and dioxane were purchased from Aldrich in Sure/Seal ${ }^{\text {TM }}$ bottles and used as received.
[00399] 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.
[00400] 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).

## Biological assays

[00401] The ability of compounds of the invention to act as TrkA inhibitors may be demonstrated by the assays described in Examples A and B. The ability of compounds of the invention to act as TrkB inhibitors may be demonstrated by the assay described in Example B.
[00402] The selectivity of compounds of Formula I for inhibiting TrkA kinase activity over inhibiting one or more JAK kinases was determined using the assays describes in Examples C, D, E and F.

## Example A

TrkA ELISA assay
[00403] An enzyme-linked immunosorbant 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 $0.025 \mathrm{mg} / \mathrm{mL}$ 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 $500 \mu \mathrm{M}$ ATP were incubated for 25 minutes at ambient temperature in the coated plates while shaking. The assay buffer consisted of 25 mM MOPS $\mathrm{pH} 7.5,0.005 \%(v / v)$ Triton X-100 and 5 mM $\mathrm{MgCl}_{2}$. 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 $0.2 \mu \mathrm{~g} / \mathrm{mL}$ 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 1 M phosphoric acid, the chromogenic substrate color intensity was quantitated via absorbance at 450 nm . $\mathrm{IC}_{50}$ values were calculated using either a 4 or 5 -parameter logistic curve fit and are provided in Table 1.

## Example B

## TrkA and TrkB Omnia Assay

[00404] Trk enzymatic selectivity was assessed using Omnia ${ }^{\text {TM }}$ 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, $500 \mu \mathrm{M}$ of ATP for TrkA assay or 1 mM ATP for TrkB assay, $10 \mu \mathrm{M}$ peptide substrate. The assay buffer consisted of 25 mM MOPS $\mathrm{pH} 7.5,0.005 \%$ $(v / v)$ Triton $\mathrm{X}-100$ and 5 mM MgCl 2 . The production of phosphorylated peptide was monitored continuously for 70 minutes using a Molecular Devices FlexStation $\mathrm{II}^{384}$ microplate reader (excitation $=360 \mathrm{~nm}$; emission $=485 \mathrm{~nm}$ ). Initial rates were calculated from the progress curves. $\mathrm{IC}_{50}$ values were calculated from these rates using either a 4 or 5parameter logistic curve fit.
[00405] In each of TrkA and TrkB Omnia assays, compounds of the invention had an average $\mathrm{IC}_{50}$ value below 1000 nM . Certain compounds had an average $\mathrm{IC}_{50}$ value below 100 nM .

## General JAK kinase Enzyme Inhibition Assay Method

[00406] The assays described in Examples C, D, E and F for the determination of JAK1, JAK2, JAK3 and Tyk2 kinase activity, respectively, utilized the Omnia ${ }^{\circledR}$ Kinase fluorescence peptide substrate-based technology (Invitrogen). The specific components of the assay mixture are described in Examples C, D and E. In each of the assays described in Examples C, D and E, $\mathrm{Mg}^{2+}$ is chelated upon phosphorylation of the Omnia peptide by the kinase to form a bridge between the chelation-enhanced fluorophore Sox and the phosphate, resulting in an increase in fluorescence emission at 485 nM when excited at 360 nM . The reactions were therefore read at excitation 360 nm and emission was measured at 485 nm every 50 seconds for 45 minutes using a PerkinElmer EnVision Multilabel Plate Reader.
[00407] The final buffer conditions for each of the JAK1, JAK2, JAK3 and Tyk2 assays were as follows: 25 mM HEPES, $\mathrm{pH} 7.4,10 \mathrm{mM} \mathrm{MgCl} 2,0.01 \%$ Triton X-100 and 1 mM DTT.

## IC ${ }_{50}$ Determinations:

[00408] Compounds were prepared at 50 x the final concentration in DMSO by conducting 3 -fold serial dilutions from a $500-\mu \mathrm{M}$ or $1000-\mu \mathrm{M}$ intermediate dilution to give a 10 -point dosing curve having a high dose of 10 or $20 \mu \mathrm{M}$. Two- $\mu \mathrm{L}$ aliquots of these were transferred to a fresh plate for a ten-fold intermediate dilution with assay buffer. Five- $\mu \mathrm{L}$ aliquots of the diluted compounds were then transferred to $20-\mu \mathrm{L}$ of assay mixtures described in Examples C, D, E and F for a final concentration of DMSO of $2 \%$. A standard or reference compound was typically included on each assay plate to validate that plate. For each plate, percent of control (POC) values were calculated for each well according to the following equation:

$$
\text { POC }=\frac{\text { Sample }-\overline{\mathrm{X}}_{\text {min }}}{\overline{\mathrm{X}}_{\text {max }}-\overline{\mathrm{X}}_{\text {min }}} \times 100,
$$

where $\bar{X}_{\text {max }}=$ Average Uninhibited Controls
$\overline{\mathrm{X}}_{\text {min }}=$ Average Background
$\mathrm{IC}_{50}$ 's were estimated from the POC's using a standard 4-parameter logistic model:

$$
\begin{aligned}
& \mathrm{Y}=\mathrm{A}+\frac{\mathrm{B}-\mathrm{A}}{1+\left(\frac{\mathrm{C}}{\mathrm{X}}\right)^{\mathrm{D}}}, \\
& \text { where } \mathrm{A}=\text { Minimum Y (Bottom Asymptote) } \\
& \mathrm{B}=\text { Maximum } \mathrm{Y} \text { (Top Asymptote) } \\
& \mathrm{C}=\mathrm{EC}_{50} \\
& \mathrm{D}=\text { Slope Factor } \\
& \mathrm{X}=\text { Compound Concentration (nM) } \\
& \mathrm{Y}=\text { POC }
\end{aligned}
$$

[00409] The $\mathrm{IC}_{50}$ is defined as the concentration of inhibitor at which the POC equals 50 for the fitted curve.

## Example C

Jak1 Inhibition Assay
[00410] Compounds of Formula I were screened for their ability to inhibit Jak1 using the general enzyme inhibition assay method, in which the assay mixture contained $500 \mu \mathrm{M}$

ATP, $8 \mu \mathrm{M}$ Omnia ${ }^{\circledR}$ Y12 peptide (Catalog \# IVGN KPZ3121C; Invitrogen Corporation, Carlsbad, CA) and 5 nM Jak1 in a total volume of $20 \mu \mathrm{~L}$. GST-tagged human Jak1 kinase domain comprising amino acids 866-1154 was purchased from Invitrogen Corporation, Carlsbad, CA (catalog \# IVGN PV4774). Results are shown in Table 2.

## Example D

## Jak2 Inhibition Assay

[00411] Compounds of Formula I were screened for their ability to inhibit Jak2 using the general enzyme inhibition assay method, in which the assay mixture contained $500 \mu \mathrm{M}$ ATP, $10 \mu \mathrm{M}$ Omnia ${ }^{\circledR} \mathrm{Y} 7$ peptide (Catalog \# IVGN KNZ3071C, Invitrogen Corporation, Carlsbad, CA) and 4 nM Jak2 in a total volume of $20 \mu \mathrm{~L}$. Human Jak2 kinase domain comprising amino acids 808-1132 was purchased from Invitrogen Corporation, Carlsbad, CA (catalog \# IVGN PV4210). Results are shown in Tables 1 and 2.

## Example E

## Jak3 Inhibition Assay

[00412] Compounds of Formula I were screened for their ability to inhibit Jak3 using the general enzyme inhibition assay method, in which the assay mixture contained $500 \mu \mathrm{M}$ ATP, $10 \mu \mathrm{M} \mathrm{Omnia}{ }^{\circledR} \mathrm{Y} 7$ peptide (Catalog \# IVGN KNZ3071C, Invitrogen Corporation, Carlsbad, CA) and 1.5 nM Jak3 in a total volume of $20 \mu \mathrm{~L}$. GST-tagged human Jak3 kinase domain comprising amino acids 781-1124 was purchased from Invitrogen Corporation, Carlsbad, CA (catalog \# IVGN PV3855). Results are shown in Table 2.

## Example F

## Tyk2 Inhibition Assay

[00413] Compounds of Formula I were screened for their ability to inhibit Tyk2 using the general enzyme inhibition assay method, in which the assay mixture contained $500 \mu \mathrm{M}$ ATP, $8 \mu \mathrm{M}$ Omnia ${ }^{\circledR}$ Y12 peptide (Catalog \# IVGN KPZ3121C; Invitrogen Corporation, Carlsbad, CA) and 1 nM Tyk2 in a total volume of $20 \mu \mathrm{~L}$. Human Tyk2 kinase domain, comprising amino acids 886 to 1187 with 10 additional histidine residues (histidine tag) on the carboxy terminus, was expressed and purified from bacculovirus in-house at Array BioPharma Inc. (Boulder, CO). The histidine tag was cleaved after purification using standard conditions. Results are shown in Table 2.
[00414] Table 1 provides $\mathrm{IC}_{50}$ values for compounds of the invention when tested in the assays of Examples A and D. The Jak2 enzyme $\mathrm{IC}_{50}$ was designated as $>1000 \mathrm{nM}$ when $>50 \%$ inhibition was not observed at a 1000 nM concentration of test compound.

Table 1

| Example \# | TrkA Enzyme $\mathrm{IC}_{50}(\mathrm{nM})$ | $\begin{gathered} \hline \text { Jak2 Enzyme } \\ \text { IC } \mathrm{C}_{50}(\mathrm{nM}) \\ (\% \text { inhibition at } 1000 \mathrm{nM}) \\ \hline \end{gathered}$ |
| :---: | :---: | :---: |
| 1 | 0.7 | $\begin{aligned} & >1000 \\ & (39.5) \end{aligned}$ |
| 2 | 0.7 | $\begin{aligned} & >1000 \\ & (19.1) \end{aligned}$ |
| 3 | 2.3 | $\begin{aligned} & >1000 \\ & (10.1) \end{aligned}$ |
| 4 | 0.95 | $\begin{aligned} & >1000 \\ & (18.8) \\ & \hline \end{aligned}$ |
| 5 | 0.95 | $\begin{aligned} & >1000 \\ & (14.2) \\ & \hline \end{aligned}$ |
| 6 | 1.55 | $\begin{aligned} & >1000 \\ & (12.9) \end{aligned}$ |
| 7 | 0.45 | $\begin{aligned} & 106.8 \\ & (90.0) \\ & \hline \end{aligned}$ |
| 8 | 1.1 | $\begin{aligned} & >1000 \\ & (25.7) \\ & \hline \end{aligned}$ |
| 9 | 3.45 | $\begin{gathered} >1000 \\ (4.6) \end{gathered}$ |
| 10 | 1.05 | $\begin{aligned} & >1000 \\ & (47.5) \end{aligned}$ |
| 11 | 777.1 | $\begin{aligned} & >1000 \\ & (10.1) \end{aligned}$ |
| 12 | 238.25 | $\begin{gathered} >1000 \\ (4.5) \end{gathered}$ |
| 13 | 0.5 | $\begin{aligned} & >1000 \\ & (41.4) \end{aligned}$ |
| 14 | 0.55 | $\begin{gathered} 470 \\ (66.7) \\ \hline \end{gathered}$ |
| 15 | 0.6 | $\begin{gathered} 156 \\ (83.1) \end{gathered}$ |
| 16 | 0.9 | $\begin{aligned} & >1000 \\ & (31.7) \\ & \hline \end{aligned}$ |
| 17 | 2.15 | $\begin{gathered} >1000 \\ (5.6) \\ \hline \end{gathered}$ |
| 18 | 38.3 | $\begin{gathered} >1000 \\ (2.8) \\ \hline \end{gathered}$ |
| 19 | 74.25 | $\begin{gathered} >1000 \\ (3.4) \\ \hline \end{gathered}$ |
| 20 | 0.6 | $\begin{gathered} 257 \\ (78.9) \\ \hline \end{gathered}$ |
| 21 | 2.95 | $\begin{gathered} >1000 \\ (5.8) \end{gathered}$ |

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| Example \# | TrkA Enzyme $\mathrm{IC}_{50}(\mathrm{nM})$ | $\begin{gathered} \hline \text { Jak2 Enzyme } \\ \mathrm{IC}_{50}(\mathrm{nM}) \\ \text { (\% inhibition at } 1000 \mathrm{nM} \text { ) } \end{gathered}$ |
| :---: | :---: | :---: |
| 22 | 2.1 | $\begin{gathered} \hline>1000 \\ (9.8) \end{gathered}$ |
| 23 | 1.1 | $\begin{aligned} & >1000 \\ & (10.1) \end{aligned}$ |
| 24 | 3.6 | $\begin{aligned} & >1000 \\ & (11.5) \end{aligned}$ |
| 25 | 0.4 | $\begin{aligned} & >1000 \\ & (19.4) \\ & \hline \end{aligned}$ |
| 26 | 1.3 | $\begin{gathered} >1000 \\ (9.9) \end{gathered}$ |
| 27 | 214.5 | $\begin{gathered} >1000 \\ (1.3) \end{gathered}$ |
| 28 | 2.8 | $\begin{gathered} >1000 \\ (5.0) \\ \hline \end{gathered}$ |
| 29 | 1.3 | $\begin{aligned} & >1000 \\ & (13.2) \\ & \hline \end{aligned}$ |
| 30 | 1.95 | $\begin{aligned} & >1000 \\ & (25.7) \\ & \hline \end{aligned}$ |
| 31 | 10.6 | $\begin{gathered} >1000 \\ (5.1) \\ \hline \end{gathered}$ |
| 32 | 5.3 | $\begin{gathered} >1000 \\ (8.6) \\ \hline \end{gathered}$ |
| 33 | 1.5 | $\begin{gathered} 23.4 \\ (99.9) \\ \hline \end{gathered}$ |
| 34 | 1.1 | $\begin{gathered} 42.3 \\ (96.9) \\ \hline \end{gathered}$ |
| 35 | 1.2 | $\begin{gathered} \hline 278 \\ (77.4) \end{gathered}$ |
| 36 | 2.1 | $\begin{aligned} & >1000 \\ & (22.2) \\ & \hline \end{aligned}$ |
| 37 | 1.65 | $\begin{aligned} & >1000 \\ & (25.0) \\ & \hline \end{aligned}$ |
| 38 | 1.3 | $\begin{aligned} & >1000 \\ & (18.2) \\ & \hline \end{aligned}$ |
| 39 | 0.7 | $\begin{aligned} & >1000 \\ & (30.4) \end{aligned}$ |
| 40 | 0.8 | $\begin{aligned} & >1000 \\ & (41.4) \end{aligned}$ |
| 41 | 28.9 | $\begin{gathered} >1000 \\ (6.0) \\ \hline \end{gathered}$ |
| 42 | 48.3 | $\begin{gathered} >1000 \\ (7.7) \\ \hline \end{gathered}$ |
| 43 | 139 | $\begin{gathered} >1000 \\ (4.2) \\ \hline \end{gathered}$ |

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| Example \# | TrkA Enzyme $\mathrm{IC}_{50}(\mathrm{nM})$ | Jak2 Enzyme $\mathrm{IC}_{50}(\mathrm{nM})$ (\% inhibition at 1000 nM ) |
| :---: | :---: | :---: |
| 44 | 1.5 | $\begin{gathered} 388 \\ (71.5) \\ \hline \end{gathered}$ |
| 45 | 1.4 | $\begin{gathered} 195 \\ (84.0) \\ \hline \end{gathered}$ |
| 46 | 3.3 | $\begin{aligned} & >1000 \\ & (13.8) \end{aligned}$ |
| 47 | 1.5 | $\begin{aligned} & >1000 \\ & (37.3) \end{aligned}$ |
| 48 | 0.6 | $\begin{gathered} 429 \\ (72.7) \\ \hline \end{gathered}$ |
| 49 | 4.2 | $\begin{aligned} & >1000 \\ & (17.2) \end{aligned}$ |
| 50 | 1.23 | $\begin{gathered} 418 \\ (73.7) \end{gathered}$ |
| 51 | 1.18 | $\begin{gathered} 186 \\ (82.5) \end{gathered}$ |
| 52 | 7.4 | $\begin{gathered} >1000 \\ (9.4) \\ \hline \end{gathered}$ |
| 53 | 10.4 | $\begin{gathered} >1000 \\ (8.7) \end{gathered}$ |
| 54 | 2.25 | $\begin{aligned} & >1000 \\ & (23.0) \end{aligned}$ |
| 55 | 1 | $\begin{aligned} & >1000 \\ & (24.1) \\ & \hline \end{aligned}$ |
| 56 | 2.4 | $\begin{aligned} & >1000 \\ & (28.0) \\ & \hline \end{aligned}$ |
| 57 | 3.93 | $\begin{gathered} >1000 \\ (9.7) \\ \hline \end{gathered}$ |
| 58 | 9.4 | $\begin{gathered} >1000 \\ (4.7) \end{gathered}$ |
| 59 | 16.95 | $\begin{aligned} & >1000 \\ & (14.5) \end{aligned}$ |
| 60 | 2.25 | $\begin{aligned} & >1000 \\ & (21.1) \\ & \hline \end{aligned}$ |
| 61 | 1.95 | $\begin{gathered} 699 \\ (54.4) \\ \hline \end{gathered}$ |
| 62 | 2.53 | $\begin{aligned} & >1000 \\ & (35.2) \\ & \hline \end{aligned}$ |
| 63 | 4.55 | $\begin{aligned} & >1000 \\ & (33.1) \\ & \hline \end{aligned}$ |
| 64 | 1.6 | $\begin{gathered} 575 \\ (60.3) \\ \hline \end{gathered}$ |
| 65 | 0.6 | $\begin{aligned} & >1000 \\ & (34.1) \\ & \hline \end{aligned}$ |

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| Example \# | TrkA Enzyme $\mathrm{IC}_{50}(\mathrm{nM})$ | Jak2 Enzyme $\mathrm{IC}_{50}(\mathrm{nM})$ (\% inhibition at 1000 nM ) |
| :---: | :---: | :---: |
| 66 | 0.57 | $\begin{aligned} & >1000 \\ & (24.7) \end{aligned}$ |
| 67 | 5.1 | $\begin{aligned} & >1000 \\ & (22.3) \end{aligned}$ |
| 68 | 6.6 | $\begin{aligned} & >1000 \\ & (23.0) \\ & \hline \end{aligned}$ |
| 69 | 60.3 | $\begin{gathered} >1000 \\ (6.0) \\ \hline \end{gathered}$ |
| 70 | 23.95 | $\begin{gathered} >1000 \\ (9.0) \\ \hline \end{gathered}$ |
| 71 | 8.65 | $\begin{gathered} >1000 \\ (6.2) \end{gathered}$ |
| 72 | 44.35 | $\begin{aligned} & >1000 \\ & (11.7) \end{aligned}$ |
| 73 | 48.55 | $\begin{gathered} >1000 \\ (4.9) \\ \hline \end{gathered}$ |
| 74 | 12.6 | $\begin{aligned} & >1000 \\ & (12.2) \\ & \hline \end{aligned}$ |
| 75 | 6.95 | $\begin{aligned} & >1000 \\ & (15.1) \end{aligned}$ |
| 76 | 90.05 | $\begin{gathered} >1000 \\ (4.8) \end{gathered}$ |
| 77 | 5.37 | $\begin{aligned} & >1000 \\ & (15.3) \\ & \hline \end{aligned}$ |
| 78 | 34.85 | $\begin{gathered} >1000 \\ (5.8) \\ \hline \end{gathered}$ |
| 79 | 1.3 | $\begin{gathered} 698 \\ (54.8) \\ \hline \end{gathered}$ |
| 80 | 1.8 | $\begin{gathered} 869 \\ (50.7) \\ \hline \end{gathered}$ |
| 81 | 1.15 | $\begin{gathered} 666 \\ (54.4) \\ \hline \end{gathered}$ |
| 82 | 2.55 | $\begin{aligned} & >1000 \\ & (10.7) \\ & \hline \end{aligned}$ |
| 83 | 1.77 | $\begin{aligned} & >1000 \\ & (26.3) \\ & \hline \end{aligned}$ |
| 84 | 21.05 | $\begin{gathered} >1000 \\ (2.7) \end{gathered}$ |
| 85 | 9.38 | $\begin{gathered} >1000 \\ (6.0) \\ \hline \end{gathered}$ |
| 86 | 26.7 | $\begin{aligned} & >1000 \\ & (17.3) \end{aligned}$ |
| 87 | 16.1 | $\begin{aligned} & >1000 \\ & (37.2) \\ & \hline \end{aligned}$ |

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| Example \# | TrkA Enzyme $\mathrm{IC}_{50}(\mathrm{nM})$ | $\begin{gathered} \text { Jak2 Enzyme } \\ \text { IC } \mathrm{C}_{50}(\mathrm{nM}) \\ (\% \text { inhibition at } 1000 \mathrm{nM}) \\ \hline \end{gathered}$ |
| :---: | :---: | :---: |
| 88 | 6.13 | $\begin{aligned} & >1000 \\ & (15.1) \end{aligned}$ |
| 89 | 3.6 | $\begin{aligned} & >1000 \\ & (33.1) \end{aligned}$ |
| 90 | 0.95 | $\begin{gathered} 472 \\ (67.3) \\ \hline \end{gathered}$ |
| 91 | 3.2 | $\begin{aligned} & >1000 \\ & (34.9) \end{aligned}$ |
| 92 | 1013.3 | $\begin{gathered} >1000 \\ (0.5) \\ \hline \end{gathered}$ |
| 93 | 5.1 | $\begin{aligned} & >1000 \\ & (34.7) \\ & \hline \end{aligned}$ |
| 94 | 568.2 | $\begin{gathered} >1000 \\ (4.4) \\ \hline \end{gathered}$ |
| 95 | 5.4 | $\begin{aligned} & >1000 \\ & (19.2) \\ & \hline \end{aligned}$ |
| 96 | 342.5 | $\begin{gathered} >1000 \\ (4.8) \\ \hline \end{gathered}$ |
| 97 | 6.2 | $\begin{gathered} >1000 \\ (6.8) \\ \hline \end{gathered}$ |
| 98 | 9.0 | $\begin{aligned} & >1000 \\ & (23.7) \end{aligned}$ |
| 99 | 7.0 | $\begin{aligned} & >1000 \\ & (45.8) \end{aligned}$ |
| 100 | 4.7 | $\begin{aligned} & >1000 \\ & (13.8) \end{aligned}$ |
| 101 | 11.7 | $\begin{aligned} & >1000 \\ & (26.2) \end{aligned}$ |
| 102 | 5.2 | $\begin{aligned} & >1000 \\ & (17.3) \end{aligned}$ |
| 103 | 87.8 | $\begin{gathered} >1000 \\ (4.5) \\ \hline \end{gathered}$ |
| 104 | 83.1 | $\begin{gathered} >1000 \\ (6.1) \\ \hline \end{gathered}$ |
| 105 | 25.4 | $\begin{aligned} & >1000 \\ & (18.7) \\ & \hline \end{aligned}$ |
| 106 | 7.7 | $\begin{gathered} >1000 \\ (8) \end{gathered}$ |
| 107 | 16.4 | $\begin{gathered} >1000 \\ (7.1) \\ \hline \end{gathered}$ |
| 108 | 1191.6 | $\begin{gathered} >1000 \\ (2.8) \end{gathered}$ |
| 109 | 36.7 | $\begin{aligned} & >1000 \\ & (-0.3) \end{aligned}$ |


| Example \# | TrkA Enzyme $\mathrm{IC}_{50}(\mathrm{nM})$ | Jak2 Enzyme $\mathrm{IC}_{50}(\mathrm{nM})$ $(\%$ inhibition at 1000 nM$)$ |
| :---: | :---: | :---: |
| 110 | 37.2 | $\begin{gathered} >1000 \\ (-0.5) \end{gathered}$ |
| 111 | 37.8 | $\begin{gathered} >1000 \\ (0.1) \end{gathered}$ |
| 112 | 30.9 | $\begin{gathered} >1000 \\ (3.2) \\ \hline \end{gathered}$ |
| 113 | 3.2 | $\begin{aligned} & >1000 \\ & (44.6) \end{aligned}$ |
| 114 | 29.9 | $\begin{gathered} >1000 \\ (5) \\ \hline \end{gathered}$ |
| 115 | 15.3 | $\begin{aligned} & >1000 \\ & (12.6) \\ & \hline \end{aligned}$ |
| 116 | 26.2 | $\begin{gathered} >1000 \\ (4.7) \\ \hline \end{gathered}$ |
| 117 | 45.0 | $\begin{gathered} >1000 \\ (-1.4) \end{gathered}$ |
| 118 | 22.5 | $\begin{aligned} & >1000 \\ & (-4.5) \end{aligned}$ |
| 119 | 131.2 | $\begin{gathered} >1000 \\ (1.7) \end{gathered}$ |
| 120 | 22.8 | $\begin{gathered} >1000 \\ (2.3) \end{gathered}$ |
| 121 | 182.5 | $\begin{gathered} >1000 \\ (3.7) \\ \hline \end{gathered}$ |
| 122 | 33.2 | $\begin{gathered} >1000 \\ (7.4) \end{gathered}$ |
| 123 | 6.4 | $\begin{aligned} & >1000 \\ & (38.8) \end{aligned}$ |
| 124 | 2.9 | $\begin{gathered} 759 \\ (53.3) \\ \hline \end{gathered}$ |
| 125 | 12.8 | $\begin{gathered} >1000 \\ (6.1) \\ \hline \end{gathered}$ |
| 126 | 218.5 | $\begin{gathered} >1000 \\ (-1) \end{gathered}$ |
| 127 | 469.8 | $\begin{gathered} >1000 \\ (0.2) \\ \hline \end{gathered}$ |
| 128 | 2595.0 | $\begin{gathered} >1000 \\ (1.2) \end{gathered}$ |
| 129 | 8.0 | $\begin{aligned} & >1000 \\ & (25.2) \\ & \hline \end{aligned}$ |
| 130 | 1.7 | $\begin{aligned} & >1000 \\ & (27.9) \end{aligned}$ |
| 131 | 5.0 | $\begin{aligned} & >1000 \\ & (14.6) \end{aligned}$ |

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$\left.\begin{array}{|c|c|c|}\hline \text { Example \# } & \begin{array}{c}\text { TrkA Enzyme } \\ \text { IC }_{50}(\mathrm{nM})\end{array} & \begin{array}{c}\text { Jak2 Enzyme } \\ \text { IC }\end{array} \\ & & (\mathrm{nM}) \\ & 44.4 & >1000 \\ \text { (\% inhibition at 1000 nM) }\end{array}\right)$

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| Example \# | TrkA Enzyme $\mathrm{IC}_{50}(\mathrm{nM})$ | Jak2 Enzyme IC $_{50}(\mathrm{nM})$ $(\%$ inhibition at 1000 nM$)$ |
| :---: | :---: | :---: |
| 154 | 1.3 | $\begin{gathered} 524 \\ (64.4) \\ \hline \end{gathered}$ |
| 155 | 0.2 | $\begin{aligned} & >1000 \\ & (33.3) \end{aligned}$ |
| 156 | 2.1 | $\begin{aligned} & >1000 \\ & (16.1) \end{aligned}$ |
| 157 | 2.8 | $\begin{gathered} >1000 \\ (9.6) \end{gathered}$ |
| 158 | 9.9 | $\begin{aligned} & >1000 \\ & (14.4) \end{aligned}$ |
| 159 | 4.3 | $\begin{aligned} & >1000 \\ & (28.9) \end{aligned}$ |
| 160 | 25.6 | $\begin{gathered} >1000 \\ (8.5) \end{gathered}$ |
| 161 | 3.0 | $\begin{aligned} & >1000 \\ & (27.4) \end{aligned}$ |
| 162 | 2.2 | $\begin{gathered} 444 \\ (66.2) \\ \hline \end{gathered}$ |
| 163 | not tested | not tested |
| 164 | not tested | not tested |
| 165 | 1.1 | $\begin{aligned} & >1000 \\ & (26.8) \\ & \hline \end{aligned}$ |
| 166 | 2.4 | $\begin{aligned} & >1000 \\ & (13.8) \end{aligned}$ |
| 167 | 2.2 | $\begin{gathered} >1000 \\ (9.8) \\ \hline \end{gathered}$ |
| 168 | 1.2 | $\begin{aligned} & >1000 \\ & (23.2) \end{aligned}$ |
| 169 | 0.9 | $\begin{gathered} 759 \\ (51.9) \end{gathered}$ |
| 170 | 11.6 | $\begin{gathered} >1000 \\ (0.7) \\ \hline \end{gathered}$ |
| 171 | 4.7 | $\begin{gathered} >1000 \\ (7.8) \end{gathered}$ |
| 172 | 2.5 | $\begin{gathered} >1000 \\ (11) \end{gathered}$ |
| 173 | 1.5 | $\begin{gathered} >1000 \\ (5.4) \\ \hline \end{gathered}$ |
| 174 | 16.3 | $\begin{gathered} >1000 \\ (6.4) \\ \hline \end{gathered}$ |
| 175 | 12.2 | $\begin{gathered} >1000 \\ (3.8) \end{gathered}$ |

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| Example \# | TrkA Enzyme $\mathrm{IC}_{50}(\mathrm{nM})$ | $\begin{gathered} \hline \text { Jak2 Enzyme } \\ \mathrm{IC}_{50}(\mathrm{nM}) \\ (\% \text { inhibition at } 1000 \mathrm{nM}) \end{gathered}$ |
| :---: | :---: | :---: |
| 176 | 27.2 | $\begin{gathered} >1000 \\ (6.3) \\ \hline \end{gathered}$ |
| 177 | 1.8 | $\begin{aligned} & >1000 \\ & (26.2) \\ & \hline \end{aligned}$ |
| 178 | 2.5 | $\begin{aligned} & >1000 \\ & (16.9) \end{aligned}$ |
| 179 | 8.5 | $\begin{aligned} & >1000 \\ & (-0.2) \\ & \hline \end{aligned}$ |
| 180 | 12.3 | $\begin{aligned} & >1000 \\ & (-0.8) \\ & \hline \end{aligned}$ |
| 181 | 17.1 | $\begin{gathered} >1000 \\ (5.2) \\ \hline \end{gathered}$ |
| 182 | 11.3 | $\begin{aligned} & >1000 \\ & (21.2) \\ & \hline \end{aligned}$ |
| 183 | 6.9 | $\begin{aligned} & >1000 \\ & (-0.8) \\ & \hline \end{aligned}$ |
| 184 | 7.4 | $\begin{aligned} & >1000 \\ & (11.8) \end{aligned}$ |
| 185 | 8.6 | $\begin{aligned} & >1000 \\ & (11.7) \\ & \hline \end{aligned}$ |
| 186 | 57.1 | $\begin{aligned} & >1000 \\ & (10.5) \end{aligned}$ |
| 187 | 61.6 | $\begin{gathered} >1000 \\ (9.1) \\ \hline \end{gathered}$ |
| 188 | 83.0 | $\begin{gathered} >1000 \\ (9.3) \\ \hline \end{gathered}$ |
| 189 | 76.4 | $\begin{gathered} >1000 \\ (4.6) \\ \hline \end{gathered}$ |
| 190 | 2.4 | $\begin{aligned} & >1000 \\ & (28.4) \\ & \hline \end{aligned}$ |
| 191 | 69.5 | $\begin{gathered} >1000 \\ (4.8) \\ \hline \end{gathered}$ |
| 192 | 437.8 | $\begin{gathered} >1000 \\ (0.3) \\ \hline \end{gathered}$ |
| 193 | 15.6 | $\begin{gathered} >1000 \\ (8.4) \\ \hline \end{gathered}$ |
| 194 | 4.7 | $\begin{aligned} & >1000 \\ & (31.2) \\ & \hline \end{aligned}$ |
| 195 | 7.7 | $\begin{aligned} & >1000 \\ & (16.2) \\ & \hline \end{aligned}$ |
| 196 | 6.8 | $\begin{aligned} & >1000 \\ & (10.6) \\ & \hline \end{aligned}$ |
| 197 | 4.8 | $\begin{gathered} >1000 \\ (3.6) \\ \hline \end{gathered}$ |

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| Example \# | TrkA Enzyme $\mathrm{IC}_{50}(\mathrm{nM})$ | Jak2 Enzyme $\mathrm{IC}_{50}(\mathrm{nM})$ $(\%$ inhibition at 1000 nM$)$ |
| :---: | :---: | :---: |
| 198 | 242.8 | $\begin{gathered} >1000 \\ (1.6) \\ \hline \end{gathered}$ |
| 199 | 3.6 | $\begin{aligned} & >1000 \\ & (38.8) \\ & \hline \end{aligned}$ |
| 200 | 12.7 | $\begin{aligned} & >1000 \\ & (12.5) \end{aligned}$ |
| 201 | 71.8 | $\begin{gathered} >1000 \\ (3.8) \end{gathered}$ |
| 202 | 19.3 | $\begin{aligned} & >1000 \\ & (11.5) \end{aligned}$ |
| 203 | not tested | not tested |
| 204 | 16.6 | $\begin{gathered} >1000 \\ (37) \\ \hline \end{gathered}$ |
| 205 | 14.3 | $\begin{gathered} >1000 \\ (7.2) \end{gathered}$ |
| 206 | 3.9 | $\begin{aligned} & >1000 \\ & (12.6) \\ & \hline \end{aligned}$ |
| 207 | 33.3 | $\begin{gathered} >1000 \\ (0.9) \end{gathered}$ |
| 208 | 1.7 | $\begin{aligned} & >1000 \\ & (21.2) \end{aligned}$ |
| 209 | 17.1 | $\begin{gathered} >1000 \\ (5.4) \end{gathered}$ |
| 210 | 3.3 | $\begin{aligned} & >1000 \\ & (32.3) \end{aligned}$ |
| 211 | 4.2 | $\begin{aligned} & >1000 \\ & (19.5) \\ & \hline \end{aligned}$ |
| 212 | 38.0 | $\begin{aligned} & >1000 \\ & (14.2) \end{aligned}$ |
| 213 | 6.8 | $\begin{aligned} & >1000 \\ & (21.9) \end{aligned}$ |
| 214 | 8.6 | $\begin{aligned} & >1000 \\ & (29.7) \\ & \hline \end{aligned}$ |
| 215 | 15.3 | $\begin{aligned} & >1000 \\ & (28.3) \\ & \hline \end{aligned}$ |
| 216 | 3.1 | $\begin{aligned} & 670 \\ & (54) \\ & \hline \end{aligned}$ |
| 217 | 5.8 | $\begin{gathered} 551 \\ (61.7) \\ \hline \end{gathered}$ |
| 218 | 33.9 | $\begin{aligned} & >1000 \\ & (24.6) \\ & \hline \end{aligned}$ |
| 219 | 187.7 | $\begin{aligned} & >1000 \\ & (25.5) \\ & \hline \end{aligned}$ |

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| Example \# | TrkA Enzyme $\mathrm{IC}_{50}(\mathrm{nM})$ | Jak2 Enzyme IC $_{50}(\mathrm{nM})$ $(\%$ inhibition at 1000 nM$)$ |
| :---: | :---: | :---: |
| 220 | 109.9 | $\begin{aligned} & >1000 \\ & (15.2) \end{aligned}$ |
| 221 | 49.3 | $\begin{aligned} & >1000 \\ & (-1.2) \\ & \hline \end{aligned}$ |
| 222 | not tested | not tested |
| 223 | not tested | not tested |
| 224 | not tested | not tested |
| 225 | 52.4 | $\begin{gathered} >1000 \\ (2.7) \end{gathered}$ |
| 226 | 10.5 | $\begin{aligned} & >1000 \\ & (100) \end{aligned}$ |
| 227 | 12.3 | $\begin{array}{r} 445.8 \\ (62.8) \\ \hline \end{array}$ |
| 228 | 13.0 | $\begin{aligned} & >1000 \\ & (31.9) \end{aligned}$ |
| 229 | 15.9 | $\begin{aligned} & >1000 \\ & (34.9) \\ & \hline \end{aligned}$ |
| 230 | 3.0 | $\begin{aligned} & 665.6 \\ & (53.3) \\ & \hline \end{aligned}$ |
| 231 | 8.7 | $\begin{aligned} & >1000 \\ & (26.6) \\ & \hline \end{aligned}$ |
| 232 | 4.5 | $\begin{aligned} & >1000 \\ & (31.9) \\ & \hline \end{aligned}$ |
| 233 | 75.9 | $\begin{gathered} >1000 \\ (6.7) \\ \hline \end{gathered}$ |
| 234 | 10.7 | $\begin{gathered} >1000 \\ (5.3) \\ \hline \end{gathered}$ |
| 235 | 2.8 | $\begin{gathered} 311 \\ (73.1) \end{gathered}$ |
| 236 | 2.2 | $\begin{gathered} 419 \\ (69.1) \\ \hline \end{gathered}$ |
| 237 | 2.1 | $\begin{gathered} 616 \\ (51.9) \\ \hline \end{gathered}$ |
| 238 | 1.9 | $\begin{gathered} 499 \\ (58.9) \end{gathered}$ |
| 239 | 10.1 | $\begin{aligned} & >1000 \\ & (15.5) \end{aligned}$ |
| 240 | 11.3 | not tested |
| 241 | 21.8 | not tested |
| 242 | 8.9 | not tested |
| 243 | 9 | not tested |

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$\left.\begin{array}{|c|c|c|}\hline \text { Example \# } & \begin{array}{c}\text { TrkA Enzyme } \\ \mathrm{IC}_{50}(\mathrm{nM})\end{array} & \begin{array}{c}\text { Jak2 Enzyme } \\ \text { IC }\end{array} \\ \hline 244 & 38.2 & \text { not } \\ \text { (\% inhibition at } 1000 \mathrm{nM})\end{array}\right]$
[00415] Representative compounds of the invention were tested in the four Jak Kinase enzyme assays described in Examples C, D, E and F. The $\mathrm{IC}_{50}$ values are shown in Table 2. These compounds were found to be even more selective for inhibiting TrkA kinase activity over inhibiting kinase activity of Jak1, Jak3 and Tyk2 than over inhibiting Jak2.

Table 2

| Ex \# | TrkA $\mathrm{IC}_{50}$ (nM) | $\begin{gathered} \hline \text { Jak1 } \\ \mathrm{IC}_{50}(\mathrm{nM}) \\ (\% \text { inhibition } \\ \text { at } 1000 \mathrm{nM}) \\ \hline \end{gathered}$ | Jak2 $\mathrm{IC}_{50}(\mathrm{nM})$ (\% inhibition at 1000 nM$)$ | Jak3 $\mathrm{IC}_{50}(\mathrm{nM})$ (\% inhibition at 1000 nM$)$ | Tyk2 IC $\mathrm{IC}_{50}(\mathrm{nM})$ $(\%$ inhibition at 1000 nM$)$ |
| :---: | :---: | :---: | :---: | :---: | :---: |
| 30 | 1.9 | $\begin{aligned} & >1000 \\ & (13.4) \end{aligned}$ | $\begin{aligned} & >1000 \\ & (30.4) \end{aligned}$ | $\begin{gathered} >1000 \\ (2.9) \\ \hline \end{gathered}$ | $\begin{aligned} & >1000 \\ & (11.3) \end{aligned}$ |
| 52 | 7.4 | $\begin{gathered} >1000 \\ (8.6) \end{gathered}$ | $\begin{aligned} & >1000 \\ & (13.0) \end{aligned}$ | $\begin{gathered} >1000 \\ (0.8) \end{gathered}$ | $\begin{aligned} & >1000 \\ & (13.8) \end{aligned}$ |
| 140 | 0.9 | $\begin{gathered} \hline 546 \\ (64.2) \\ \hline \end{gathered}$ | $\begin{gathered} \hline 76.7 \\ (98.5) \\ \hline \end{gathered}$ | $\begin{aligned} & >1000 \\ & (20.2) \\ & \hline \end{aligned}$ | $\begin{aligned} & >1000 \\ & (34.8) \\ & \hline \end{aligned}$ |
| 93 | 5.1 | $\begin{aligned} & >1000 \\ & (19.7) \end{aligned}$ | $\begin{aligned} & >1000 \\ & (42.2) \\ & \hline \end{aligned}$ | $\begin{aligned} & >1000 \\ & (10.6) \end{aligned}$ | $\begin{aligned} & >1000 \\ & (17.2) \end{aligned}$ |
| 106 | 7.6 | $\begin{gathered} >1000 \\ (8.2) \end{gathered}$ | $\begin{aligned} & >1000 \\ & (21.0) \end{aligned}$ | $\begin{gathered} >1000 \\ (9.7) \end{gathered}$ | $\begin{aligned} & >1000 \\ & (14.8) \end{aligned}$ |
| 114 | 17.1 | $\begin{aligned} & >1000 \\ & (10.9) \\ & \hline \end{aligned}$ | $\begin{aligned} & >1000 \\ & (15.6) \\ & \hline \end{aligned}$ | $\begin{gathered} >1000 \\ (8.5) \\ \hline \end{gathered}$ | $\begin{aligned} & >1000 \\ & (11.4) \end{aligned}$ |
| 181 | 29.8 | $\begin{aligned} & >1000 \\ & (12.8) \end{aligned}$ | $\begin{aligned} & >1000 \\ & (18.1) \end{aligned}$ | $\begin{gathered} >1000 \\ (8.9) \\ \hline \end{gathered}$ | $\begin{aligned} & >1000 \\ & (10.7) \end{aligned}$ |
| 91 | 3.2 | $\begin{aligned} & >1000 \\ & (20.3) \\ & \hline \end{aligned}$ | $\begin{aligned} & >1000 \\ & (42.1) \end{aligned}$ | $\begin{gathered} >1000 \\ (8.3) \\ \hline \end{gathered}$ | $\begin{aligned} & >1000 \\ & (14.8) \\ & \hline \end{aligned}$ |
| 123 | 6.3 | $\begin{aligned} & >1000 \\ & (22.0) \end{aligned}$ | $\begin{gathered} >1000 \\ (49.1) \end{gathered}$ | $\begin{gathered} >1000 \\ (8.9) \end{gathered}$ | $\begin{aligned} & >1000 \\ & (14.4) \end{aligned}$ |
| 124 | 2.9 | $\begin{aligned} & >1000 \\ & (36.4) \\ & \hline \end{aligned}$ | $\begin{gathered} \hline 759 \\ (72.3) \\ \hline \end{gathered}$ | $\begin{gathered} >1000 \\ (7.2) \\ \hline \end{gathered}$ | $\begin{aligned} & >1000 \\ & (16.2) \\ & \hline \end{aligned}$ |
| 190 | 2.4 | $\begin{aligned} & >1000 \\ & (14.3) \\ & \hline \end{aligned}$ | $\begin{aligned} & >1000 \\ & (33.9) \\ & \hline \end{aligned}$ | $\begin{gathered} >1000 \\ (7.2) \\ \hline \end{gathered}$ | $\begin{aligned} & >1000 \\ & (13.4) \\ & \hline \end{aligned}$ |
| 98 | 9.0 | $\begin{gathered} >1000 \\ (8.8) \end{gathered}$ | $\begin{aligned} & >1000 \\ & (27.8) \end{aligned}$ | $\begin{gathered} >1000 \\ (5.5) \end{gathered}$ | $\begin{gathered} >1000 \\ (9.2) \\ \hline \end{gathered}$ |
| 194 | 4.6 | $\begin{gathered} >1000 \\ (7.4) \\ \hline \end{gathered}$ | $\begin{array}{r} >1000 \\ (37.6) \\ \hline \end{array}$ | $\begin{gathered} >1000 \\ (2.6) \\ \hline \end{gathered}$ | $\begin{gathered} >1000 \\ (8.1) \\ \hline \end{gathered}$ |

## Preparation A



## (R)-2-(2,5-difluorophenyl)pyrrolidine

[00416] Step A: Preparation of (R)-tert-butyl 2-(2,5-difluorophenyl)pyrrolidine-1carboxylate. A solution of tert-butyl pyrrolidine-1-carboxylate ( $20 \mathrm{~g}, 116.8 \mathrm{mmol}$ ) and (-)sparteine $(32.9,140 \mathrm{mmol})$ in MTBE $(360 \mathrm{~mL})$ was cooled to $-78{ }^{\circ} \mathrm{C}$ and $\mathrm{sec}-\mathrm{BuLi}(100 \mathrm{~mL}$, $140 \mathrm{mmol}, 1.4 \mathrm{M}$ in cyclohexane) was introduced drop-wise via cannula, keeping the internal temperature under $-70^{\circ} \mathrm{C}$. The resulting solution was stirred for 3 hours at $-78^{\circ} \mathrm{C}$, followed by addition of a solution of $\mathrm{ZnCl}_{2}\left(93.4 \mathrm{~mL}, 93.4 \mathrm{mmol}, 1 \mathrm{M}\right.$ in $\left.\mathrm{Et}_{2} \mathrm{O}\right)$ drop-wise with rapid stirring, keeping the internal temperature below $-65^{\circ} \mathrm{C}$. The resulting light suspension was stirred at $-78^{\circ} \mathrm{C}$ for 30 minutes and then warmed to ambient temperature. The resulting mixture was sequentially charged with 2-bromo-1,4-difluorobenzene ( $14.5 \mathrm{~mL}, 128 \mathrm{mmol}$ ), $\mathrm{Pd}(\mathrm{OAc})_{2}(1.31 \mathrm{~g}, 5.8 \mathrm{mmol})$ and $t-\mathrm{Bu}_{3} \mathrm{P}-\mathrm{HBF}_{4}(2.03 \mathrm{~g}, 7.0 \mathrm{mmol})$ in one portion. After stirring overnight at ambient temperature, concentrated $\mathrm{NH}_{4} \mathrm{OH}(10.5 \mathrm{~mL})$ was added and the reaction was stirred for 1 hour. The resulting slurry was filtered through Celite and the filter cake washed with $\mathrm{Et}_{2} \mathrm{O}(1 \mathrm{~L})$. The filtrate was washed with a 1 M aqueous HCl solution ( 0.5 L) and brine. The organic layer was filtered and concentrated, and the crude product was purified by silica column chromatography, eluting with $5-10 \% \mathrm{EtOAc} /$ hexanes to give product (R)-tert-butyl 2-(2,5-difluorophenyl)pyrrolidine-1-carboxylate as yellow oil ( 23.9 g , $72 \%$ yield).
[00417] Step B: Preparation of (R)-2-(2,5-difluorophenyl)pyrrolidine. To (R)-tertbutyl 2-(2,5-difluorophenyl)pyrrolidine-1-carboxylate ( $23.9 \mathrm{~g}, 84.4 \mathrm{mmol}$ ) was added 4 N HCl in dioxane ( 56.2 mL ). After stirring at ambient temperature for 2 hours, ether ( 200 mL ) was added and the mixture was stirred for 10 minutes. The resulting slurry was filtered, yielding the title compound hydrochloride salt 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 ( $100 \mathrm{~mL}, 2 \mathrm{Naq)}$. 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 ( $13.2 \mathrm{~g}, 85 \%$ yield).
[00418] The enantiomeric excess (\% ee) of (R)-2-(2,5-difluorophenyl)pyrrolidine was determined as follows: 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 analyzed by HPLC (YMC ODS-AQ $4.6 \times 50 \mathrm{~mm} 3 \mu \mathrm{~m} 120 \AA$ column; mobile phase: $5-95 \%$ solvent B in A; solvent A: $\mathrm{H}_{2} \mathrm{O} / 1 \%$ iPrOH $/ 10 \mathrm{mM}$ ammonium acetate, and solvent $\mathrm{B}: \mathrm{ACN} / 1 \% \mathrm{iPrOH} / 10 \mathrm{mM}$ ammonium acetate; flow rate: $2 \mathrm{~mL} / \mathrm{min}$ ). The enantiomeric excess (ee\%) was determined from the peak areas of the two diastereomeric derivatives formed. A 1:1 racemic standard was prepared according the same procedure described herein, replacing (R)-2-(2,5difluorophenyl)pyrrolidine with (rac)-2-(2,5-difluorophenyl)pyrrolidine. The ee\% of the title compound obtained as described above was determined to be $>93 \%$.

## Preparation B



Ethyl 5-chloropyrazolo[1,5-a]pyrimidine-3-carboxylate
[00419] Step A: Preparation of ethyl 5-hydroxypyrazolo[1,5-a]pyrimidine-3carboxylate. Ethyl 3-amino-1H-pyrazole-4-carboxylate ( $25.0 \mathrm{~g}, 161 \mathrm{mmol}$ ) and (E)-ethyl 3ethoxyacrylate ( $35.8 \mathrm{ml}, 242 \mathrm{mmol}$ ) were mixed in DMF ( 537 mL ). Cesium carbonate ( 78.7 $\mathrm{g}, 242 \mathrm{mmol}$ ) was added and the mixture heated to $110^{\circ} \mathrm{C}$ for 15 hours. The reaction mixture was cooled to ambient temperature and acidified with HOAc to pH 4 . The resultant precipitate was filtered and washed with water and EtOAc, yielding the title compound as a fluffy white solid. Additional material was obtained by an aqueous workup. The filtrate was concentrated to remove the DMF, was diluted in $\mathrm{EtOAc}\left(500 \mathrm{~mL}\right.$ ) and washed with $\mathrm{H}_{2} \mathrm{O}$. The resultant precipitate in the EtOAc layer was filtered and washed with water and EtOAc to obtain additional product. The solids were pooled and dried in vacuum to afford ethyl 5-hydroxypyrazolo[1,5-a]pyrimidine-3-carboxylate ( $33.3 \mathrm{~g}, 100 \%$ yield) as a fluffy white solid. MS (apci) m/z = $206.2(\mathrm{M}-\mathrm{H})$.
[00420] Step B: Preparation of ethyl 5-chloropyrazolo[1,5-a]pyrimidine-3-carboxylate. Ethyl 5-hydroxypyrazolo[1,5-a]pyrimidine-3-carboxylate ( $22.7 \mathrm{~g}, 110 \mathrm{mmol}$ ) was suspended in phosphoryl trichloride ( 100 mL ) and heated to reflux. After heating for 2 hours, the reaction mixture was cooled and concentrated to remove the excess $\mathrm{POCl}_{3}$. The residue was diluted in DCM $(100 \mathrm{~mL})$ and slowly added to a flask containing ice water. The mixture was separated and the aqueous layer extracted with DCM. The combined organics were dried
with $\mathrm{MgSO}_{4}$, filtered and concentrated to afford ethyl 5-chloropyrazolo[1,5-a]pyrimidine-3carboxylate ( $24.2 \mathrm{~g}, 97.6 \%$ yield) as a pale yellow solid. MS (apci) m/z $=225.9(\mathrm{M}+\mathrm{H})$.

Preparation C

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid [00421] Step A: Preparation of (R)-ethyl 5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylate. A mixture of ethyl 5-chloropyrazolo[1,5-a]pyrimidine-3-carboxylate (Preparation B, $2.00 \mathrm{~g}, \quad 8.86 \mathrm{mmol}$ ), (R)-2-(2,5difluorophenyl)pyrrolidine (Preparation A, $1.62 \mathrm{~g}, 8.86 \mathrm{mmol}$ ), diisopropylethylamine ( 3.09 $\mathrm{mL}, 17.7 \mathrm{mmol})$ and butan-1-ol ( $2.95 \mathrm{ml}, 8.86 \mathrm{mmol}$ ) was heated at $100^{\circ} \mathrm{C}$ for 15 hours. The reaction mixture was cooled to ambient temperature and was diluted with EtOAc ( 30 mL ) and water ( 10 mL ). Undissolved solid was filtered and washed with $\mathrm{Et}_{2} \mathrm{O}$ to afford the title compound as a light orange solid $(2.13 \mathrm{~g})$. The organic layer was separated from the filtrate, washed with brine ( 10 mL ) and dried over $\mathrm{MgSO}_{4}$. The solution was filtered and concentrated to provide additional solid that was purified by silica chromatography using gradient elution with $50-100 \% \mathrm{EtOAc} /$ hexanes. This afforded the title compound $(0.50 \mathrm{~g})$ as a light yellow solid. The combined yield was $2.63 \mathrm{~g}, 79.7 \%$. MS (apci) $\mathrm{m} / \mathrm{z}=373.1(\mathrm{M}+\mathrm{H})$.
[00422] Step B: Preparation of (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid. (R)-ethyl 5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylate ( $2.13 \mathrm{~g}, 5.72 \mathrm{mmol}$ ) was suspended in $\mathrm{EtOH}(28.6 \mathrm{~mL})$ and heated at $90^{\circ} \mathrm{C}$ for 20 min (homogeneous). 1 M aq. $\mathrm{LiOH}(11.4 \mathrm{~mL}, 11.4 \mathrm{mmol})$ was added and the reaction mixture was heated for 15 hours at $90^{\circ} \mathrm{C}$. After cooling, the reaction mixture was concentrated, diluted with water and washed with EtOAc to remove any unreacted starting material. The aqueous layer was then acidified to pH 1 using 2 N HCl . After extracting with DCM and EtOAc, the combined organic fractions were dried with $\mathrm{MgSO}_{4}$, filtered and concentrated to afford (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid ( $1.82 \mathrm{~g}, 92.4 \%$ ) as a light yellow solid. $\mathrm{MS}(\mathrm{apci}) \mathrm{m} / \mathrm{z}=345.0(\mathrm{M}+\mathrm{H})$.

## Preparation D



## (R)-2-(3-fluorophenyl)pyrrolidine

[00423] Prepared by the method of Preparation A, substituting 2-bromo-1,4difluorobenzene with 1-bromo-3-fluorobenzene in Step A. MS (apci) m/z = $166.0(\mathrm{M}+\mathrm{H})$. The ee\% of the title compound was determined to be $94 \%$.

## Preparation E


(R)-5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid [00424] Step A: Preparation of (R)-ethyl 5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylate. Prepared according to the method of Preparation C, substituting (R)-2-(2,5-difluorophenyl)pyrrolidine in Step A with (R)-2-(3fluorophenyl)pyrrolidine. MS (apci) $\mathrm{m} / \mathrm{z}=355.0(\mathrm{M}+\mathrm{H})$.
[00425] Step B: Preparation of (R)-5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid. (R)-ethyl 5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylate ( $0.76 \mathrm{~g}, 2.14 \mathrm{mmol}$ ) was suspended in $\mathrm{EtOH}(10.7 \mathrm{~mL})$ and the mixture was heated at $90^{\circ} \mathrm{C}$ for 20 minutes (homogeneous). 1 M aqueous $\mathrm{LiOH}(4.29 \mathrm{ml}$, 4.29 mmol ) was added and the reaction mixture was heated for 15 hours at $90^{\circ} \mathrm{C}$. After cooling, the reaction mixture was concentrated, diluted with water and washed with EtOAc to remove any unreacted starting material. The aqueous layer was then acidified to pH 4 using 2 N HCl . After extracting with DCM and EtOAc , the combined organic layers were dried with $\mathrm{MgSO}_{4}$, filtered and concentrated to afford (R)-5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid $(0.60 \mathrm{~g}, 85.7 \%$ yield) as a glassy yellow solid. MS (apci) $\mathrm{m} / \mathrm{z}=327.0(\mathrm{M}+\mathrm{H})$.

## Preparation $F$



## (R)-2-(5-fluoro-2-methoxyphenyl)pyrrolidine

[00426] Prepared by the method of Preparation A, substituting 2-bromo-1,4difluorobenzene with 2-bromo-4-fluoro-1-methoxybenzene in Step A. MS (apci) m/z = $196.1(\mathrm{M}+\mathrm{H})$. The ee\% of the title compound was determined to be $>99 \%$.

## Preparation G


(R)-5-(2-(5-fluoro-2-methoxyphenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid
[00427] In a sealed tube, ethyl 5-chloropyrazolo[1,5-a]pyrimidine-3-carboxylate (Preparation B, $500 \mathrm{mg}, 2.22 \mathrm{mmol}$ ), (R)-2-(5-fluoro-2-methoxyphenyl)pyrrolidine hydrochloride salt ( $513 \mathrm{mg}, 2.22 \mathrm{mmol}$ ), and diisopropylethylamine ( $0.774 \mathrm{~mL}, 4.43 \mathrm{mmol}$ ) were combined in isopropanol ( 2 mL ) and heated at $160^{\circ} \mathrm{C}$ for 3 days. $2 \mathrm{~N} \mathrm{NaOH}(6 \mathrm{~mL})$ and $\mathrm{MeOH}(5 \mathrm{~mL})$ were added and the reaction mixture stirred at ambient temperature for 24 hours, followed by heating to $40^{\circ} \mathrm{C}$ for 3 hours. The reaction was partially concentrated, treated with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}(10 \mathrm{~mL})$ and the mixture extracted with EtOAc. The combined organic extracts were filtered, concentrated and the residue purified by reverse phase chromatography eluting with $0-60 \%$ acetonitrile/water to yield the title compound as a pink solid ( $254 \mathrm{mg}, 32.2 \%$ yield). MS (apci) m/z $=357.0(\mathrm{M}+\mathrm{H})$.

Preparation H

[00428] Prepared by the method of Preparation A, substituting 2-bromo-1,4difluorobenzene with 3-bromo-5-fluoropyridine in Step A. MS (apci) m/z=167.1(M+H). The ee\% of the title compound was determined to be $92 \%$.

## Preparation I


(R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid [00429] Step A: Preparation of ethyl 5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylate. Ethyl 5-chloropyrazolo[1,5-a]pyrimidine-3carboxylate (Preparation B; $0.50 \mathrm{~g}, 2.22 \mathrm{mmol}$ ), (R)-3-fluoro-5-(pyrrolidin-2-yl)pyridine dihydrochloride ( $0.53 \mathrm{~g}, 2.22 \mathrm{mmol}$ ) and diisopropylethylamine ( $1.46 \mathrm{~mL}, 8.86 \mathrm{mmol}$ ) were combined in isopropanol ( 2 mL ) and heated at $95^{\circ} \mathrm{C}$ for 70 hours. The crude product was purified by reverse phase chromatography, eluting with $0-50 \%$ acetonitrile/water to yield the title compound ( $540 \mathrm{mg}, 68.6 \%$ yield). MS (apci) m/z $=356.0(\mathrm{M}+\mathrm{H})$.
[00430] Step B: Preparation of 5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid. Ethyl 5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylate ( $0.540 \mathrm{~g}, 1.52 \mathrm{mmol}$ ) was dissolved in MeOH $(20 \mathrm{~mL})$ and treated with $1 \mathrm{~N} \mathrm{NaOH}(13 \mathrm{~mL})$. After stirring for 5 days, citric acid (solid) was added to acidify the mixture to $\mathrm{pH} 4-5$. Saturated aqueous $\mathrm{NaCl}(10 \mathrm{~mL})$ was added and the reaction mixture extracted with DCM and EtOAc. The combined organic layers were combined to afford 5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3carboxylic acid $(0.49 \mathrm{~g}, 99 \%$ yield). MS (apci) m/z $=328.0(\mathrm{M}+\mathrm{H})$.

Preparation J

(R)-5-fluoro-2-methoxy-3-(pyrrolidin-2-yl)pyridine
[00431] Step A: Preparation of 3-bromo-5-fluoro-2-methoxypyridine. 3-Bromo-5-fluoropyridin- $2\left(1 \mathrm{H}\right.$ )-one ( $10.0 \mathrm{~g}, 52.1 \mathrm{mmol}$ ) and $\mathrm{Ag}_{2} \mathrm{CO}_{3}(10.0 \mathrm{~g}, 36.5 \mathrm{mmol})$ were combined in toluene ( 100 mL ) and iodomethane ( $3.89 \mathrm{~mL}, 62.5 \mathrm{mmol}$ ) was added drop-wise.

The reaction was stirred at ambient temperature overnight, filtered through Celite and the solids were washed with toluene. The filtrate was concentrated and the residue was purified on a silica gel column (5-25\% EtOAc/hexanes) to afford 3-bromo-5-fluoro-2methoxypyridine $(4.70 \mathrm{~g}, 43.8 \%)$ as a clear oil.
[00432] Step B: Preparation of (R)-5-fluoro-2-methoxy-3-(pyrrolidin-2-yl)pyridine. Prepared by the method of Preparation A, substituting 2-bromo-1,4-difluorobenzene with 3-bromo-5-fluoro-2-methoxypyridine in Step A. MS (apci) m/z=197.1(M+H). The ee\% of the title compound was determined to be $98 \%$.

## Preparation K


(R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3carboxylic acid
[00433] Step A: Preparation of (R)-ethyl 5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylate. Ethyl 5-chloropyrazolo[1,5-a]pyrimidine-3-carboxylate (Preparation B, $0.75 \mathrm{~g}, 3.32 \mathrm{mmol}$ ), (R)-5-fluoro-2-methoxy-3-(pyrrolidin-2-yl)pyridine dihydrochloride ( $0.984 \mathrm{~g}, 3.66 \mathrm{mmol}$ ), diisopropylethylamine ( 2.32 $\mathrm{mL}, 13.3 \mathrm{mmol})$ and n -butanol $(1.11 \mathrm{~mL})$ were heated at $90^{\circ} \mathrm{C}$ for 48 hours. The reaction mixture was diluted with EtOAc and the mixture was washed with water, brine and saturated $\mathrm{NaHCO}_{3}$. The organic layer was dried with $\mathrm{MgSO}_{4}$, filtered and concentrated afford a dark orange oil. The oil was purified by silica chromatography, eluting with a $50-80 \%$ EtOAc/Hexane gradient, to afford (R)-ethyl 5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylate ( $0.72 \mathrm{~g}, 56.2 \%$ ) as a yellow foam. MS (apci) $\mathrm{m} / \mathrm{z}=386.0(\mathrm{M}+\mathrm{H})$.
[00434] Step B: (R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid. To a suspension of (R)-ethyl 5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylate ( 0.72 $\mathrm{g}, 1.868 \mathrm{mmol})$ in $\mathrm{MeOH}(9.34 \mathrm{~mL})$ was added $1 \mathrm{~N} \mathrm{LiOH}(3.74 \mathrm{ml}, 3.74 \mathrm{mmol})$ and the reaction mixture heated to $70^{\circ} \mathrm{C}$ for 15 hours. After cooling, the reaction mixture was concentrated and the resulting residue diluted in water. After acidifying with citric acid (solid), the aqueous layer was extracted with DCM. The combined organics were dried with
$\mathrm{MgSO}_{4}$, filtered and concentrated to afforded (R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid ( $0.67 \mathrm{~g}, 100 \%$ ) as a yellow solid. MS (apci) m/z=357.9(M+H).

## Preparation L


(R)-2-(5-fluoro-2-(trifluoromethyl)phenyl)pyrrolidine
[00435] Prepared by the method of Preparation A, substituting 2-bromo-1,4difluorobenzene with 2-bromo-4-fluoro-1-(trifluoromethyl)benzene in Step A. MS (apci) m/z $=234.1(\mathrm{M}+\mathrm{H})$. The ee $\%$ of the title compound was determined to be $90 \%$.

## Preparation M


(R)-5-(2-(5-fluoro-2-(trifluoromethyl)phenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3carboxylic acid
[00436] Step A: Preparation of (R)-ethyl 5-(2-(5-fluoro-2-(trifluoromethyl)phenyl) pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylate. Ethyl 5-chloropyrazolo[1,5-a]pyrimidine-3-carboxylate (Preparation B, $0.51 \mathrm{~g}, 2.26 \mathrm{mmol}$ ), (R)-2-(5-fluoro-2(trifluoromethyl)phenyl)pyrrolidine hydrochloride ( $0.610 \mathrm{~g}, 2.26 \mathrm{mmol})$ and diisopropylethylamine ( $1.12 \mathrm{~mL}, 6.78 \mathrm{mmol}$ ) were suspended in isopropanol $(2.5 \mathrm{~mL})$ and heated to $120{ }^{\circ} \mathrm{C}$ for 24 hours. The reaction mixture was purified by reverse phase chromatography eluting with $0-75 \%$ acetonitrile/water to yield the title compound $(0.92 \mathrm{~g}$, $96.4 \%$ yield). MS (apci) $\mathrm{m} / \mathrm{z}=423.0 .0(\mathrm{M}+\mathrm{H})$.
[00437] Step B: Preparation of 5-(2-(5-fluoro-2-(trifluoromethyl)phenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid. (R)-ethyl 5-(2-(5-fluoro-2-(trifluoromethyl) phenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylate ( $0.92 \mathrm{~g}, 2.2 \mathrm{mmol}$ ) was combined with $1 \mathrm{~N} \mathrm{NaOH}(25 \mathrm{~mL})$ and $\mathrm{MeOH}(40 \mathrm{~mL})$. The reaction mixture was stirred at ambient temperature for 20 hours, followed by heating to $40^{\circ} \mathrm{C}$ until complete. Citric acid (solid) was added until the mixture was $\mathrm{pH} 4-5$. Brine ( 10 mL ) was added and this was
extracted with DCM and EtOAc. The combined organic layers were concentrated and the crude product was purified by reverse phase silica gel column chromatography eluting with $0-60 \%$ acetonitrile/water to yield 5-(2-(5-fluoro-2-(trifluoromethyl)phenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid ( $0.45 \mathrm{~g}, 52 \%$ ). MS (apci) m/z $=395.0$ (M+H).

## Preparation $\mathbf{N}$



## (R)-5-fluoro-2-methyl-3-(pyrrolidin-2-yl)pyridine

[00438] Step A: Preparation of 3-bromo-5-fluoro-2-methylpyridine: 2,3-Dibromo-5fluoropyridine ( $5.0 \mathrm{~g}, 19.6 \mathrm{mmol}), \mathrm{Pd}\left(\mathrm{PPh}_{3}\right)_{4}(1.13 \mathrm{~g}, 0.98 \mathrm{mmol})$ and methyl boronic acid $(3.52 \mathrm{~g}, 58.9 \mathrm{mmol})$ were combined in dioxane $(50 \mathrm{~mL})$ then treated with $\mathrm{K}_{2} \mathrm{CO}_{3}(8.13,58.9$ $\mathrm{mmol})$ and water $(10 \mathrm{~mL})$. The mixture was purged with $\mathrm{N}_{2}$ then heated to $110^{\circ} \mathrm{C}$ in a sealed vessel for 16 hours. The cooled mixture was partitioned between water ( 100 mL ) and EtOAc $(50 \mathrm{~mL})$ and the layers separated. The aqueous layer was extracted with EtOAc $(2 \times 50 \mathrm{~mL})$ and the combined organic phases were washed with brine ( 50 mL ), dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and concentrated. The residue was purified by silica gel column chromatography eluting with $1-3 \%$ EtOAc/hexanes to afford the product as a white solid ( $1.20 \mathrm{~g}, 32 \%$ yield). MS (apci) m/z $=190.2(\mathrm{M}+$ ).
[00439] Step B: Preparation of (R)-5-fluoro-2-methyl-3-(pyrrolidin-2-yl)pyridine: Prepared by the method of Preparation A, substituting 2-bromo-1,4-difluorobenzene with 3-bromo-5-fluoro-2-methylpyridine in Step A. MS (apci) $\mathrm{m} / \mathrm{z}=181.1(\mathrm{M}+\mathrm{H})$.

## Preparation O


(R)-5-(2-(5-fluoro-2-methylpyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3carboxylic acid
[00440] Step A: Preparation of (R)-ethyl 5-(2-(5-fluoro-2-methylpyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylate: To a solution of ethyl 5-
hydroxypyrazolo[1,5-a]pyrimidine-3-carboxylate (Preparation B, Step A, $372 \mathrm{mg}, 1.8 \mathrm{mmol}$ ) in DMF ( 10 mL ) was added (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate ( $874 \mathrm{mg}, 1.98 \mathrm{mmol}$ ). The mixture was stirred at ambient temperature for 10 minutes then treated with DIEA ( $1.57 \mathrm{~mL}, 8.99 \mathrm{mmol}$ ) and (R)-5-fluoro-2-methyl-3-(pyrrolidin-2-yl)pyridine dihydrochloride ( $455 \mathrm{mg}, 1.80 \mathrm{mmol}$ ). After stirring at ambient temperature for 4 hours the mixture was partitioned between $10 \%$ citric acid ( 50 mL ) and EtOAc ( 50 mL ). The layers were separated and the aqueous layer was extracted with EtOAc $(2 \times 30 \mathrm{~mL})$. The combined organic phases were washed successively with water ( 30 mL ), saturated $\mathrm{NaHCO}_{3}(30 \mathrm{~mL})$, water ( 30 mL ) and brine $(2 \times 30 \mathrm{~mL})$, then dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and concentrated. The residue was purified by silica gel column chromatography eluting with $1 \% \mathrm{MeOH} / \mathrm{DCM}$ to afford the product as white foam ( $480 \mathrm{mg}, 72 \%$ yield). MS (арсі) $\mathrm{m} / \mathrm{z}=370.0(\mathrm{M}+\mathrm{H})$.
[00441] Step B: Preparation of (R)-5-(2-(5-fluoro-2-methylpyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid: To a solution of (R)-ethyl 5-(2-(5-fluoro-2-methylpyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylate ( $480 \mathrm{mg}, 1.3$ mmol ) in a $1: 1: 1$ mixture of THF:MeOH:water ( 30 mL ) was added lithium hydroxide monohydrate ( $164 \mathrm{mg}, 3.9 \mathrm{mmol}$ ). The mixture was stirred at ambient temperature for 16 hours then concentrated to $1 / 3$ volume, acidified to pH 3 with 1 N HCl and extracted with EtOAc $(3 \times 30 \mathrm{~mL})$. The combined organic phases were washed with brine ( 20 mL ), dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and concentrated to afford the title product as a white solid ( 381 mg , $86 \%$ yield). MS (apci) m/z $=342.0(\mathrm{M}+\mathrm{H})$.

## Preparation $\mathbf{P}$


(R)-2-ethyl-5-fluoro-3-(pyrrolidin-2-yl)pyridine
[00442] Prepared by the method of Preparation N, substituting methyl boronic acid with ethyl boronic acid in Step A. MS (apci) m/z $=195.1(\mathrm{M}+\mathrm{H})$.

## Preparation Q



## (R)-5-(2-(2-ethyl-5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-

carboxylic acid
[00443] Prepared by the method of Preparation O, substituting (R)-5-fluoro-2-methyl-3-(pyrrolidin-2-yl)pyridine dihydrochloride with (R)-2-ethyl-5-fluoro-3-(pyrrolidin-2yl)pyridine dihydrochloride in Step A. MS (apci) m/z $=356.0(\mathrm{M}+\mathrm{H})$.

Preparation $R$

(R)-5-(2-(5-fluoro-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid
[00444] Step A: Preparation of (R)-ethyl 5-(2-(5-fluoro-2-oxo-1,2-dihydropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylate. To a mixture of (R)-ethyl 5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylate ( $1.0 \mathrm{~g}, 2.60 \mathrm{mmol}$, Preparation K, Step A) and AcOH ( $7.44 \mathrm{~mL}, 130 \mathrm{mmol}$ ) was added HBr $(4.76 \mathrm{~mL}, 33 \mathrm{wt} \%$ in acetic acid, 26 mmol ) at ambient temperature. The reaction mixture was heated at $90^{\circ} \mathrm{C}$ for 2 hours. After cooling, the reaction mixture was diluted with EtOAc, washed with water, saturated NaHCO 3 , and brine, dried with MgSO 4 , filtered and concentrated. The crude material was purified by silica column chromatography, eluting with $2-3 \% \mathrm{MeOH} / \mathrm{DCM}$ to yield the title product ( $0.73 \mathrm{~g}, 76 \%$ ). MS (apci) m/z=372.0 $(\mathrm{M}+\mathrm{H})$.
[00445] Step B: Preparation of (R)-ethyl 5-(2-(5-fluoro-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylate. To a suspension of (R)-ethyl 5-(2-(5-fluoro-2-oxo-1,2-dihydropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylate ( $0.73 \mathrm{~g}, 1.97 \mathrm{mmol}$ ) in DMF ( 10 mL ) at $0{ }^{\circ} \mathrm{C}$ was added $\mathrm{LiH}(20 \mathrm{mg}, 2.36 \mathrm{mmol})$. After stirring for 30 minutes, a solution of $\mathrm{MeI}(0.56 \mathrm{~g}$,
3.93 mmol ) in DMF ( 2 mL ) was added and the reaction was stirred at ambient temperature for 17 hours. The reaction mixture was cooled to $0^{\circ} \mathrm{C}$ and quenched with ice-water ( 30 mL ). The mixture was extracted with EtOAc (3x), washed with water and brine, dried with MgSO 4 , filtered and concentrated. The crude material was purified by silica column chromatography, eluting with $2.5 \% \mathrm{MeOH} / \mathrm{DCM}$ to yield the title product ( $0.64 \mathrm{~g}, 85 \%$ ). MS (арсі) $\mathrm{m} / \mathrm{z}=386.0(\mathrm{M}+\mathrm{H})$.
[00446] Step C: Preparation of (R)-5-(2-(5-fluoro-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid. Prepared by the method described in Preparation K, Step B using (R)-ethyl 5-(2-(5-fluoro-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylate to yield the title compound ( $0.571 \mathrm{~g}, 96 \%$ yield). MS (apci) $\mathrm{m} / \mathrm{z}=358.0(\mathrm{M}+\mathrm{H})$.

## Example 1


(R)-N-tert-butyl-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3carboxamide
[00447] To a solution of (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (Preparation C, $20.0 \mathrm{mg}, 0.058 \mathrm{mmol}$ ) and HATU ( 24.3 mg , 0.064 mmol ) in dry DMF ( 0.4 mL ) was added tert-butyl amine ( $12.7 \mathrm{mg}, 0.174 \mathrm{mmol}$ ) followed by diisopropylethylamine ( $22.5 \mathrm{mg}, 0.174 \mathrm{mmol}$ ). The mixture was stirred under an atmosphere of $\mathrm{N}_{2}$ for 18 hours and was added to $\mathrm{H}_{2} \mathrm{O}(3 \mathrm{~mL})$ and mixed. The mixture was extracted with EtOAc and combined extracts were washed with $1 \mathrm{M} \mathrm{HCl}, \mathrm{H}_{2} \mathrm{O}$, saturated $\mathrm{NaHCO}_{3}$ and dried over $\mathrm{MgSO}_{4}$. The solution was eluted through a SPE SiOH column eluting first with 50\% EtOAc-hexanes then with EtOAc. The EtOAc pool was concentrated and the residual colorless glass was treated with hexanes give a white suspension. The hexanes were removed, and the solid was washed with hexanes and dried in vacuum to afford the title compound as a white solid ( $20 \mathrm{mg}, 90 \%$ ). MS (apci) $\mathrm{m} / \mathrm{z}=400.1(\mathrm{M}+\mathrm{H})$.

## Example 2


(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-(pyridin-2-yl)pyrazolo[1,5-a]pyrimidine-3carboxamide
[00448] The title compound was prepared according to the procedure outlined for Example 1, using 2-aminopyridine ( 2 equivalents) heating at $90^{\circ} \mathrm{C}$ for 7 hours. The crude material was purified out by $\mathrm{SiO}_{2}$ column chromatography ( $50 \% \mathrm{EtOAc}$-hexanes) to give the title compound as a white solid ( $45 \%$ yield). MS (apci) $\mathrm{m} / \mathrm{z}=421.1(\mathrm{M}+\mathrm{H})$.

## Example 3



## (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-(3-methylpyridin-2-yl)pyrazolo[1,5-

 a]pyrimidine-3-carboxamide[00449] To a suspension of (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (Preparation C, $25.0 \mathrm{mg}, 0.072 \mathrm{mmol}$ ) in $\mathrm{CCl}_{4}(1.0 \mathrm{~mL})$ was added thionyl chloride $(0.10 \mathrm{~mL})$ and the mixture heated at reflux for 4 hours. The mixture was cooled to ambient temperature and was concentrated to a brittle foam. The foam was dissolved in pyridine ( 2 mL ), 2-amino-3-methyl-pyridine ( $9.3 \mathrm{mg}, 0.086 \mathrm{mmol}$ ) was added and the mixture was heated at $90{ }^{\circ} \mathrm{C}$ for 20 hours. The reaction was cooled to ambient temperature and the pyridine evaporated. The residue was partitioned into 1 M NaOH and EtOAc, mixed and the EtOAc layer removed. The aqueous layer was extracted with EtOAc and combined EtOAc fractions were washed with $\mathrm{H}_{2} \mathrm{O}$, saturated NaCl and dried over $\mathrm{MgSO}_{4}$. The solution was filtered and concentrated, and the resulting solid was washed with dry $\mathrm{Et}_{2} \mathrm{O}$ to afford the title compound as a white solid ( $7 \mathrm{mg}, 29 \%$ ). MS (apci) $\mathrm{m} / \mathrm{z}=435.1$ $(\mathrm{M}+\mathrm{H})$.

## Example 4


(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-(2-morpholinoethyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide
[00450] The title compound was prepared according to the procedure outlined for Example 1 using 2-morpholinoethanamine ( 1.5 equiv). The combined EtOAc extracts were washed with $1 \mathrm{M} \mathrm{Na} 2_{2} \mathrm{CO}_{3}, \mathrm{H}_{2} \mathrm{O}$, saturated NaCl and dried over $\mathrm{MgSO}_{4}$. The solution was filtered through a SPE SiOH column eluting first with EtOAc and then with $10 \%$ $\mathrm{MeOH} / \mathrm{EtOAc}$. The $\mathrm{MeOH} / \mathrm{EtOAc}$ pool was concentrated and the residual colorless glass was triturated with hexanes to give fine white precipitate. The solvent was decanted and the solid was washed with hexanes and dried in vacuum. This afforded the title compound as a white solid ( $79 \%$ ). MS (apci) $\mathrm{m} / \mathrm{z}=457.1(\mathrm{M}+\mathrm{H})$.

## Example 5


(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-((5-methylfuran-2-yl)methyl)pyrazolo[1,5-
a]pyrimidine-3-carboxamide
[00451] The title compound was prepared according to the procedure outlined for Example 1 using (5-methylfuran-2-yl)methanamine (1.5 equiv.) The dried EtOAc solution was filtered through a packed Celite plug and concentrated. The residual colorless glass was treated with $\mathrm{Et}_{2} \mathrm{O}$ until dissolved then diluted with hexanes to give a white suspension. Solvents were decanted, the solid washed with hexanes and dried in vacuum. This provided the title compound as a white solid ( $43 \%$ yield). MS (apci) $\mathrm{m} / \mathrm{z}=438.1(\mathrm{M}+\mathrm{H})$.

## Example 6


(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-(1-methyl-1H-pyrazol-3-yl)pyrazolo[1,5-
a]pyrimidine-3-carboxamide
[00452] The title compound was prepared according to the procedure outlined for Example 3 using 1-methyl-1H-pyrazol-3-amine ( 1.5 equiv.) at ambient temperature for 64 hours. The crude EtOAc solution was eluted through a SPE SiOH column (EtOAc elution) and concentrated. The residual white solid was washed with $10 \% \mathrm{Et}_{2} \mathrm{O}$-hexanes and dried in vacuum to afford the title compound ( $47 \%$ yield). MS (apci) $\mathrm{m} / \mathrm{z}=424.1(\mathrm{M}+\mathrm{H})$.

## Example 7



## 5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-((trans)-4-hydroxycyclohexyl)pyrazolo[1,5-

 alpyrimidine-3-carboxamide[00453] The title compound was prepared according to the procedure outlined for Example 1 using trans-4-aminocyclohexanol (1.5 equiv). The combined EtOAc extracts were washed with $1 \mathrm{M} \mathrm{Na} 2 \mathrm{CO}_{3}, \mathrm{H}_{2} \mathrm{O}$, saturated NaCl and dried over $\mathrm{MgSO}_{4}$. The solution was filtered through a Celite plug, concentrated and the residual colorless glass was treated with hexanes to give a white suspension. The hexanes were decanted and the solid washed with hexanes and dried in vacuum. This afforded the title compound as a white solid ( $86 \%$ yield). MS (apci) $\mathrm{m} / \mathrm{z}=442.1(\mathrm{M}+\mathrm{H})$.

## Example 8


(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-(1-hydroxy-2-methylpropan-2-
yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide
[00454] The compound was prepared according to Example 3 using 2-amino-2-methylpropan-1-ol (4 equiv.). In this instance, the amine was added to the crude acid chloride in THF at $0{ }^{\circ} \mathrm{C}$ and the mixture was stirred for 15 hours during which time the temperature reached ambient temperature after 1-2 hours. The reaction mixture was partitioned into $\mathrm{H}_{2} \mathrm{O}$ and $50 \%$ EtOAc-hexanes. The organic layer removed and the aqueous layer was extracted with $50 \%$ EtOAc-hexanes. The combined organic fractions were washed with $1 \mathrm{M} \mathrm{NaOH}, \mathrm{H}_{2} \mathrm{O}$ and saturated NaCl . The solution was dried over $\mathrm{MgSO}_{4}$ and eluted through a SPE SiOH column eluting first with $50 \%$ EtOAc-hexanes then with EtOAc. The EtOAc pool was concentrated and residual colorless glass was dissolved in $\mathrm{Et}_{2} \mathrm{O}$. Hexane was added and the resulting white suspension was concentrated to afford the title compound as a white solid ( $57 \%$ yield). MS (apci) $\mathrm{m} / \mathrm{z}=416.1(\mathrm{M}+\mathrm{H})$.

## Example 9


(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-(2-methyl-1-morpholinopropan-2-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide
[00455] The title compound was prepared according to Example 4 using 2-methyl-1-morpholinopropan-2-amine ( 1.5 equiv). The compound was isolated as a white solid after $\mathrm{SiO}_{2}$ chromatography using EtOAc for elution ( $83 \%$ yield). MS (apci) m/z $=485.2(\mathrm{M}+\mathrm{H})$.

## Example 10



## (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-methylpyrazolo[1,5-a]pyrimidine-3carboxamide

[00456] Prepared by the method as described in Example 1, substituting tert-butyl amine with methyl amine, to provide the final product as a white solid ( $34 \mathrm{mg}, 83 \%$ yield). MS (apci) m/z=358.1 (M+H).

## Example 11


(R)-1-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carbonyl)piperidine-4-carboxylic acid
[00457] Step A: Preparation of (R)-ethyl 1-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl) pyrazole [1,5-a]pyrimidine-3-carbonyl)piperidine-4-carboxylate: Prepared by the method as described in Example 1, substituting tert-butyl amine with ethyl piperidine-4-carboxylate. The crude material was purified by preparative TLC plate, eluting first with EtOAc and then $10 \% \mathrm{MeOH} / \mathrm{EtOAc}$ to afford the title compound ( $49 \mathrm{mg}, 88 \%$ yield). MS (apci) $\mathrm{m} / \mathrm{z}=484.1$ (M+H).
[00458] Step B: (R)-1-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a] pyrimidine-3-carbonyl)piperidine-4-carboxylic acid: (R)-ethyl 1-(5-(2-(2,5-di fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carbonyl)piperidine-4-carboxylate $(49 \mathrm{mg}, 0.10 \mathrm{mmol})$ was dissolved in $1: 1 \mathrm{THF} / \mathrm{MeOH}(1.0 \mathrm{~mL})$ and $1 \mathrm{M} \mathrm{LiOH}(0.20 \mathrm{~mL}, 0.20$ mmol) was added. The mixture was stirred at ambient temperature for 2 hours and the reaction mixture was concentrated. The residue was diluted in water and the mixture acidified with 2 N HCl . The mixture was extracted with DCM and EtOAc. The combined organics were washed with brine, dried with $\mathrm{MgSO}_{4}$, filtered and concentrated. The residue was triturated with hexanes and the resulting white suspension was concentrated to afford the final product ( $43 \mathrm{mg}, 92 \%$ yield) as a white solid. MS (apci) $\mathrm{m} / \mathrm{z}=456.1(\mathrm{M}+\mathrm{H})$.

## Example 12


(R)-2-(1-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carbonyl)piperidin-4-yl)acetic acid
[00459] Step A: Preparation of (R)-ethyl 2-(1-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carbonyl)piperidin-4-yl)acetate: Prepared by the method as described in Example 11, substituting ethyl piperidine-4-carboxylate with ethyl 2-(piperidin4 -yl)acetate in step A ( $48 \mathrm{mg}, 83 \%$ yield). MS (apci) $\mathrm{m} / \mathrm{z}=498.1(\mathrm{M}+\mathrm{H})$.
[00460] Step B: Preparation of (R)-2-(1-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carbonyl)piperidin-4-yl)acetic acid: Prepared as described in Example 11 Step B to afford the final product ( $30 \mathrm{mg}, 66 \%$ yield) as a white solid. MS (apci) $m / z=470.1(M+H)$.

## Example 13


(R)-N-cyclopropyl-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3carboxamide
[00461] Prepared by the method as described in Example 1 substituting tert-butyl amine with cyclopropanamine. The crude material was purified by preparative TLC eluting with EtOAc then $10 \% \mathrm{MeOH} / \mathrm{EtOAc}$ to provide the final product as a white solid ( 28 mg , $63 \%$ yield). MS (apci) $\mathrm{m} / \mathrm{z}=384.1(\mathrm{M}+\mathrm{H})$

## Example 14


(R)-N-cyclobutyl-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3carboxamide
[00462] Prepared by the method as described in Example 1 substituting tert-butyl amine with cyclobutanamine, to provide the final product as a white solid ( $41 \mathrm{mg}, 88 \%$ yield). MS (apci) m/z=398.1 (M+H).

## Example 15



## N -((2S)-bicyclo[2.2.1]heptan-2-yl)-5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-

yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide
[00463] Prepared by the method as described in Example 1, substituting tert-butyl amine with (2R)-bicyclo[2.2.1]heptan-2-amine. The crude material was purified by reverse phase chromatography eluting with $0-100 \%$ acetonitrile/water to yield the title compound as a white solid ( $47 \mathrm{mg}, 92 \%$ yield.). MS (apci) m/z $=438.2(\mathrm{M}+\mathrm{H})$.

## Example 16



## (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-(1-

(hydroxymethyl)cyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide
[00464] Prepared by the method as described in Example 8, using (1aminocyclopropyl)methanol ( 1.5 equiv.) the procedure described for Example 8. The title compound was obtained as a white solid ( $35 \%$ yield). MS (apci) $\mathrm{m} / \mathrm{z}=414.1(\mathrm{M}+\mathrm{H})$.

## Example 17


(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-(2-hydroxy-2-methylpropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide
[00465] Prepared by the method as described in Example 8, using 1-amino-2-methylpropan-2-ol ( 4.0 equiv.). The title compound was obtained as a white solid ( $62 \%$ yield). MS (apci) $\mathrm{m} / \mathrm{z}=416.1(\mathrm{M}+\mathrm{H})$.

## Example 18



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

hydroxypyrrolidin-1-yl)methanone
[00466] The title compound was prepared by the method as described in Example 1 using (S)-pyrrolidin-3-ol (2.0 equiv). The EtOAc pool was concentrated and the residual colorless glass was dissolved in EtOAc. Hexanes were added and resulting white suspension was concentrated to give the title compound as a white solid ( $42 \%$ yield). MS (apci) $\mathrm{m} / \mathrm{z}=$ $414.1(\mathrm{M}+\mathrm{H})$.

## Example 19



## (5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)((R)-3- <br> hydroxypyrrolidin-1-yl)methanone

[00467] Prepared by the method as described in Example 18 using (R)-pyrrolidin-3-ol (2.0 equiv.). The title compound was obtained as a white solid ( $99 \%$ yield). MS (apci) $\mathrm{m} / \mathrm{z}=$ $414.1(\mathrm{M}+\mathrm{H})$.

## Example 20



## (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-(tetrahydro-2H-pyran-4-yl)pyrazolo[1,5-

 a]pyrimidine-3-carboxamide[00468] The title compoundg was prepared following the method of Example 1, using tetrahydro-2H-pyran-4-amine ( 2.0 equiv.). The EtOAc pool was concentrated and the residual colorless glass was dissolved in EtOAc. Hexanes were added and resulting white suspension was concentrated to give the title compound as a white solid ( $68 \%$ yield). MS (apci) $m / z=428.1(M+H)$.

## Example 21


(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-((1-methyl-1H-imidazol-4-yl)methyl) pyrazole[1,5-a]pyrimidine-3-carboxamide
[00469] Prepared by the method described in Example 1 substituting tert-butyl amine with (1-methyl-1H-imidazol-4-yl)methanamine. The crude material was purified by reverse phase chromatography, eluting with $0-100 \%$ acetonitrile/water to yield the title compound as a white solid ( $22 \mathrm{mg}, 43 \%$ yield.). MS (apci) $\mathrm{m} / \mathrm{z}=438.1(\mathrm{M}+\mathrm{H})$.

Example 22

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-((1-methyl-1H-pyrazol-4-yl)methyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide
[00470] Prepared by the method described in Example 1 substituting tert-butyl amine with (1-methyl-1H-pyrazol-4-yl)methanamine. The crude material was purified by reverse phase chromatography, eluting with $0-100 \%$ acetonitrile/water to yield the title compound as a white solid ( $34 \mathrm{mg}, 67 \%$ yield.). MS (apci) $\mathrm{m} / \mathrm{z}=438.1(\mathrm{M}+\mathrm{H})$.

## Example 23



## (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-(2-(1-methyl-1H-imidazol-5-yl)ethyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide

[00471] Prepared by the method described in Example 1 substituting tert-butyl amine with 2-(1-methyl-1H-imidazol-5-yl)ethanamine. The crude material was purified by reverse phase chromatography, eluting with $0-100 \%$ acetonitrile/water to yield the title compound as a white solid ( $26 \mathrm{mg}, 49 \%$ yield.). MS (apci) $\mathrm{m} / \mathrm{z}=452.2(\mathrm{M}+\mathrm{H})$.

## Example 24


(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-(2-(2-oxoimidazolidin-1-yl)ethyl) pyrazole[1,5-a]pyrimidine-3-carboxamide
[00472] Prepared by the method described in Example 1, substituting tert-butyl amine with 1-(2-aminoethyl)imidazolidin-2-one. The crude material was purified by reverse phase chromatography, eluting with $0-100 \%$ acetonitrile/water to yield the title compound as a white solid (23 mg, 43\% yield.). MS (apci) m/z=456.1(M+H).

## Example 25


(R)-N-(2-(1H-imidazol-4-yl)ethyl)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazole [1,5-a]pyrimidine-3-carboxamide
[00473] Prepared by the method described in Example 1, substituting tert-butyl amine with histamine. The crude material was purified by reverse phase chromatography, eluting with $0-100 \%$ acetonitrile/water to yield the title compound as a white solid ( $17 \mathrm{mg}, 34 \%$ yield.). MS (apci) m/z=438.2 (M+H).

## Example 26



5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-((R)-2,3-dihydroxypropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide
[00474] Prepared by the method described in Example 1, substituting tert-butyl amine with (R)-3-aminopropane-1,2-diol. The crude material was purified by preparative TLC using EtOAc then $10 \% \mathrm{MeOH} / \mathrm{EtOAc}$ for elution to afford the title compound ( $19 \mathrm{mg}, 39 \%$ yield) as a white solid. MS (apci) $\mathrm{m} / \mathrm{z}=418.1(\mathrm{M}+\mathrm{H})$.

Example 27

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N,N-dimethylpyrazolo[1,5-a]pyrimidine-3carboxamide
[00475] Prepared by the method described in Example 1 substituting tert-butyl amine with dimethylamine. The crude material was purified by preparative TLC eluting with EtOAc then $10 \% \mathrm{MeOH} / \mathrm{EtOAc}$ to afford the title compound ( $7 \mathrm{mg}, 19 \%$ yield) as a white solid. MS (apci) m/z=372.1 (M+H).

## Example 28


(R)-N-(2-(1H-imidazol-1-yl)ethyl)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide
[00476] Prepared by the method described in Example 1 substituting tert-butyl amine with 2-(1H-imidazol-1-yl)ethanamine dihydrobromide. The crude material was purified by reverse phase chromatography eluting with $0-100 \%$ acetonitrile/water to yield the title compound as a white solid ( $25 \mathrm{mg}, 57 \%$ yield.). MS (apci) m/z $=438.1(\mathrm{M}+\mathrm{H})$.

## Example 29



5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-((S)-2,3-dihydroxypropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide
[00477] A mixture of (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (Preparation C, $400 \mathrm{mg}, 1.16 \mathrm{mmol}$ ), HATU ( $486 \mathrm{mg}, 1.28$ mmol ), and (S)-3-aminopropane-1,2-diol ( $318 \mathrm{mg}, 3.49 \mathrm{mmol}$ ) in dry DMF ( 3.0 mL ) was stirred for 1-2 minutes at ambient temperature. Diisopropylethylamine (DIEA) ( 0.62 mL , 3.49 mmol ) was added and the reaction was flushed with $\mathrm{N}_{2}$, sealed and stirred at ambient temperature for 18 hours. The reaction mixture was added to $\mathrm{H}_{2} \mathrm{O}(15 \mathrm{~mL})$, mixed and extracted with EtOAc. The combined EtOAc extracts were washed with $\mathrm{H}_{2} \mathrm{O}$, saturated $\mathrm{NaHCO}_{3}$ and dried over $\mathrm{MgSO}_{4} /$ activated carbon. The solution was eluted through a $\mathrm{SiO}_{2}$
column eluting first with EtOAc then $10 \% \mathrm{MeOH} / \mathrm{EtOAc}$. The $10 \% \mathrm{MeOH} / \mathrm{EtOAc}$ pool was concentrated and the residual, colorless glass was dissolved in a minimal amount of $\mathrm{CH}_{2} \mathrm{Cl}_{2}$. Hexane was added and the resulting white suspension was sonicated and concentrated to give the title product as a white solid ( $205 \mathrm{mg}, 42 \%$ ). MS (apci) $\mathrm{m} / \mathrm{z}=418.1(\mathrm{M}+\mathrm{H})$.

## Example 30


(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide
[00478] Step A: Preparation of 5-hydroxypyrazolo[1,5-a]pyrimidine-3-carbonitrile. To a mixture of 5-amino-1H-pyrazole-4-carbonitrile ( $2.70 \mathrm{~g}, 25.0 \mathrm{mmol}$ ) and $\mathrm{Cs}_{2} \mathrm{CO}_{3}(16.3 \mathrm{~g}$, 50.0 mmol ) in dry DMF ( 70 mL ) was added ethyl 3-ethoxyacrylate ( $5.41 \mathrm{~g}, 37.5 \mathrm{mmol}$ ) and the mixture was heated at $100{ }^{\circ} \mathrm{C}$ for 4 hours. The mixture was cooled to ambient temperature and the resultant slurry was poured into deionized $\mathrm{H}_{2} \mathrm{O}(150 \mathrm{~mL})$. The resulting aqueous solution was cooled on an ice bath and concentrated HCl was added slowly with mixing to $\mathrm{pH}=3.5$. The resulting precipitate was collected, washed with $\mathrm{H}_{2} \mathrm{O}$ followed by $\mathrm{Et}_{2} \mathrm{O}$. The solid was dried in vacuum to afford the product as a light beige powder $(3.87 \mathrm{~g}$, $97 \%$ ). MS (apci) $\mathrm{m} / \mathrm{z}=159.0(\mathrm{M}-1)$.
[00479] Step B: Preparation of (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1yl)pyrazolo[ 1,5 -a]pyrimidine-3-carbonitrile. A flask was charged with the product from Step A $(2.80 \mathrm{~g}, \quad 17.5 \mathrm{mmol})$, benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate $(9.28 \mathrm{~g}, 21.0 \mathrm{mmol})$ and dry DMF ( 35 mL ). The suspension was stirred at ambient temperature for 2 minutes and (R)-2-(2,5-difluorophenyl)pyrrolidine (Preparation A, $3.84 \mathrm{~g}, 21.0 \mathrm{mmol}$ ) and diisopropylethylamine ( $6.78 \mathrm{~g}, 62.5 \mathrm{mmol}$ ) were sequentially added (mild exotherm). The mixture was stirred at ambient temperature for 3 hours and poured into $\mathrm{H}_{2} \mathrm{O}(175 \mathrm{~mL})$. The mixture was extracted with $50 \%$ EtOAc-hexanes and the combined organic fractions were washed sequentially with $1 \mathrm{M} \mathrm{HCl}, \mathrm{H}_{2} \mathrm{O}, 1 \mathrm{M} \mathrm{Na} \mathrm{N}_{2} \mathrm{CO}_{3}$ and saturated NaCl . The solution was dried over $\mathrm{MgSO}_{4} /$ activated carbon and filtered through a short $\mathrm{SiO}_{2}$ plug ( 350 mL course frit funnel, $1 / 4$ full of $\mathrm{SiO}_{2}$, capped with a layer of $\mathrm{MgSO}_{4}$ ) using $50 \%$ EtOAc-hexanes for elution. The solution was concentrated to give the title
compound as a brittle white foam that was crushed to a flowing white solid and dried in vacuum ( $5.50 \mathrm{~g}, 97 \%$ ). MS (apci) $\mathrm{m} / \mathrm{z}=326.2(\mathrm{M}+\mathrm{H})$.
[00480] Step C : Preparation of (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide. The product from Step B ( $3.00 \mathrm{~g}, 8.85 \mathrm{mmol}$ ) was added in small portions over 5 minutes to concentrated $\mathrm{H}_{2} \mathrm{SO}_{4}(30 \mathrm{~mL})$ and the mixture was stirred at ambient temperature for 2 hours (homogeneous after 5 minutes). The solution was slowly added to chilled $\mathrm{H}_{2} \mathrm{O}(300 \mathrm{~mL})$ with stirring and the mixture was extracted with EtOAc. The combined EtOAc portions were washed with $\mathrm{H}_{2} \mathrm{O}, 1 \mathrm{M} \mathrm{Na} \mathrm{Na}_{2} \mathrm{CO}_{3}$ and saturated NaCl . The EtOAc solution was dried over $\mathrm{MgSO}_{4} /$ activated carbon, filtered through a packed Celite pad and concentrated to give a white foam. The foam was dissolved in minimal $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ and hexane was added to induce formation of a white precipitate. The mixture was concentrated to provide the title compound as a flowing white solid after drying in vacuum ( $2.80 \mathrm{~g}, 92 \%$ ). MS (apci) m/z=344.1 (M+H).

## Example 31


(R)-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)(3-hydroxyazetidin-1-yl)methanone
[00481] The title compound was prepared according to the method of Example 1, using azetidin-3-ol hydrochloride ( 2.0 equiv.). In this instance, the dried EtOAc solution was eluted through a SPE SiOH column eluting first with EtOAc then with $10 \% \mathrm{MeOH}-\mathrm{EtOAc}$. The MeOH-EtOAc pool was concentrated to afford the title compound as a white solid ( $43 \%$ yield). MS (apci) $m / z=400.0(M+H)$.

## Example 32


(R)-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)(3-hydroxy-3-methylazetidin-1-yl)methanone
[00482] The title compound was prepared according to the method of Example 1, using 3-methyl-azetidin-3-ol trifluoroacetate ( 2.0 equiv.). The dried EtOAc solution was eluted through a SPE SiOH column eluting first with EtOAc then with $10 \% \mathrm{MeOH}-\mathrm{EtOAc}$. The MeOH-EtOAc pool was concentrated to afford the title compound as a white solid ( $71 \%$ yield). MS (apci) m/z=414.1 (M+H).

## Example 33



## Trans-4-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3carboxamido)cyclohexanecarboxylic acid

[00483] Step A: Preparation of (trans)-methyl 4-aminocyclohexanecarboxylate hydrochloride. (Trans)-4-aminocyclohexanecarboxylic acid ( $200 \mathrm{mg}, 1.40 \mathrm{mmol}$ ) was suspended in $\mathrm{MeOH}(5.5 \mathrm{~mL})$ and cooled to $-10^{\circ} \mathrm{C}$. To this was added $\mathrm{SOCl}_{2}(204 \mu \mathrm{~L}, 2.79$ mmol ) dropwise and the mixture stirred for 15 minutes. The reaction mixture was warmed to ambient temperature for 15 minutes, followed by heating at reflux for 1 hour. After cooling, the mixture was concentrated to afford the title compound ( $260 \mathrm{mg}, 96.1 \%$ yield). MS (apci) $\mathrm{m} / \mathrm{z}=158.0(\mathrm{M}+\mathrm{H})$.
[00484] Step B: Preparation of (Trans)-methyl 4-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-
carboxamido)cyclohexanecarboxylate. Prepared by the method described in Example 1 substituting tert-butyl amine with (trans)-methyl 4-aminocyclohexanecarboxylate hydrochloride. The crude material was purified by preparative TLC using EtOAc then 10\% $\mathrm{MeOH} / \mathrm{EtOAc}$ for elution to afford the title compound ( $38 \mathrm{mg}, 91 \%$ yield) as a colorless oil. MS (apci) $\mathrm{m} / \mathrm{z}=484.1(\mathrm{M}+\mathrm{H})$.
[00485] Step C: Preparation of (trans)-4-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a] pyrimidine-3-carboxamido)cyclohexanecarboxylic acid. Prepared by the method as described in Example 11, step B to afford the title compound ( $29 \mathrm{mg}, 79 \%$ yield) as a white solid. $\mathrm{MS}(\mathrm{apci}) \mathrm{m} / \mathrm{z}=4701(\mathrm{M}+\mathrm{H})$.

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## Example 34



## 5-((R)-2-(5-fluoro-2-methoxyphenyl)pyrrolidin-1-yl)-N-((trans)-4-hydroxycyclohexyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide

[00486] Prepared by the method as described in Example 1 using (R)-5-(2-(5-fluoro-2-methoxyphenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (Preparation G) and (trans)-4-aminocyclohexanol. The crude material was purified by reverse phase chromatography, eluting with $0-60 \%$ acetonitrile/water to yield the title compound as a white solid ( $32 \mathrm{mg}, 97 \%$ yield.). MS (apci) $\mathrm{m} / \mathrm{z}=454.1(\mathrm{M}+\mathrm{H}$ ).

## Example 35



5-((R)-2-(3-fluorophenyl)pyrrolidin-1-yl)-N-((trans)-4-hydroxycyclohexyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide
[00487] Prepared by the method as described in Example 1 using ( R )-5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (Preparation E) and (trans)-4-aminocyclohexanol to yield the title compound as a white solid ( $31 \mathrm{mg}, 62 \%$ yield.). MS (apci) $\mathrm{m} / \mathrm{z}=424.1(\mathrm{M}+\mathrm{H})$.

## Example 36


(R)-N-tert-butyl-5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3carboxamide
[00488] Prepared by the method as described in Example 1 using ( R )-5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (Preparation E) to yield the title compound as a white solid ( $33 \mathrm{mg}, 74 \%$ yield.). MS (apci) $\mathrm{m} / \mathrm{z}=382.1$ (M+H).

## Example 37


(R)-N-cyclopropyl-5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3carboxamide
[00489] Prepared by the method as described in Example 1 using (R)-5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (Preparation E) and cyclopropylamine to yield the title compound as a white solid ( $23 \mathrm{mg}, 54 \%$ yield.). MS (apci) $m / z=366.1(M+H)$.

Example 38

(R)-N-(2-cyanopropan-2-yl)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-
a]pyrimidine-3-carboxamide
[00490] Prepared by the method described in Example 1 substituting tert-butyl amine with 2-amino-2-methylpropanenitrile. The crude material was purified by preparative TLC using EtOAc then $10 \% \mathrm{MeOH} / \mathrm{EtOAc}$ for elution to afford the title compound ( $15 \mathrm{mg}, 41 \%$ yield) as a white solid. MS (apci) $\mathrm{m} / \mathrm{z}=411.1(\mathrm{M}+\mathrm{H})$.

## Example 39


(R)-N-(cyanomethyl)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3carboxamide
[00491] Prepared by the method described in Example 1 substituting tert-butyl amine with 2-aminoacetonitrile to provide the final product as a white solid ( $31 \mathrm{mg}, 94 \%$ yield). MS (apci) $\mathrm{m} / \mathrm{z}=383.0(\mathrm{M}+\mathrm{H})$.

## Example 40



## (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-(1-fluoro-2-methylpropan-2-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide

[00492] Prepared by the method described in Example 1 substituting tert-butyl amine with 1-fluoro-2-methylpropan-2-amine to provide the title compound as a white solid ( 31 mg , 84\% yield). MS (apci) $\mathrm{m} / \mathrm{z}=418.0(\mathrm{M}+\mathrm{H})$.

## Example 41



N-cyclopropyl-5-((2R,4R)-2-(3-fluorophenyl)-4-hydroxypyrrolidin-1-
yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide
[00493] Step A: Preparation of (R)-3-(tert-butyldimethylsilyloxy)-4chlorobutanenitrile. Tert-butyldimethylsilanecarbonitrile ( $20.0 \mathrm{~g}, 142 \mathrm{mmol}$ ), (R)-2(chloromethyl)oxirane $(13.1 \mathrm{~g}, 142 \mathrm{mmol})$ and tetrabutylammonium cyanide $(0.380 \mathrm{~g}, 1.42$ mmol) were mixed and heated at $100{ }^{\circ} \mathrm{C}$ for 15 hours. After cooling, the crude mixture was concentrated and the residue purified by silica chromatography eluting with $5 \%$

EtOAc/hexanes to afford (R)-3-(tert-butyldimethylsilyloxy)-4-chlorobutanenitrile (17.9 g, $54 \%$ ) as a clear oil.
[00494] Step B: Preparation of (R)-3-(tert-butyldimethylsilyloxy)-5-(3-fluorophenyl)-3.4-dihydro-2H-pyrrole. (3-fluorophenyl)magnesium bromide ( $203 \mathrm{~mL}, 102 \mathrm{mmol}, 0.5 \mathrm{M}$ in ether) was slowly added via syringe to a solution of (R)-3-(tert-butyldimethylsilyloxy)-4chlorobutanenitrile ( $9.50 \mathrm{~g}, 40.6 \mathrm{mmol}$ ) in MTBE ( 120 mL ). The reaction was stirred for two hours and DME ( 35 mL ) was slowly added over 15 minutes followed by EtOH ( 23 mL ). After stirring overnight, brine ( 50 mL ) and $1 \mathrm{M} \mathrm{NaOH}(50 \mathrm{~mL})$ were added and the reaction stirred for 1 hour. The reaction mixture was filtered through a pad of Celite and the collected solids were washed with EtOAc. The filtrate was washed with 1 N NaOH and brine, filtered through phase-separator paper and concentrated to provide the title compound that was used directly in the next step. MS (apci) $\mathrm{m} / \mathrm{z}=294.2(\mathrm{M}+\mathrm{H})$.
[00495] Step C: Preparation of (2R,4R)-4-(tert-butyldimethylsilyloxy)-2-(3-fluoro phenyl) pyrrolidine. (R)-3-(tert-butyldimethylsilyloxy)-5-(3-fluorophenyl)-3,4-dihydro-2Hpyrrole ( $6.21 \mathrm{~g}, 21.2 \mathrm{mmol}$ ) was dissolved in methanol ( 100 mL ) and $\mathrm{AcOH}(10 \mathrm{~mL})$. The reaction was cooled to $-78{ }^{\circ} \mathrm{C}$ and the sodium borohydride ( $2.00 \mathrm{~g}, 52.9 \mathrm{mmol}$ ) was slowly added in small portions. The reaction was allowed to warm to ambient temperature overnight. The reaction mixture was concentrated and the residue was diluted with EtOAc and 1 N NaOH . Additional NaOH pellets were added to basify the aqueous layer. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried with $\mathrm{MgSO}_{4}$, filtered and concentrated. The residual oil was purified by silica chromatography eluting with $5 \% \mathrm{MeOH} / \mathrm{EtOAc}$ to afford (2R,4R)-4-(tert-butyldimethylsilyloxy)-2-(3-fluorophenyl)pyrrolidine ( $4.82 \mathrm{~g}, 77.1 \%$ ) as a brown oil. MS (арсі) $\mathrm{m} / \mathrm{z}=296.1(\mathrm{M}+\mathrm{H})$.
[00496] Step D: Preparation of ethyl 5-((2R,4R)-4-(tert-butyldimethylsilyloxy)-2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylate. Prepared according to the method of Preparation C , using (2R,4R)-4-(tert-butyldimethylsilyloxy)-2-(3fluorophenyl)pyrrolidine in Step A. MS (apci) $\mathrm{m} / \mathrm{z}=485.1(\mathrm{M}+\mathrm{H})$.
[00497] Step E: Preparation of 5-((2R,4R)-2-(3-fluorophenyl)-4-hydroxypyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid. Ethyl 5-((2R,4R)-4-(tert-butyldimethyl silyloxy)-2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylate (205 $\mathrm{mg}, 0.422 \mathrm{mmol}$ ) was suspended in EtOH ( 2.0 mL ) and $1 \mathrm{M} \mathrm{LiOH}(0.845 \mathrm{ml}, 0.845 \mathrm{mmol})$ was added. The mixture was heated at reflux for 4 hours and another portion of 1 M LiOH
( $0.845 \mathrm{ml}, 0.845 \mathrm{mmol}$ ) was added. The mixture was heated at reflux overnight, cooled to ambient temperature and concentrated. The residue was diluted in water and the mixture was treated with 2 N HCl to achieve pH 1 . The mixture was extracted with DCM and EtOAc and the combined extracts were dried with $\mathrm{MgSO}_{4}$, filtered and concentrated to afford 5-((2R,4R)-2-(3-fluorophenyl)-4-hydroxypyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3carboxylic acid ( $124 \mathrm{mg}, 86 \%$ ) as a light orange solid.
[00498] Step F: Preparation of N-cyclopropyl-5-((2R,4R)-2-(3-fluorophenyl)-4-hydroxypyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide. Prepared by the method described in Example 1 using 5-((2R,4R)-2-(3-fluorophenyl)-4-hydroxypyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid and substituting tert-butyl amine with cyclopropylamine to provide the final product as a white solid ( $15 \mathrm{mg}, 66 \%$ yield). MS (apci) $\mathrm{m} / \mathrm{z}=382.1(\mathrm{M}+\mathrm{H})$.

## Example 42



N-tert-butyl-5-((2R,4R)-2-(3-fluorophenyl)-4-hydroxypyrrolidin-1-yl)pyrazolo[1,5-

## a]pyrimidine-3-carboxamide

[00499] Prepared by the method described in Example 1 using 5-((2R,4R)-2-(3-fluorophenyl)-4-hydroxypyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid and tert-butyl amine to provide the final product as a white solid ( $24 \mathrm{mg}, 100 \%$ yield). MS (apci) $\mathrm{m} / \mathrm{z}=398.1(\mathrm{M}+\mathrm{H})$.

## Example 43



5-((2R,4R)-2-(3-fluorophenyl)-4-hydroxypyrrolidin-1-yl)-N-methylpyrazolo[1,5-
a]pyrimidine-3-carboxamide
[00500] Prepared by the method described in Example 1 using 5-((2R,4R)-2-(3-fluorophenyl)-4-hydroxypyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid and methylamine to provide the final product as a white solid ( $9.4 \mathrm{mg}, 45 \%$ yield). MS (apci) $m / z=356.1(M+H)$.

## Example 44



## (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-(1-(methylsulfonyl)piperidin-4-

yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide
[00501] Prepared by the method described in Example 1 using 1-(methylsulfonyl)piperidin-4-amine hydrochloride ( 1.5 equiv.). The title compound was isolated as a white solid ( $83 \%$ yield) after purification by $\mathrm{SiO}_{2}$ column (eluting with $50 \%$ EtOAc-hexanes, then EtOAc, and then $10 \% \mathrm{MeOH}-\mathrm{EtOAc})$. MS (apci) m/z $=505.0(\mathrm{M}+\mathrm{H})$.

## Example 45



## (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-(1-sulfamoylpiperidin-4-yl)pyrazolo[1,5-

a]pyrimidine-3-carboxamide
[00502] Prepared by the method described in Example 1 using 4-aminopiperidine-1sulfonamide ( 1.5 equiv.). The title compound was isolated as a white solid ( $80 \%$ yield) after $\mathrm{SiO}_{2}$ column purification (eluting with $50 \%$ EtOAc-hexanes, then EtOAc, then $10 \% \mathrm{MeOH}-$ EtOAc). MS (apci) m/z = $506.0(\mathrm{M}+\mathrm{H})$.

## Example 46


(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-(2-(methylsulfonamido)ethyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide
[00503] Prepared by the method described in Example 1 using N -(2aminoethyl)methanesulfonamide hydrochloride ( 2.0 equiv.). The title compound was isolated as a white solid ( $67 \%$ yield) after $\mathrm{SiO}_{2}$ column purification (eluting with $50 \% \mathrm{EtOAc}$ hexanes, then EtOAc, then $10 \% \mathrm{MeOH}-E t O A c) . \mathrm{MS}(\mathrm{apci}) \mathrm{m} / \mathrm{z}=465.0(\mathrm{M}+\mathrm{H})$.

## Example 47



## (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-(2-sulfamoylethyl)pyrazolo[1,5-

a]pyrimidine-3-carboxamide
[00504] Prepared by the method described in Example 1 using 2aminoethanesulfonamide ( 2.0 equiv.). The title compound was isolated as a white solid ( $67 \%$ yield) after $\mathrm{SiO}_{2}$ column purification (eluting with $50 \% \mathrm{EtOAc}$-hexanes, then EtOAc, then $10 \% \mathrm{MeOH}-E t O A c) . \mathrm{MS}($ apci $) \mathrm{m} / \mathrm{z}=451.0(\mathrm{M}+\mathrm{H})$.

## Example 48


(R)-N-cyclopropyl-5-(2-(5-fluoro-2-methoxyphenyl)pyrrolidin-1-yl)pyrazolo[1,5-
a]pyrimidine-3-carboxamide
[00505] Prepared by the method described in Example 1 using (R)-5-(2-(5-fluoro-2-methoxyphenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (Preparation G)
and cyclopropylamine to yield the title compound as a white solid ( $19 \mathrm{mg}, 68 \%$ yield). MS (apci) $\mathrm{m} / \mathrm{z}=396.0(\mathrm{M}+\mathrm{H})$.

## Example 49



## (R)-5-(2-(5-fluoro-2-methoxyphenyl)pyrrolidin-1-yl)-N-(2-hydroxy-2-methylpropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide

[00506] Prepared by the method described in Example 1 using (R)-5-(2-(5-fluoro-2-methoxyphenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (Preparation G) and 1-amino-2-methylpropan-2-ol to yield the title compound as a white solid ( $17 \mathrm{mg}, 55 \%$ yield). MS (apci) $\mathrm{m} / \mathrm{z}=428.1(\mathrm{M}+\mathrm{H})$.

## Example 50



5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-(4-hydroxy-4-methyl cyclohexyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (Diastereomer 1)
[00507] Step A: Preparation of diastereomeric tert-butyl-4-hydroxy-4methylcyclohexyl carbamates. A solution of tert-butyl 4-oxocyclohexylcarbamate ( 1.20 g , 5.63 mmol ) in dry THF ( $28.1 \mathrm{~mL}, 5.63 \mathrm{mmol}$ ) was cooled to $-7{ }^{\circ}{ }^{\circ} \mathrm{C}$ and 3.0 M MeMgCl $(5.72 \mathrm{~mL}, 17.2 \mathrm{mmol})$ was added. The reaction mixture was allowed to warm to ambient temperature and stirred for 48 hours. The reaction was quenched with saturated $\mathrm{NH}_{4} \mathrm{Cl}(10$ mL ) and concentrated in vacuo. The residue was diluted in water and DCM and solid citric acid was added until the phases separated. The organic layer was removed and washed with saturated $\mathrm{NaHCO}_{3}$, water and brine. The solution was dried with $\mathrm{MgSO}_{4}$ filtered and concentrated to give a mixture of diastereomeric products as a white solid. The two diastereomers were separated using silica chromatography eluting with a gradient of $20-80 \%$

EtOAc/Hexanes: Minor isomer ( $45.1 \mathrm{mg}, 7 \%$ yield), major isomer ( $113 \mathrm{mg}, 18 \%$ yield). MS (арсі) $\mathrm{m} / \mathrm{z}=130.0(\mathrm{M}+\mathrm{H}-\mathrm{Boc})$.
[00508] Step B: Preparation of 5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-(4-hydroxy-4-methylcyclohexyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (Diasteromer 1). The minor isomer from Step A ( $45.1 \mathrm{mg}, 0.197 \mathrm{mmol}$ ) was dissolved in DCM ( 1.0 mL ) and 4 N HCl in dioxane ( $492 \mu \mathrm{~L}, 1.97 \mathrm{mmol}$ ) was added. The reaction mixture was stirred at ambient temperature for 1 hour and was concentrated to afford 4-amino-1-methylcyclohexanol (minor isomer). The 4-amino-1-methylcyclohexanol was reacted with (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (Preparation C) according to the procedure outlined in Example 1 to provide the title product as a white solid ( $14 \mathrm{mg}, 48 \%$ yield). MS (apci) m/z $=456.1(\mathrm{M}+\mathrm{H})$.

## Example 51



## 5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-(4-hydroxy-4-

methylcyclohexyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (Diasteromer 2)
[00509] The major isomer from Step A in Example $50(45.1 \mathrm{mg}, 0.197 \mathrm{mmol})$ was dissolved in DCM ( 1.0 mL ) and 4 N HCl in dioxane ( $492 \mu \mathrm{~L}, 1.97 \mathrm{mmol}$ ) was added. The reaction mixture was stirred at ambient temperature for 1 hour and was concentrated to afford 4-amino-1-methylcyclohexanol (major isomer). The 4-amino-1-methylcyclohexanol was reacted with (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3carboxylic acid (Preparation C) according to the procedure outlined in Example 1 to provide the title product as a white solid ( $10.7 \mathrm{mg}, 38 \%$ yield). MS (apci) $\mathrm{m} / \mathrm{z}=456.1(\mathrm{M}+\mathrm{H})$.

## Example 52



## (R)-N-cyclopropyl-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3carboxamide

[00510] To a solution of (R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (Preparation I, $30.0 \mathrm{mg}, 0.092 \mathrm{mmol}$ ) and HATU ( 52.1 mg , 0.137 mmol ) in dry DMF ( 0.5 mL ) was added cyclopropylamine ( $10.5 \mathrm{mg}, 0.183 \mathrm{mmol}$ ) followed by diisopropylethylamine ( $35.5 \mathrm{mg}, 0.275 \mathrm{mmol}$ ). The mixture was stirred under an atmosphere of $\mathrm{N}_{2}$ for 43 hours. The crude mixture was purified by reverse phase chromatography eluting with $0-50 \%$ acetonitrile/water to yield the title compound as a white solid ( $26 \mathrm{mg}, 78 \%$ yield). MS (apci) m/z $=367.0(\mathrm{M}+\mathrm{H}$ ).

## Example 53



## (R)-N-tert-butyl-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5- <br> a]pyrimidine-3-carboxamide

[00511] Prepared by the method as described in Example 1 using (R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (Preparation I) and 2-methylpropan-2-amine to yield the title compound as a white solid ( $23 \mathrm{mg}, 67 \%$ yield). MS (apci) $\mathrm{m} / \mathrm{z}=383.1(\mathrm{M}+\mathrm{H})$.

## Example 54



## (R)-5-(2-(5-fluoro-2-methoxyphenyl)pyrrolidin-1-yl)-N-(2-morpholinoethyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide

[00512] Prepared by the method as described in Example 4, using (R)-5-(2-(5-fluoro-2-methoxyphenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (Preparation
G) and 2-morpholinoethanamine ( 1.5 equiv.). The title compound was obtained as a white solid ( $65 \%$ yield). MS (apci) m/z $=469.1(\mathrm{M}+\mathrm{H})$.

Example 55


N-((S)-2,3-dihydroxypropyl)-5-((R)-2-(5-fluoro-2-methoxyphenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide
[00513] Prepared by the method of Example 1, using (R)-5-(2-(5-fluoro-2-methoxyphenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (Preparation G) and (S)-3-aminopropane-1,2-diol ( 2.0 equiv). The crude material was purified by $\mathrm{SiO}_{2}$ column chromatography, eluting with EtOAc then $10 \% \mathrm{MeOH}-\mathrm{EtOAc}$ to afford the title compound as a white solid ( $53 \%$ yield). MS (apci) $\mathrm{m} / \mathrm{z}=430.1(\mathrm{M}+\mathrm{H})$.

Example 56


N-((R)-2,3-dihydroxypropyl)-5-((R)-2-(5-fluoro-2-methoxyphenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide
[00514] Prepared by the method of Example 1, using (R)-5-(2-(5-fluoro-2-methoxyphenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (Preparation G) and ( R )-3-aminopropane-1,2-diol ( 2.0 equiv). The crude material was purified by $\mathrm{SiO}_{2}$ column chromatography, eluting with EtOAc then $10 \% \mathrm{MeOH}-\mathrm{EtOAc}$ to afford the title compound as a white solid ( $46 \%$ yield). MS (apci) $m / z=430.1(M+H)$.

## Example 57


(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-(2-methyl-1-(methylsulfonamido)propan-2-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide
[00515] Step A: Preparation of tert-butyl 2-amino-2-methylpropylcarbamate. Tertbutyl phenyl carbonate ( $0.421 \mathrm{~mL}, 2.270 \mathrm{mmol}$ ) was added to a solution of 2-methylpropane-1,2-diamine ( $200 \mathrm{mg}, 2.270 \mathrm{mmol}$ ) in $\mathrm{EtOH}(4.5 \mathrm{~mL})$ and the reaction mixture was heated at reflux overnight. The mixture was concentrated and the residue diluted in water. The mixture was acidified with 2 N HCl to pH 4 and washed with DCM. The aqueous layer was treated with $1 \mathrm{M} \mathrm{NaOH}(2 \mathrm{~mL})$ and extracted with DCM . The combined organic layers were dried with $\mathrm{MgSO}_{4}$, filtered and concentrated to afford tert-butyl 2-amino-2methylpropylcarbamate ( $158 \mathrm{mg}, 37 \%$ yield) as a colorless oil. MS (apci) m/z $=188.9$ $(\mathrm{M}+\mathrm{H})$.
[00516] Step B: Preparation of (R)-tert-butyl 2-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamido)-2-methylpropylcarbamate. Prepared by the method described in Example 1 using tert-butyl 2-amino-2-methylpropylcarbamate to provide the title compound as a colorless oil ( $109 \mathrm{mg}, 100 \%$ yield). MS (apci) $\mathrm{m} / \mathrm{z}=515.2$ $(\mathrm{M}+\mathrm{H})$.
[00517] Step C: Preparation of (R)-N-(1-amino-2-methylpropan-2-yl)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide hydrochloride. (R)-tert-butyl 2-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamido)-2-methylpropylcarbamate ( $109 \mathrm{mg}, 0.212 \mathrm{mmol}$ ) was dissolved in DCM ( 1.0 $\mathrm{mL})$ and 4 N HCl in dioxane ( $0.530 \mathrm{~mL}, 2.12 \mathrm{mmol}$ ) was added. The mixture was stirred at ambient temperature for 4 hours and was concentrated afford the title compound ( 105 mg ). MS (apci) $\mathrm{m} / \mathrm{z}=415.2(\mathrm{M}+\mathrm{H})$.
[00518] Step D: Preparation of (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-(2methyl -1-(methylsulfonamido)propan-2-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide. (R)N -(1-amino-2-methylpropan-2-yl)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a] pyrimidine-3-carboxamide hydrochloride ( $24.0 \mathrm{mg}, 0.0532 \mathrm{mmol}$ ) was dissolved in DCM $(0.53 \mathrm{~mL})$ and triethylamine $(15.2 \mu \mathrm{~L}, 0.109 \mathrm{mmol})$ followed by $\mathrm{MeSO}_{2} \mathrm{Cl}(4.34 \mu \mathrm{~L}, 0.0559$
mmol ) were added sequentially. The mixture was stirred at ambient temperature for 2 hours and was diluted with EtOAc. The mixture was washed with water and brine and was dried with $\mathrm{MgSO}_{4}$. The solution was filtered and concentrated to afford the title compound (8.0 $\mathrm{mg}, 30 \%$ yield) as a white solid. MS (apci) m/z $=493.1(\mathrm{M}+\mathrm{H})$.

## Example 58


(R)-N-(2-amino-2-methylpropyl)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide
[00519] Prepared by the method described in Example 1, using 2-methylpropane-1,2diamine. The crude product was purified by reverse phase chromatography eluting with 0 $100 \%$ acetonitrile/water to yield the title compound as a white solid ( $3.9 \mathrm{mg}, 6.0 \%$ yield). MS (apci) m/z=415.1 (M+H).

## Example 59


(R)-N-tert-butyl-5-(4,4-difluoro-2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide
[00520] Step A: Preparation of (R)-N-tert-butyl-5-(2-(3-fluorophenyl)-4-oxopyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide: N-tert-butyl-5-((2R,4R)-2-(3-fluorophenyl)-4-hydroxypyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (Example $42,10 \mathrm{mg}, 0.025 \mathrm{mmol})$ and the Dess-Martin reagent ( $16 \mathrm{mg}, 0.038 \mathrm{mmol}$ ) in DCM ( 2.0 mL ) were stirred at ambient temperature overnight. $1 \mathrm{~N} \mathrm{NaOH}(2.5 \mathrm{~mL})$ was added and the reaction stirred for 30 minutes. Brine ( 2.5 mL ) was added and the reaction was filtered through a phase separator frit, washing with several portions of DCM. The DCM solution was concentrated and the residue purified by reverse phase chromatography ( $20-70 \%$
acetonitrile/water) to provide the title compound ( $2.7 \mathrm{mg}, 27 \%$ yield) as a clear oil. MS (apci) $\mathrm{m} / \mathrm{z}=396.0(\mathrm{M}+\mathrm{H})$.
[00521] Step B: Preparation of (R)-N-tert-butyl-5-(4,4-difluoro-2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide: (R)-N-tert-butyl-5-(2-(3-fluorophenyl)-4-oxopyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide $\mathrm{mg}, 3.54 \mu \mathrm{~mol}$ ) and bis-(2-methoxyethyl)aminosulfur trifluoride ( $1.57 \mathrm{mg}, 7.08 \mu \mathrm{~mol}$ ) were mixed in DCM $(2.0 \mathrm{~mL})$ and the reaction was stirred at ambient temperature overnight. 1 N $\mathrm{NaOH}(1.0 \mathrm{~mL})$ was added and the reaction was stirred for 30 minutes. Brine $(1.0 \mathrm{~mL})$ was added and the mixture was filtered through a phase separator frit, washing with several portions of DCM. The DCM solution was concentrated and the residue purified by reverse phase chromatography ( $0-70 \%$ acetonitrile/water) to provide the title compound ( 1.30 mg , $88.0 \%$ yield) as a white solid. MS (apci) m/z $=418.1(\mathrm{M}+\mathrm{H})$.

## Example 60


(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-(1,3-dihydroxy-2-methylpropan-2-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide
[00522] Prepared according to the method of Example 1, using 2-amino-2-methylpropane-1,3-diol ( 2.0 equiv). The crude material was purified by $\mathrm{SiO}_{2}$ column chromatography, eluting with EtOAc and then $10 \% \mathrm{MeOH}-\mathrm{EtOAc}$ to provide the title compound as a white solid ( $54 \%$ yield). MS (apci) $\mathrm{m} / \mathrm{z}=432.1(\mathrm{M}+\mathrm{H})$.

## Example 61


[00523] Step A: Preparation of (3S,4R)-tert-butyl 4-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamido)-3-
fluoropiperidine-1-carboxylate. Prepared according to the method of Example 1, using (3S,4R)-tert-butyl 4-amino-3-fluoropiperidine-1-carboxylate ( 1.5 equiv). The title compound was obtained as a white solid ( $79 \%$ yield). MS (apci) $\mathrm{m} / \mathrm{z}=545.21(\mathrm{M}+\mathrm{H})$.
[00524] Step B: Preparation of 5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-((3S,4R)-3-fluoropiperidin-4-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide hydrochloride.

To a solution of the title compound from Step A ( $50.0 \mathrm{mg}, 0.092 \mathrm{mmol}$ ) in EtOAc ( 1.5 mL ) was added 4 M HCl in dioxane ( $0.460 \mathrm{~mL}, 1.85 \mathrm{mmol}$ ) and the mixture was stirred at ambient temperature for 6 hours (white precipitate formed). The mixture was diluted with dry $\mathrm{Et}_{2} \mathrm{O}$ (2 volumes) and sonicated to afford a fine white suspension. The solid was collected, washed with dry $\mathrm{Et}_{2} \mathrm{O}$ and dried under vacuum to give the title compound as a white solid ( 42 mg , $95 \%$ yield). MS (apci) $\mathrm{m} / \mathrm{z}=445.1(\mathrm{M}+\mathrm{H})$.

## Example 62



N-((S)-2,3-dihydroxypropyl)-5-((R)-2-(5-fluoro-2-(trifluoromethyl)phenyl) pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide
[00525] Prepared by the method described in Example 1 using (R)-5-(2-(5-fluoro-2-(trifluoromethyl)phenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (Preparation M) and (S)-3-aminopropane-1,2-diol. The crude material was purified by reverse phase HPLC ( $0-60 \%$ acetonitrile/water) to provide the title compound ( $26 \mathrm{mg}, 73 \%$ yield). MS (apci) $m / z=468.1(M+H)$.

Example 63


## N-((R)-2,3-dihydroxypropyl)-5-((R)-2-(5-fluoro-2-(trifluoromethyl)phenyl) pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide

[00526] Prepared by the method described in Example 1 using (R)-5-(2-(5-fluoro-2-(trifluoromethyl)phenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (Preparation M) and (R)-3-aminopropane-1,2-diol. The crude material was purified by reverse phase HPLC ( $0-60 \%$ acetonitrile/water) to provide the title compound ( $34 \mathrm{mg}, 73 \%$ yield). MS (apci) $\mathrm{m} / \mathrm{z}=468.1(\mathrm{M}+\mathrm{H})$.

## Example 64


(R)-5-(2-(5-fluoro-2-(trifluoromethyl)phenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3carboxamide
[00527] Prepared by the method described in Example 1 using (R)-5-(2-(5-fluoro-2-(trifluoromethyl)phenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (Preparation M) and ammonium chloride. The crude material was purified by reverse phase HPLC ( $0-60 \%$ acetonitrile/water) to yield the title compound ( $23 \mathrm{mg}, 78 \%$ yield.). MS (apci) $\mathrm{m} / \mathrm{z}=394.0(\mathrm{M}+\mathrm{H})$.

## Example 65


(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-methoxypyrazolo[1,5-a]pyrimidine-3carboxamide
[00528] Prepared by the method described in Example 1 using Omethylhydroxylamine hydrochloride ( 2.0 equiv). The title compound was obtained as a white solid ( $53 \%$ yield). MS (apci) $m / z=374.1(M+H)$.

## Example 66

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(R)-N-(cyclopropylmethoxy)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide
[00529] Prepared by the method described in Example 1 using O(cyclopropylmethyl)hydroxylamine ( 2.0 equiv). The title compound was obtained as a white solid ( $31 \%$ yield). MS (apci) $\mathrm{m} / \mathrm{z}=414.1(\mathrm{M}+\mathrm{H})$.

## Example 67


(R)-5-(5-(2,5-difluorophenyl)-2,2-dimethylpyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-
carboxamide
[00530] Step A: Preparation of (R)-tert-butyl 5-(2,5-difluorophenyl)-2,2-dimethyl pyrrolidine-1-carboxylate. Prepared by the method described in Preparation A, Step A substituting tert-butyl pyrrolidine-1-carboxylate with tert-butyl 2,2-dimethylpyrrolidine-1carboxylate to provide the title compound as a white solid ( $640 \mathrm{mg}, 37 \%$ yield). MS (apci) $\mathrm{m} / \mathrm{z}=212.1(\mathrm{M}+\mathrm{H}-\mathrm{Boc})$.
[00531] Step B: Preparation of (R)-5-(2,5-difluorophenyl)-2,2-dimethylpyrrolidine hydrochloride. Prepared by the method as described in Preparation A, Step B, using (R)-tertbutyl 5-(2,5-difluorophenyl )-2,2-dimethyl pyrrolidine-1-carboxylate to afford the title compound ( $420 \mathrm{mg}, 97 \%$ yield). MS (apci) m/z $=212.1(\mathrm{M}+\mathrm{H})$.
[00532] Step C : Preparation of (R)-ethyl 5-(5-(2,5-difluorophenyl)-2,2-dimethylpyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylate. A sealed pressure tube was charged with (R)-5-(2,5-difluoro phenyl)-2,2-dimethylpyrrolidine HCl salt ( $300 \mathrm{mg}, 1.21$ mmol ), diisopropylethylamine ( $423 \mu \mathrm{~L}, 2.42 \mathrm{mmol}$ ), ethyl 5 -chloropyrazolo[1,5-a]pyrimidine3 -carboxylate ( $273 \mathrm{mg}, 1.21 \mathrm{mmol}$ ) and isopropanol ( 2.0 mL ). The tube was sealed and the mixture was heated at $160{ }^{\circ} \mathrm{C}$ for 3 days. Additional ethyl 5-chloropyrazolo[1,5-
a]pyrimidine-3-carboxylate ( $273 \mathrm{mg}, 1.21 \mathrm{mmol}$ ) was added and the reaction was heated at $160{ }^{\circ} \mathrm{C} 2$ days. The reaction mixture was concentrated and the residue purified by reverse phase HPLC (eluting with $0-60 \%$ acetonitrile $/ \mathrm{H}_{2} \mathrm{O}$ ) to provide the title compound ( 136 mg , $28 \%$ ) as a beige solid. MS (apci) $\mathrm{m} / \mathrm{z}=401.1(\mathrm{M}+\mathrm{H})$.
[00533] Step D: Preparation of (R)-5-(5-(2,5-difluorophenyl)-2,2-dimethylpyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid. (R)-ethyl 5-(5-(2,5-difluorophenyl)-2,2-dimethylpyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylate ( $136 \mathrm{mg}, 0.340 \mathrm{mmol}$ ) was dissolved in $\mathrm{MeOH}(5.0 \mathrm{~mL})$ and $1 \mathrm{~N} \mathrm{NaOH}(3.40 \mathrm{~mL}, 3.40 \mathrm{mmol})$ was added. The reaction was stirred at ambient temperature for 5 days and then heated at reflux for 4 hours. The reaction mixture was cooled, poured onto a mixture of brine ( 10 mL ) and $2 \mathrm{~N} \mathrm{HCl}(5 \mathrm{~mL})$ and extracted with DCM. The combined organic extracts were filtered through PS paper and concentrated to provide the title compound ( $123 \mathrm{mg}, 97 \%$ yield) as a beige solid. MS (apci) $m / z=373.0(M+H)$.
[00534] Step E: Preparation of (R)-5-(5-(2,5-difluorophenyl)-2,2-dimethylpyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide. Prepared by the method described in Example 1 using (R)-5-(5-(2,5-difluorophenyl)-2,2-dimethylpyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid and ammonium chloride. The crude material was purified by reverse phase HPLC ( $0-70 \%$ acetonitrile/water) to provide the title compound ( $8.5 \mathrm{mg}, 33 \%$ yield.). MS (apci) m/z=372.1 (M+H).

## Example 68


(R)-N-cyclopropyl-5-(5-(2,5-difluorophenyl)-2,2-dimethylpyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide
[00535] Prepared by the method described in Example 1 using (R)-5-(5-(2,5-difluorophenyl)-2,2-dimethylpyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid and cyclopropylamine in Step D. The crude material was purified by reverse phase HPLC ( $0-75 \%$ acetonitrile/water) to provide the title compound ( $11 \mathrm{mg}, 39 \%$ yield.). MS (apci) m/z $=412.1(\mathrm{M}+\mathrm{H})$.

## Example 69


(R)-N-(2-cyanopropan-2-yl)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide
[00536] Prepared by the method described in Example 1 using (R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (Preparation I) and 2-amino-2-methylpropanenitrile to yield the title compound as a white solid ( 21 mg , $57 \%$ yield). MS (apci) $\mathrm{m} / \mathrm{z}=394.1(\mathrm{M}+\mathrm{H})$.

## Example 70


(R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-(methylsulfonyl)piperidin-4-
yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide
[00537] Prepared by the method as described in Example 1 using (R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (Preparation I) and 1-(methylsulfonyl)piperidin-4-amine to yield the title compound as a white solid (44 $\mathrm{mg}, 100 \%$ yield). MS (apci) $\mathrm{m} / \mathrm{z}=488.1(\mathrm{M}+\mathrm{H})$.

## Example 71


(R)-N-(1-fluoro-2-methylpropan-2-yl)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide

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[00538] Prepared by the method described in Example 1 using (R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (Preparation I) and 1-fluoro-2-methylpropan-2-amine to yield the title compound as a white solid ( 37 mg , $100 \%$ yield). MS (apci) $\mathrm{m} / \mathrm{z}=401.0(\mathrm{M}+\mathrm{H})$.

## Example 72


(R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(tetrahydro-2H-pyran-4-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide
[00539] Prepared by the method as described in Example 1 using (R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (Preparation I) and tetrahydro-2H-pyran-4-amine to yield the title compound as a white solid ( $34 \mathrm{mg}, 90 \%$ yield). MS (apci) $\mathrm{m} / \mathrm{z}=411.1(\mathrm{M}+\mathrm{H})$.

## Example 73



## (R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-methoxypyrazolo[1,5-a]pyrimidine-3-

 carboxamide[00540] Prepared by the method as described in Example 1 using (R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (Preparation I) and O-methylhydroxylamine to yield the title compound as a white solid ( $15 \mathrm{mg}, 35 \%$ yield). MS (apci) $\mathrm{m} / \mathrm{z}=357.0(\mathrm{M}+\mathrm{H})$.

## Example 74


(R)-5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide
[00541] To a suspension of (R)-5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (Preparation E, $50.0 \mathrm{mg}, 0.153 \mathrm{mmol}$ ) in $\mathrm{CCl}_{4}(1.0 \mathrm{~mL})$ was added thionyl chloride ( $182 \mathrm{mg}, 1.53 \mathrm{mmol}$ ) and the mixture was heated at reflux for 4 hours (homogeneous after 5 minutes). The mixture was cooled to ambient temperature and was concentrated to give a brittle foam. The foam was dissolved in dry THF ( 2 mL ) and dimethylaminopyridine (DMAP) ( $3.74 \mathrm{mg}, 0.031 \mathrm{mmol}$ ) was added. Anhydrous ammonia was bubbled into the mixture with stirring for 5 minutes. The reaction vessel was sealed and the reaction was stirred at ambient temperature for 18 hours. The mixture was added to $\mathrm{H}_{2} \mathrm{O}$ ( 4 mL ) and extracted with EtOAc. The combined extracts were washed with $1 \mathrm{M} \mathrm{Na}_{2} \mathrm{CO}_{3}$, $\mathrm{H}_{2} \mathrm{O}$ and saturated NaCl . The solution was dried over $\mathrm{MgSO}_{4} /$ activated carbon and filtered through a $\mathrm{SiO}_{2}$ plug (EtOAc then $10 \% \mathrm{MeOH} / \mathrm{EtOAc}$ for elution). The solution was concentrated to give the title compound as a white solid ( $38 \mathrm{mg}, 76 \%$ ). MS (apci) $\mathrm{m} / \mathrm{z}=$ $326.0(\mathrm{M}+\mathrm{H})$.

## Example 75



## ((R)-5-(2-(3-fluorophenyl)pyrrolidin-1-yl)-N-methoxypyrazolo[1,5-a]pyrimidine-3-

 carboxamide[00542] To a suspension of (R)-5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (Preparation E, $50.0 \mathrm{mg}, 0.153 \mathrm{mmol}$ ) in $\mathrm{CCl}_{4}(1.5 \mathrm{~mL})$ was added thionyl chloride ( $182 \mathrm{mg}, 1.53 \mathrm{mmol}$ ) and mixture heated at reflux for 4 hours (homogeneous). The mixture was cooled to ambient temperature and was concentrated to a brittle beige foam. DMAP ( $3.7 \mathrm{mg}, 0.031 \mathrm{mmol}$ ), methylhydroxyl amine $\mathrm{HCl}(38.4 \mathrm{mg}$, 0.460 mmol ) and dry THF ( 2 mL ) were added and mixed. Diisopropylethylamine ( 79.2 mg , 0.613 mmol ) was added, and the reaction flushed with $\mathrm{N}_{2}$ and stirred at ambient temperature for 18 hours. The mixture was diluted with $\mathrm{H}_{2} \mathrm{O}(4 \mathrm{~mL})$ and extracted with EtOAc and the combined extracts were washed with $1 \mathrm{M} \mathrm{Na} \mathrm{Na}_{2} \mathrm{CO}_{3}, \mathrm{H}_{2} \mathrm{O}$ and saturated NaCl . The solution was dried over $\mathrm{MgSO}_{4} /$ activated carbon and filtered through a $\mathrm{SiO}_{2}$ plug eluting with EtOAc . The mixture was concentrated to give a white foam that was dissolved in minimal $\mathrm{CH}_{2} \mathrm{Cl}_{2}$
and treated with dry hexanes to give a fine white suspension. The mixture was concentrated to give the title compound as white solid ( $42 \mathrm{mg}, 77 \%$ ). MS (apci) $\mathrm{m} / \mathrm{z}=356.0(\mathrm{M}+\mathrm{H})$.

## Example 76


(R)-5-(2-(3-fluoro-5-(2-morpholinoethoxy)phenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide
[00543] Step A: Preparation of (R)-tert-butyl 2-(3-fluoro-5-hydroxyphenyl)pyrrolidine-1-carboxylate. Prepared by the method as described in Preparation A, Step A, substituting 2-bromo-1,4-difluorobenzene with 3-bromo-5fluorophenyl acetate to afford the title compounds ( $10.3 \mathrm{~g}, 62 \%$ yield). MS (apci) $\mathrm{m} / \mathrm{z}=$ 182.1 (M+H - Boc).
[00544] Step B: Preparation of (R)-3-fluoro-5-(pyrrolidin-2-yl)phenol hydrochloride. To a solution of (R)-tert-butyl 2-(3-fluoro-5-hydroxyphenyl)pyrrolidine-1carboxylate ( $10.3 \mathrm{~g}, 36.5 \mathrm{mmol}$ ) in $\mathrm{DCM}(20 \mathrm{~mL})$ was added 4 N HCl in dioxane ( 36.5 mL , 146 mmol ) and the mixture was stirred at ambient temperature for 15 hours. The resulting precipitate was filtered and washed with DCM to afford (R)-3-fluoro-5-(pyrrolidin-2yl)phenol hydrochloride ( $5.81 \mathrm{~g}, 73.3$ \% yield).
[00545] Step C: Preparation of (R)-ethyl 5-(2-(3-fluoro-5-hydroxyphenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylate. Prepared by the method as described in Preparation C, Step A, using (R)-2-(2,5-difluorophenyl)pyrrolidine and (R)-3-fluoro-5-(pyrrolidin-2-yl)phenol hydrochloride. The crude material was purified by reverse phase HPLC ( $0-60 \%$ acetonitrile/water) to provide yield the title compound ( $775 \mathrm{mg}, 94 \%$ yield). MS (apci) m/z=370.9 (M+H).
[00546] Step D: Preparation of (R)-ethyl 5-(2-(3-fluoro-5-(2-morpholinoethoxy) phenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylate. (R)-ethyl 5-(2-(3-fluoro -5-hydroxyphenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylate (167 mg, 0.451 mmol ), 4-(2-chloroethyl)morpholine hydrochloride ( $168 \mathrm{mg}, 0.902 \mathrm{mmol}$ ), and $\mathrm{K}_{2} \mathrm{CO}_{3}(312$ $\mathrm{mg}, 2.25 \mathrm{mmol})$ were suspended in DMF ( 5 mL ) and stirred at ambient temperature for 15 hours. The crude reaction mixture was purified by reverse phase HPLC ( $0-60 \%$
acetonitrile/water) to provide the title compound ( $218 \mathrm{mg}, 100 \%$ yield). MS (apci) $\mathrm{m} / \mathrm{z}=$ 484.1 (M+H).
[00547] Step E: Preparation of (R)-5-(2-(3-fluoro-5-(2-morpholinoethoxy)phenyl) pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid. Prepared using the hydrolysis conditions described in Preparation C, Step B. The crude material was purified by reverse phase HPLC ( $0-40 \%$ acetonitrile/water) to yield the title compound ( $208 \mathrm{mg}, 94 \%$ yield). MS (apci) m/z=456.1 (M+H).
[00548] Step F: Preparation of (R)-5-(2-(3-fluoro-5-(2-morpholinoethoxy)phenyl) pyrrolidin -1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide. Prepared by the method described in Example 1 using (R)-5-(2-(3-fluoro-5-(2-morpholinoethoxy)phenyl) pyrrolidin1 -yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid ammonium chloride to yield the title compound as a white solid ( $19 \mathrm{mg}, 69 \%$ yield.). MS (apci) m/z $=455.1(\mathrm{M}+\mathrm{H})$.

Example 77

(R)-N-cyclopropyl-5-(2-(3-fluoro-5-(2-methoxyethoxy)phenyl)pyrrolidin-1-yl)pyrazole [1,5-a]pyrimidine-3-carboxamide
[00549] Step A: Preparation of (R)-ethyl 5-(2-(3-fluoro-5-(2-methoxyethoxy )phenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylate. (R)-ethyl 5-(2-(3-fluoro-5-hydroxyphenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylate (Example 76 Step B, $174 \mathrm{mg}, 0.470 \mathrm{mmol}$ ), 1-bromo-2-methoxyethane ( $196 \mathrm{mg}, 1.41 \mathrm{mmol}$ ), and $\mathrm{K}_{2} \mathrm{CO}_{3}$ ( 325 $\mathrm{mg}, 2.35 \mathrm{mmol}$ ) were suspended in DMF ( 5 mL ) and stirred at ambient temperature for 15 hours. The crude reaction mixture was purified by reverse phase HPLC ( $0-60 \%$ acetonitrile/water) to provide yield the title compound ( $183 \mathrm{mg}, 91 \%$ yield). MS (apci) $\mathrm{m} / \mathrm{z}=$ $429.0(\mathrm{M}+\mathrm{H})$.
[00550] Step B: Preparation of (R)-5-(2-(3-fluoro-5-(2-methoxyethoxy)phenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid. (R)ethyl 5-(2-(3-fluoro-5-(2-methoxy ethoxy)phenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylate ( $178 \mathrm{mg}, 0.415 \mathrm{mmol}$ ) was suspended in a mixture of $1 \mathrm{~N} \mathrm{NaOH} \mathrm{( } 5 \mathrm{~mL}$ ) and $\mathrm{MeOH}(5 \mathrm{~mL})$. The reaction mixture was stirred at ambient temperature until complete and
quenched with $2 \mathrm{~N} \mathrm{HCl}(25 \mathrm{~mL})$. The mixture was extracted with ethyl acetate and the combined organic fractions were concentrated to give the title compound ( $177 \mathrm{mg}, 100 \%$ yield). MS (apci) $\mathrm{m} / \mathrm{z}=401.0(\mathrm{M}+\mathrm{H})$.
[00551] Step C: Preparation of (R)-N-cyclopropyl-5-(2-(3-fluoro-5-(2methoxyethoxy) phenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide. Prepared by the method described in Example 1 using (R)-5-(2-(3-fluoro-5-(2-methoxyethoxy)phenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid and cyclopropylamine to yield the title compound as a white solid ( $16 \mathrm{mg}, 52 \%$ yield). MS (apci) $m / z=440.1(M+H)$.

## Example 78


(R)-5-(2-(3-fluoro-5-(2-methoxyethoxy)phenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3carboxamide
[00552] Prepared by the method described in Example 77 using ammonium chloride in Step C. The crude material was purified by reverse phase HPLC ( $0-60 \%$ acetonitrile/water) to provide the title compound ( $16 \mathrm{mg}, 53 \%$ yield.). MS (apci) m/z $=400.1(\mathrm{M}+\mathrm{H})$.

## Example 79


(R)-N-cyclopropyl-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-alpyrimidine-3-carboxamide
[00553] Prepared by the method described in Example 1 using (R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (Preparation K) and cyclopropanamine. The combined organic extracts were concentrated and the residue was purified by reverse phase HPLC ( $0-70 \%$ acetonitrile/water) to provide the title compound ( $19 \mathrm{mg}, 57 \%$ yield.). MS (apci) $\mathrm{m} / \mathrm{z}=397.0(\mathrm{M}+\mathrm{H})$.

## Example 80


(R)-N-tert-butyl-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide
[00554] Prepared by the method described in Example 1 using (R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (Preparation K). The combined organic extracts were concentrated and the residue was purified by reverse phase HPLC ( $0-80 \%$ acetonitrile/water) to provide the title compound ( 23 $\mathrm{mg}, 68 \%$ yield). MS (apci) $\mathrm{m} / \mathrm{z}=413.0(\mathrm{M}+\mathrm{H})$.

## Example 81


(R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-(1-fluoro-2-methylpropan-2-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide
[00555] Prepared by the method described in Example 1 using (R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (Preparation K) and 1-fluoro-2-methylpropan-2-amine. The combined organic extracts were concentrated and the residue was purified by reverse phase HPLC ( $0-90 \%$ acetonitrile/water) to provide the title compound ( $28 \mathrm{mg}, 78 \%$ yield). MS (apci) $\mathrm{m} / \mathrm{z}=431.0(\mathrm{M}+\mathrm{H})$.

## Example 82


(R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3carboxamide
[00556] Prepared by the method described in Example 1 using (R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (Preparation K ) and $7 \mathrm{~N} \mathrm{NH}_{3}$ in MeOH . The combined organic extracts were concentrated and the residue was purified by reverse phase HPLC ( $0-80 \%$ acetonitrile/water) to provide the title compound ( $15 \mathrm{mg}, 38 \%$ yield). MS (apci) $\mathrm{m} / \mathrm{z}=357.0(\mathrm{M}+\mathrm{H})$.

Example 83

(R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-methoxypyrazolo[1,5-a]pyrimidine-3-carboxamide
[00557] Prepared by the method described in Example 1 using (R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (Preparation K) and O-methylhydroxylamine. The combined organic extracts were concentrated and the residue was purified by reverse phase HPLC ( $0-80 \%$ acetonitrile/water) to yield the title compound ( $29 \mathrm{mg}, 67 \%$ yield). MS (apci) m/z $=387.0(\mathrm{M}+\mathrm{H})$.

## Example 84


(R)-1-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3carboxamido)cyclopropanecarboxylic acid
[00558] Step A: Preparation of (R)-ethyl 1-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamido)cyclopropanecarboxylate. Using ethyl 1aminocyclopropanecarboxylate hydrochloride ( 2.0 equiv) in the procedure described for the synthesis of Example 1, the title compound was obtained as a white solid ( $61 \%$ yield). MS (apci) $\mathrm{m} / \mathrm{z}=456.1(\mathrm{M}+\mathrm{H})$.
[00559] Step B: Preparation of (R)-1-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamido)cyclopropanecarboxylic acid. To a solution of the above ester ( $39 \mathrm{mg}, 0.086 \mathrm{mmol}$ ) in 2:1 THF-MeOH ( 1.5 mL ) was added 1 M aq . LiOH $(0.257 \mathrm{~mL}, 257 \mathrm{mmol})$ and the mixture was stirred at ambient temperature for 18 hours. The mixture was concentrated and the residual solid was dissolved in $\mathrm{H}_{2} \mathrm{O}(3 \mathrm{~mL})$. The solution was treated with 1 M HCl to $\mathrm{pH}=3$. The resulting precipitate was collected, washed with water and dried in vacuum to yield the title compound as a white solid ( $31 \mathrm{mg}, 83 \%$ ). MS (apci) $\mathrm{m} / \mathrm{z}=428.0(\mathrm{M}+\mathrm{H})$.

## Example 85


(R)-N-cyclopropyl-5-(2-(3-fluoro-5-(2-morpholinoethoxy)phenyl)pyrrolidin-1-
yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide
[00560] Prepared by the method described in Example 76, substituting ammonium chloride with cyclopropylamine in Step F. The crude material was purified by reverse phase HPLC ( $0-60 \%$ acetonitrile/water) to provide the title compound ( $30 \mathrm{mg}, 99 \%$ yield.). MS (apci) $m / z=495.1(M+H)$.

## Example 86


(R)-5-(2-(5-fluoro-2-(2-morpholinoethoxy) phenyl) pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide
[00561] Step A: Preparation of (R)-tert-butyl 2-(2-acetoxy-5-
fluorophenyl)pyrrolidine-1-carboxylate. Prepared by the method as described in Preparation A, Step A, substituting 2-bromo-1,4-difluorobenzene with 2-bromo-4-fluorophenyl acetate to afford the title compound ( $5.75 \mathrm{~g}, 35 \%$ yield). MS (apci) m/z $=224.1(\mathrm{M}+\mathrm{H}-\mathrm{Boc})$.
[00562] Step B: Preparation of (R)-4-fluoro-2-(pyrrolidin-2-yl)phenol hydrochloride. Prepared according to the procedure outlined for Example 76, Step B, to afford the title compound ( $2.64 \mathrm{~g}, 59.3 \%$ yield). MS (apci) m/z $=182.1(\mathrm{M}+\mathrm{H})$.
[00563] Step C: Preparation of (R)-ethyl 5-(2-(3-fluoro-5-hydroxyphenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylate. Prepared by the method as described in Preparation C, Step A, using ethyl 5-chloropyrazolo[1,5-a]pyrimidine-3-carboxylate and (R)-4-fluoro-2-(pyrrolidin-2-yl)phenol hydrochloride. The crude material was purified by reverse phase HPLC ( $0-65 \%$ acetonitrile/water) to provide the title compound ( $686 \mathrm{mg}, 84 \%$ yield). MS (apci) m/z = $371.0(\mathrm{M}+\mathrm{H})$.
[00564] Step D: Preparation of (R)-ethyl 5-(2-(3-fluoro-5-(2-morpholinoethoxy) phenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylate. Prepared according to the procedure described in Example 76, Step D, using (R)-ethyl 5-(2-(3-fluoro-5-hydroxyphenyl)pyrrolidin-1-yl)pyrazolo[1,5pyrimidine-3-carboxylate. The crude reaction mixture was purified by reverse phase HPLC ( $0-60 \%$ acetonitrile/water) to provide the title compound ( $250 \mathrm{mg}, 96 \%$ yield). MS (apci) $\mathrm{m} / \mathrm{z}=484.1(\mathrm{M}+\mathrm{H})$.
[00565] Step E: Preparation of (R)-5-(2-(5-fluoro-2-(2-morpholinoethoxy) phenyl) pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid hydrochloride. To a solution of (R)-ethyl 5-(2-(3-fluoro-5-(2-morpholinoethoxy) phenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylate ( $250 \mathrm{mg}, 535 \mathrm{mmol}$ ) in MeOH ( 10 ml ) was added 1 N NaOH (aqueous, 6 mL ). The reaction was stirred at ambient temperature for 1 week, then concentrated, treated with 4 N HCl in dioxane ( 5 ml ) and concentrated. The crude material was purified by reverse phase HPLC ( $0-50 \%$ acetonitrile/water) to yield the title compound. MS (apci) m/z=456.1 (M+H).
[00566] Step F: Preparation of (R)-5-(2-(5-fluoro-2-(2-morpholinoethoxy) phenyl) pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide. Prepared by the method described in Example 76, Step F, using ((R)-5-(2-(5-fluoro-2-(2-morpholinoethoxy) phenyl)pyrrolidin1 -yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid hydrochloride and ammonium chloride to yield the title compound as a white solid ( $42.2 \mathrm{mg}, 91 \%$ yield.). MS (apci) $\mathrm{m} / \mathrm{z}=455.1$ (M+H).

## Example 87


(R)-N-cyclopropyl-5-(2-(5-fluoro-2-(2-morpholinoethoxy)phenyl) pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide
[00567] Prepared by the method described in Example 76, Step F using ((R)-5-(2-(5-fluoro-2-(2-morpholinoethoxy)phenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3carboxylic acid hydrochloride and cyclopropylamine to yield the title compound as a white solid ( $35.4 \mathrm{mg}, 70 \%$ yield.). MS (apci) m/z $=495.1(\mathrm{M}+\mathrm{H}$ ).

## Example 88



5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-((S)-2,3-dihydroxypropoxy)pyrazolo[1,5-a]pyrimidine-3-carboxamide
[00568] Step A: Preparation of 5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazolo[1,5-a]pyrimidine-3-carboxamide. To a suspension of (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3carboxylic acid (Preparation C, $100 \mathrm{mg}, 0.290 \mathrm{mmol}$ ) in $\mathrm{CCl}_{4}(1.5 \mathrm{~mL})$ was added thionyl chloride ( $0.10 \mathrm{~mL}, 1.37 \mathrm{mmol}$ ) and the mixture was heated at reflux for 2.5 hours. The mixture was cooled to ambient temperature and was concentrated to give a residual brittle foam. The foam was dissolved in dry THF $(2.0 \mathrm{~mL})$ and the solution was sequentially treated with DMAP, DIEA and (S)-O-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)hydroxylamine (85.5 $\mathrm{mg}, 0.581 \mathrm{mmol})$. The reaction was stirred at ambient temperature for 4.5 hours and was concentrated to approx. 0.5 mL . The mixture was diluted with $\mathrm{H}_{2} \mathrm{O}(5 \mathrm{~mL})$ and extracted with $50 \%$ EtOAc-hexanes. The combined extracts were washed with $1 \mathrm{M} \mathrm{HCl}, \mathrm{H}_{2} \mathrm{O}, 1 \mathrm{M}$ $\mathrm{Na}_{2} \mathrm{CO}_{3}$ and saturated NaCl . The solution was dried over $\mathrm{MgSO}_{4}$ and activated carbon, then
filtered through a short $\mathrm{SiO}_{2}$ plug, eluting first with $50 \%$ EtOAc-hexanes then $10 \% \mathrm{MeOH}-$ EtOAc. The MeOH-EtOAc pool was concentrated to give a colorless foam. The foam was dissolved in minimal $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ and treated with hexanes to give a white suspension. The suspension was concentrated to afford the title compound as white solid that was dried in vacuum ( $137 \mathrm{mg}, 100 \%$ ). MS (apci) m/z $=474.1(\mathrm{M}+\mathrm{H})$.
[00569] Step B: Preparation of 5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-((S)-2,3-dihydroxypropoxy)pyrazolo[1,5-a]pyrimidine-3-carboxamide To a solution of 5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy) pyrazolo[1,5-a]pyrimidine-3-carboxamide ( $135 \mathrm{mg}, 0.285 \mathrm{mmol}$ ) in THF ( 4.0 mL ) was added $6 \mathrm{M} \mathrm{HCl}(1.0 \mathrm{~mL})$ dropwise and the mixture was stirred at ambient temperature for 1.5 hours. The reaction mixture was concentrated to approximately 1 mL and was diluted with $\mathrm{H}_{2} \mathrm{O}$ (5 mL ). The resulting milky white mixture was extracted with EtOAc and the combined extracts were washed with $1 \mathrm{M} \mathrm{Na}_{2} \mathrm{CO}_{3}$ and saturated NaCl . The EtOAc solution was dried over $\mathrm{MgSO}_{4}$ and filtered through a packed Celite pad capped with a layer of $\mathrm{MgSO}_{4}$. The solution was concentrated to give a colorless foam that was dissolved in minimal $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ and treated with hexanes to give a white suspension. The suspension was concentrated to give the title compound as a white solid that was dried in vacuum ( $102 \mathrm{mg}, 82 \%$ ). MS (apci) m/z $=434.0(\mathrm{M}+\mathrm{H})$.

## Example 89


(R)-5-(2-(5-fluoro-2-(2-methoxyethoxy)phenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3carboxamide
[00570] Step A: Preparation of (R)-methyl 5-(2-(5-fluoro-2-(2-methoxyethoxy)phenyl) pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylate. Prepared by the method described in Example 86, Step D, substituting 4-(2-chloroethyl)morpholine hydrochloride with 1-bromo-2-methoxyethane to afford the title compound ( $209 \mathrm{mg}, 80 \%$ yield). MS (apci) m/z $=$ $415.0(\mathrm{M}+\mathrm{H})$.
[00571] Step B: Preparation of (R)-5-(2-(5-fluoro-2-(2-methoxyethoxy)phenyl) pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid. Prepared from (R)-methyl 5-(2-(5-fluoro-2-(2-methoxyethoxy)phenyl) pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-
carboxylate by the method described in Example 77, Step B to afford the title compound (163 $\mathrm{mg}, 84 \%$ yield). MS (apci) $\mathrm{m} / \mathrm{z}=401.0(\mathrm{M}+\mathrm{H})$.
[00572] Step C: Preparation (R)-5-(2-(5-fluoro-2-(2-methoxyethoxy)phenyl) pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide. Prepared by the method described in Example 76, Step F using (R)-5-(2-(5-fluoro-2-(2-methoxyethoxy)phenyl) pyrrolidin-1-yl)pyrazolo[1,5-a] pyrimidine-3-carboxylic acid and ammonium chloride to yield the title compound as a white solid ( $32.6 \mathrm{mg}, 55 \%$ yield.). MS (apci) m/z $=400.1(\mathrm{M}+\mathrm{H})$.

## Example 90


(R)-N-cyclopropyl-5-(2-(5-fluoro-2-(2-methoxyethoxy)phenyl) pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide
[00573] Prepared by the method described in Example 89, Step C substituting ammonium chloride with cyclopropylamine to yield the title compound as a white solid (7.9 $\mathrm{mg}, 12 \%$ yield.). MS (apci) $\mathrm{m} / \mathrm{z}=495.1(\mathrm{M}+\mathrm{H})$.

## Example 91


(R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-methylcyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide
[00574] Step A: Preparation of tert-butyl 1-methylcyclopropylcarbamate. Diphenylphosphoryl azide ( $2.63 \mathrm{~mL}, 12.2 \mathrm{mmol}$ ) was added to a mixture of 1 methylcyclopropanecarboxylic acid ( $1.22 \mathrm{~g}, 12.2 \mathrm{mmol}$ ) and TEA ( $1.70 \mathrm{~mL}, 12.2 \mathrm{mmol}$ ) in anhydrous tert- $\mathrm{BuOH}\left(25 \mathrm{~mL}, 12.2 \mathrm{mmol}\right.$ ) under nitrogen, followed by heating first at $50^{\circ} \mathrm{C}$ for 15 minutes, then at $100{ }^{\circ} \mathrm{C}$ for 16 hours. After cooling to ambient temperature, the reaction was concentrated. The crude material was taken up in ether $(50 \mathrm{~mL})$, washed with saturated $\mathrm{NaHCO}_{3}$ and water ( 50 mL each), and dried $\left(\mathrm{MgSO}_{4}\right)$, giving the crude product as
white solid ( $0.81 \mathrm{~g}, 38 \%$ yield), which was used directly in the next step without further purification.
[00575] Step B: Preparation of 1-methylcyclopropanamine hydrochloride. A solution of 1-methylcyclopropylcarbamate ( $250 \mathrm{mg}, 1.46 \mathrm{mmol}$ ) in $\mathrm{HCl}(4 \mathrm{~N}$ dioxane, $3.65 \mathrm{~mL}, 14.6$ $\mathrm{mmol})$ was stirred at ambient temperature for 1 hour. It was then concentrated, triturated with ether, and filtered, giving the product as white solid ( $78 \mathrm{mg}, 50 \%$ ).
[00576] Step C: Preparation of (R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-methylcyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide. To a DMF ( 0.6 mL ) solution of (R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (Preparation I, $10.5 \mathrm{mg}, 0.0321 \mathrm{mmol}$ ) and HATU ( $14.6 \mathrm{mg}, 0.0385 \mathrm{mmol}$ ) was added 1-methylcyclopropanamine hydrochloride $(4.14 \mathrm{mg}, 0.0385 \mathrm{mmol})$ and DIEA $(0.0168 \mathrm{~mL}$, 0.0962 mmol ). After stirring for 10 minutes, the reaction mixture was directly purified by reverse-phase chromatography ( 5 to $50 \%$ acetonitrile/water) to yield the final product as white solid ( $10 \mathrm{mg}, 82 \%$ ). LCMS (apci) $\mathrm{m} / \mathrm{z}=381.1(\mathrm{M}+\mathrm{H})$.

## Example 92


(R)-(5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)(3-hydroxy-3-methylazetidin-1-yl)methanone
[00577] Step A: Preparation of 3-methylazetidin-3-ol 2,2,2-trifluoroacetate. To a solution of 1-benzhydryl-3-methylazetidin-3-ol ( $0.46 \mathrm{~g}, 1.82 \mathrm{mmol}$ ) in EtOH ( 15 mL ) was added TFA $(0.14 \mathrm{~mL}, 1.82 \mathrm{mmol})$ and $\mathrm{Pd}(\mathrm{OH})_{2} / \mathrm{C}(0.127 \mathrm{~g}, 0.182 \mathrm{mmol})$. The reaction was subjected to hydrogenation ( 50 psi ) on a Parr shaker at ambient temperature overnight. The reaction mixture was filtered, concentrated and triturated with $\mathrm{Et}_{2} \mathrm{O}$. The fine white solid was filtered to yield the product as a TFA salt.
[00578] Step B: Preparation of (R)-(5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)(3-hydroxy-3-methylazetidin-1-yl)methanone. To a DMF $(1.0 \mathrm{~mL})$ solution of (R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (Preparation $\mathrm{I}, 85 \mathrm{mg}, 0.26 \mathrm{mmol}$ ) was added HATU (118 $\mathrm{mg}, 0.31 \mathrm{mmol}$ ) and 3-methylazetidin-3-ol $2,2,2$-trifluoroacetate ( $63 \mathrm{mg}, 0.31 \mathrm{mmol}$ ) at
ambient temperature, followed by addition of DIEA ( $0.14 \mathrm{~mL}, 0.78 \mathrm{mmol}$ ) at $0^{\circ} \mathrm{C}$. After stirring for 5 minutes at ambient temperature, the reaction was directly purified by reversephase chromatography ( 5 to $45 \%$ acetonitrile/water) to yield the final product as white solid ( $84 \mathrm{mg}, 82 \%$ ). LCMS (apci) m/z $=397.1(\mathrm{M}+\mathrm{H})$.

## Example 93



## (R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-isopropylpyrazolo[1,5-

a]pyrimidine-3-carboxamide
[00579] To a DMF ( 1.0 mL ) solution of (R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (Preparation I, $80 \mathrm{mg}, 0.244 \mathrm{mmol}$ ) was added HATU ( $112 \mathrm{mg}, 0.293 \mathrm{mmol}$ ) and propan-2-amine ( $0.0250 \mathrm{ml}, 0.293 \mathrm{mmol}$ ) at ambient temperature, followed by drop-wise addition of DIEA ( $0.128 \mathrm{ml}, 0.733 \mathrm{mmol}$ ) at 0 ${ }^{\circ} \mathrm{C}$. After stirring for 5 minutes at ambient temperature, the reaction was poured into $1: 1$ water/saturated $\mathrm{NaHCO}_{3}(15 \mathrm{~mL})$ and the layers were separated. The aqueous layer was extracted with EtOAc ( $3 \times 15 \mathrm{~mL}$ ). The combined organic layers were dried $\left(\mathrm{Na}_{2} \mathrm{SO}_{4}\right)$, filtered and concentrated. The crude material was purified by reverse-phase chromatography ( 5 to $54 \%$ acetonitrile/water) to yield the final product as white solid ( $26 \mathrm{mg}, 29 \%$ ). LCMS (apci) $\mathrm{m} / \mathrm{z}=369.1(\mathrm{M}+\mathrm{H})$.

## Example 94



## (R)-(5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)(pyrrolidin-1-yl)methanone

[00580] To a solution of (R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (Preparation I, $50 \mathrm{mg}, 0.15 \mathrm{mmol}$ ) in anhydrous $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ (2 mL ) was added $\mathrm{HOBt}(41 \mathrm{mg}, 0.31 \mathrm{mmol}$ ) followed by EDCI ( $88 \mathrm{mg}, 0.46 \mathrm{mmol}$ ). The solution was stirred for 15 minutes, then treated with triethylamine ( $64 \mu \mathrm{~L}, 0.46 \mathrm{mmol}$ ) followed by pyrrolidine ( $38 \mu \mathrm{~L}, 0.46 \mathrm{mmol}$ ). After stirring at ambient temperature overnight,
the reaction mixture was partitioned between saturated $\mathrm{NH}_{4} \mathrm{Cl}(20 \mathrm{~mL})$ and $\mathrm{CH}_{2} \mathrm{Cl}_{2}(20 \mathrm{~mL})$. The aqueous layer was extracted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}(2 \times 10 \mathrm{~mL})$. The combined organic phases were washed with brine ( 10 mL ), dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and concentrated. The crude material was purified by silica chromatography ( 2 to $5 \% \mathrm{MeOH} / \mathrm{CH}_{2} \mathrm{Cl}_{2}$ ) to yield the final product as white solid ( $38 \mathrm{mg}, 65 \%$ ). LCMS (apci) $\mathrm{m} / \mathrm{z}=381.1(\mathrm{M}+\mathrm{H})$.

## Example 95


(R)-N-(5-fluoropyridin-2-yl)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide
[00581] To a DMF ( 0.25 mL ) solution of (R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (Preparation I, $25 \mathrm{mg}, 0.076 \mathrm{mmol}$ ) and HATU ( $35 \mathrm{mg}, 0.092 \mathrm{mmol}$ ) was added 5 -fluoropyridin-2-amine ( $10 \mathrm{mg}, 0.092 \mathrm{mmol}$ ), followed by drop-wise addition of DIEA ( $0.040 \mathrm{~mL}, 0.23 \mathrm{mmol}$ ) at ambient temperature. The reaction was heated at $70^{\circ} \mathrm{C}$ overnight, cooled, and directly purified by reverse-phase chromatography ( 5 to $66 \%$ acetonitrile/water) to yield the final product as white solid ( 25 $\mathrm{mg}, 78 \%$ ). LCMS (apci) $\mathrm{m} / \mathrm{z}=422.0(\mathrm{M}+\mathrm{H})$.

Example 96

[00582] Step A: Preparation of 3-methoxyazetidine 2,2,2-trifluoroacetate. A solution of tert-butyl 3-methoxyazetidine-1-carboxylate ( $270 \mathrm{mg}, 1.44 \mathrm{mmol}$ ) in 1:1 TFA/DCM (1 mL ) was stirred at ambient temperature for 1 hour and concentrated. The crude product was directly used in the next step assuming quantitative yield.
[00583] Step B: Preparation of (R)-(5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)(3-methoxyazetidin-1-yl)methanone. To a DMF ( 0.3 mL ) solution of (R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3carboxylic acid (Preparation I, $30 \mathrm{mg}, 0.092 \mathrm{mmol}$ ) and HATU ( $42 \mathrm{mg}, 0.11 \mathrm{mmol}$ ) was
added 3-methoxyazetidine 2,2,2-trifluoroacetate ( $22 \mathrm{mg}, 0.11 \mathrm{mmol}$ ), followed by dropwise addition of DIEA ( $0.048 \mathrm{~mL}, 0.27 \mathrm{mmol}$ ). After stirring for 30 minutes at ambient temperature, the reaction was directly purified by reverse-phase chromatography ( 5 to $50 \%$ acetonitrile/water) to yield the final product as white solid ( $25 \mathrm{mg}, 69 \%$ ). LCMS (apci) m/z $=397.1(\mathrm{M}+\mathrm{H})$.

## Example 97



## N-(3-chloro-2-fluoropropyl)-5-((R)-2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide

[00584] To a DMF ( 0.3 mL ) solution of (R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (Preparation I, $30 \mathrm{mg}, 0.092 \mathrm{mmol}$ ) and HATU ( $42 \mathrm{mg}, 0.11 \mathrm{mmol}$ ) was added 3-fluoroazetidine hydrochloride ( $12 \mathrm{mg}, 0.11 \mathrm{mmol}$ ), followed by DIEA ( $0.048 \mathrm{ml}, 0.27 \mathrm{mmol}$ ) at ambient temperature. After stirring for 2 hours, the reaction was directly purified by reverse-phase chromatography (5 to 58\% acetonitrile/water) to yield the product as white solid ( $8.8 \mathrm{mg}, 23 \%$ ). The isolated product was presumed to result from ring-opening of the azetidine starting material. LCMS (apci) $\mathrm{m} / \mathrm{z}=421.0(\mathrm{M}+\mathrm{H})$.

## Example 98


(R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-
(trifluoromethyl)cyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide
[00585]
Step A: Preparation of tert-butyl 1-(trifluoromethyl)cyclopropylcarbamate. Diphenylphosphoryl azide ( $0.462 \mathrm{~mL}, 2.14 \mathrm{mmol}$ ) was added drop-wise to a stirred mixture of 1-(trifluoromethyl)cyclopropanecarboxylic acid ( $300 \mathrm{mg}, 1.95 \mathrm{mmol}$ ), TEA ( 0.271 mL , 1.95 mmol ) and 4A molecular sieves in anhydrous tert- $\mathrm{BuOH}(4 \mathrm{~mL}$ ) under nitrogen at ambient temperature. The reaction was heated to reflux for 18 hours, then cooled, filtered,
and concentrated, and the residue was taken up in ether ( 20 mL ). The organic layer was washed with saturated $\mathrm{NaHCO}_{3}$ and water ( 20 mL each), dried $\left(\mathrm{Na}_{2} \mathrm{SO}_{4}\right)$, filtered and concentrated, giving the crude product as white solid ( $0.32 \mathrm{~g}, 72 \%$ ). The crude product was used directly in the next step without further purification.
[00586] Step B: Preparation of 1-(trifluoromethyl)cyclopropanamine hydrochloride. A solution of tert-butyl 1-(trifluoromethyl)cyclopropylcarbamate ( $0.3 \mathrm{~g}, 1.3 \mathrm{mmol}$ ) in HCl ( 4 N dioxane, $6.7 \mathrm{~mL}, 27 \mathrm{mmol}$ ) was stirred at ambient temperature overnight. The reaction was then concentrated to yield the crude product as white solid, which was used directly in the next step assuming quantitative yield.
[00587] Step C: Preparation of (R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-(trifluoromethyl)cyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide. To a DMF ( 0.4 mL ) solution of (R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3carboxylic acid (Preparation I, $50 \mathrm{mg}, 0.15 \mathrm{mmol}$ ) and HATU ( $87 \mathrm{mg}, 0.23 \mathrm{mmol}$ ) was charged 1-(trifluoromethyl)cyclopropanamine hydrochloride ( $37 \mathrm{mg}, 0.23 \mathrm{mmol}$ ), followed by drop-wise addition of DIEA ( $0.080 \mathrm{~mL}, 0.46 \mathrm{mmol}$ ). After stirring first at ambient temperature for 15 minutes and then at $85^{\circ} \mathrm{C}$ overnight, the reaction was cooled and directly purified by reverse-phase chromatography ( 5 to $60 \%$ acetonitrile/water) to yield the final product as off-white solid ( $15 \mathrm{mg}, 23 \%$ ). LCMS (apci) $\mathrm{m} / \mathrm{z}=435.0(\mathrm{M}+\mathrm{H})$.
[00588] The compounds listed in Table A were prepared according to the method described in Example 91, 92, 93 or 94, by reacting (R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (Preparation I) with appropriate amine starting materials in the presence of an amide coupling reagent (e.g. HATU, EDCI/HOBt) and an organic base (e.g. DIEA, TEA) in an appropriate solvent (e.g. DMF, DCM).

Table A

| Ex. \# | Structure | Chemical Name | Data |
| :---: | :---: | :---: | :---: |
| 99 |  | 5-((R)-2-(5-fluoropyridin-3- <br> yl)pyrrolidin-1-yl)-N-((trans)-4- <br> hydroxycyclohexyl)pyrazolo[1,5- <br> a]pyrimidine-3-carboxamide | LCMS (apci) <br> $\mathrm{m} / \mathrm{z}=425.1$ <br> $(\mathrm{M}+\mathrm{H})$ |


| Ex. \# | Structure | Chemical Name | Data |
| :---: | :---: | :---: | :---: |
| 100 |  | 5-((R)-2-(5-fluoropyridin-3- <br> yl)pyrrolidin-1-yl)-N-((cis)-4-hydroxycyclohexyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide | $\begin{aligned} & \text { LCMS (apci) } \\ & \mathrm{m} / \mathrm{z}=425.1 \\ & (\mathrm{M}+\mathrm{H}) \end{aligned}$ |
| 101 |  | (R)-N-cyclobutyl-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3carboxamide | $\begin{aligned} & \text { LCMS (apci) } \\ & \mathrm{m} / \mathrm{z}=381.1 \\ & (\mathrm{M}+\mathrm{H}) \end{aligned}$ |
| 102 |  | (R)-5-(2-(5-fluoropyridin-3- <br> yl)pyrrolidin-1-yl)-N-(1-methylcyclobutyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide | $\begin{aligned} & \text { LCMS (apci) } \\ & \mathrm{m} / \mathrm{z}=395.1 \\ & (\mathrm{M}+\mathrm{H}) \end{aligned}$ |
| 103 |  | 5-((R)-2-(5-fluoropyridin-3- <br> yl)pyrrolidin-1-yl)-N-((1S,2S)-2- <br> hydroxycyclopentyl)pyrazolo[1,5- <br> a]pyrimidine-3-carboxamide | $\begin{aligned} & \text { LCMS (apci) } \\ & \mathrm{m} / \mathrm{z}=411.1 \\ & (\mathrm{M}+\mathrm{H}) \end{aligned}$ |
| 104 |  | 5-((R)-2-(5-fluoropyridin-3- <br> yl)pyrrolidin-1-yl)-N-((1S,2R)-2- <br> hydroxycyclopentyl)pyrazolo[1,5- <br> a]pyrimidine-3-carboxamide | $\begin{aligned} & \text { LCMS (apci) } \\ & \mathrm{m} / \mathrm{z}=411.1 \\ & (\mathrm{M}+\mathrm{H}) \end{aligned}$ |
| 105 |  | 5-((R)-2-(5-fluoropyridin-3- <br> yl)pyrrolidin-1-yl)-N-((1S,3S)-3- <br> hydroxycyclopentyl)pyrazolo[1,5- <br> a]pyrimidine-3-carboxamide | $\begin{aligned} & \text { LCMS (apci) } \\ & \mathrm{m} / \mathrm{z}=411.1 \\ & (\mathrm{M}+\mathrm{H}) \end{aligned}$ |
| 106 |  | (R)-N-(cyclopropylmethyl)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3carboxamide | $\begin{aligned} & \text { LCMS (apci) } \\ & \mathrm{m} / \mathrm{z}=381.1 \\ & (\mathrm{M}+\mathrm{H}) \end{aligned}$ |
| 107 |  | (R)-5-(2-(5-fluoropyridin-3- <br> yl)pyrrolidin-1-yl)-N-(1- <br> (hydroxymethyl)cyclopropyl)pyrazolo <br> [1,5-a]pyrimidine-3-carboxamide | $\begin{aligned} & \text { LCMS (apci) } \\ & \mathrm{m} / \mathrm{z}=397.1 \\ & (\mathrm{M}+\mathrm{H}) \end{aligned}$ |


| Ex. \# | Structure | Chemical Name | Data |
| :---: | :---: | :---: | :---: |
| 108 |  | (R)-(5-(2-(5-fluoropyridin-3- <br> yl)pyrrolidin-1-yl)pyrazolo[1,5- <br> a]pyrimidin-3-yl)(3-hydroxyazetidin- <br> 1 -yl)methanone | $\begin{aligned} & \text { LCMS (apci) } \\ & \mathrm{m} / \mathrm{z}=383.1 \\ & (\mathrm{M}+\mathrm{H}) \end{aligned}$ |
| 109 |  | 5-((R)-2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-((S)-2-hydroxypropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide | $\begin{aligned} & \text { LCMS (apci) } \\ & \mathrm{m} / \mathrm{z}=385.1 \\ & (\mathrm{M}+\mathrm{H}) \end{aligned}$ |
| 110 |  | 5-((R)-2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-((R)-2-hydroxypropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide | $\begin{aligned} & \text { LCMS (apci) } \\ & \mathrm{m} / \mathrm{z}=385.1 \\ & (\mathrm{M}+\mathrm{H}) \end{aligned}$ |
| 111 |  | (R)-5-(2-(5-fluoropyridin-3- <br> yl)pyrrolidin-1-yl)-N-(2-hydroxy-2- <br> methylpropyl)pyrazolo[1,5- <br> a]pyrimidine-3-carboxamide | $\begin{aligned} & \text { LCMS (apci) } \\ & \mathrm{m} / \mathrm{z}=399.1 \\ & (\mathrm{M}+\mathrm{H}) \end{aligned}$ |
| 112 |  | (R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(2-hydroxyethyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide | $\begin{aligned} & \text { LCMS (apci) } \\ & \mathrm{m} / \mathrm{z}=371.1 \\ & (\mathrm{M}+\mathrm{H}) \end{aligned}$ |
| 113 |  | N-(1-cyclopropylethyl)-5-((R)-2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3carboxamide | $\begin{aligned} & \text { LCMS (apci) } \\ & \mathrm{m} / \mathrm{z}=395.1 \\ & (\mathrm{M}+\mathrm{H}) \end{aligned}$ |
| 114 |  | (R)-5-(2-(5-fluoropyridin-3- <br> yl)pyrrolidin-1-yl)-N- <br> methylpyrazolo[1,5-a]pyrimidine-3- <br> carboxamide | $\begin{aligned} & \text { LCMS (apci) } \\ & \mathrm{m} / \mathrm{z}=341.1 \\ & (\mathrm{M}+\mathrm{H}) \end{aligned}$ |
| 115 |  | 5-((R)-2-(5-fluoropyridin-3- <br> yl)pyrrolidin-1-yl)-N-((R)-1- <br> hydroxypropan-2-yl)pyrazolo[1,5- <br> a]pyrimidine-3-carboxamide | $\begin{aligned} & \text { LCMS (apci) } \\ & \mathrm{m} / \mathrm{z}=385.1 \\ & (\mathrm{M}+\mathrm{H}) \end{aligned}$ |


| Ex. \# |  | Data |
| :--- | :--- | :--- | :--- | :--- |


| Ex. \# | Structure | Chemical Name | Data |
| :---: | :---: | :---: | :---: |
| 124 |  | N-((S)-1-cyclopropylethyl)-5-((R)-2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3carboxamide | $\begin{aligned} & \text { LCMS (apci) } \\ & \mathrm{m} / \mathrm{z}=395.1 \\ & (\mathrm{M}+\mathrm{H}) \end{aligned}$ |
| 125 |  | (R)-5-(2-(5-fluoropyridin-3- <br> yl)pyrrolidin-1-yl)-N-(3-hydroxy-2,2- <br> dimethylpropyl)pyrazolo[1,5- <br> a]pyrimidine-3-carboxamide | $\begin{aligned} & \text { LCMS (apci) } \\ & \mathrm{m} / \mathrm{z}=413.1 \\ & (\mathrm{M}+\mathrm{H}) \end{aligned}$ |
| 126 |  | (R)-azetidin-1-yl(5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3yl)methanone | $\begin{aligned} & \text { LCMS (apci) } \\ & \mathrm{m} / \mathrm{z}=367.1 \\ & (\mathrm{M}+\mathrm{H}) \end{aligned}$ |
| 127 |  | (R)-(5-(2-(5-fluoropyridin-3- <br> yl)pyrrolidin-1-yl)pyrazolo[1,5- <br> a]pyrimidin-3-yl)(3- <br> (hydroxymethyl)azetidin-1- <br> yl)methanone | $\begin{aligned} & \text { LCMS (apci) } \\ & \mathrm{m} / \mathrm{z}=397.1 \\ & (\mathrm{M}+\mathrm{H}) \end{aligned}$ |
| 128 |  | (5-((R)-2-(5-fluoropyridin-3- <br> yl)pyrrolidin-1-yl)pyrazolo[1,5- <br> a]pyrimidin-3-yl)((S)-3- <br> hydroxypyrrolidin-1-yl)methanone | $\begin{aligned} & \text { LCMS (apci) } \\ & \mathrm{m} / \mathrm{z}=397.1 \\ & (\mathrm{M}+\mathrm{H}) \end{aligned}$ |
| 129 |  | 5-((R)-2-(5-fluoropyridin-3- <br> yl)pyrrolidin-1-yl)-N-((R)-1,1,1- <br> trifluoropropan-2-yl)pyrazolo[1,5- <br> a]pyrimidine-3-carboxamide | $\begin{aligned} & \text { LCMS (apci) } \\ & \mathrm{m} / \mathrm{z}=423.0 \\ & (\mathrm{M}+\mathrm{H}) \end{aligned}$ |
| 130 |  | 5-((R)-2-(5-fluoropyridin-3- <br> yl)pyrrolidin-1-yl)-N-((S)-1,1,1- <br> trifluoropropan-2-yl)pyrazolo[1,5- <br> a]pyrimidine-3-carboxamide | $\begin{aligned} & \text { LCMS (apci) } \\ & \mathrm{m} / \mathrm{z}=423.0 \\ & (\mathrm{M}+\mathrm{H}) \end{aligned}$ |


| Ex. \# | Structure | Chemical Name | Data |
| :---: | :---: | :---: | :---: |
| 131 |  | (R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(2,2,2-trifluoroethyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide | $\begin{aligned} & \text { LCMS (apci) } \\ & \mathrm{m} / \mathrm{z}=409.0 \\ & (\mathrm{M}+\mathrm{H}) \end{aligned}$ |
| 132 |  | (R)-5-(2-(5-fluoropyridin-3- <br> yl)pyrrolidin-1-yl)-N-(1-hydroxy-2- <br> methylpropan-2-yl)pyrazolo[1,5- <br> a]pyrimidine-3-carboxamide | $\begin{aligned} & \text { LCMS (apci) } \\ & \mathrm{m} / \mathrm{z}=399.1 \\ & (\mathrm{M}+\mathrm{H}) \end{aligned}$ |
| 133 |  | 5-((R)-2-(5-fluoropyridin-3- <br> yl)pyrrolidin-1-yl)-N-((1R,2R)-2- <br> hydroxycyclopentyl)pyrazolo[1,5- <br> a]pyrimidine-3-carboxamide | $\begin{aligned} & \text { LCMS (apci) } \\ & \mathrm{m} / \mathrm{z}=411.1 \\ & (\mathrm{M}+\mathrm{H}) \end{aligned}$ |
| 134 |  | (R)-N-(2,2-difluoroethyl)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3carboxamide | $\begin{aligned} & \text { LCMS (apci) } \\ & \mathrm{m} / \mathrm{z}=391.0 \\ & (\mathrm{M}+\mathrm{H}) \end{aligned}$ |
| 135 |  | 5-((R)-2-(5-fluoropyridin-3- <br> yl)pyrrolidin-1-yl)-N-((1R,2S)-2- <br> hydroxycyclopentyl)pyrazolo[1,5- <br> a]pyrimidine-3-carboxamide | $\begin{aligned} & \text { LCMS (apci) } \\ & \mathrm{m} / \mathrm{z}=411.1 \\ & (\mathrm{M}+\mathrm{H}) \end{aligned}$ |
| 136 |  | 5-((R)-2-(5-fluoropyridin-3- <br> yl)pyrrolidin-1-yl)-N-((1R,2R)-2- <br> hydroxycyclohexyl)pyrazolo[1,5- <br> a]pyrimidine-3-carboxamide | $\begin{aligned} & \text { LCMS (apci) } \\ & \mathrm{m} / \mathrm{z}=425.1 \\ & (\mathrm{M}+\mathrm{H}) \end{aligned}$ |
| 137 |  | (R)-(5-(2-(5-fluoropyridin-3- <br> yl)pyrrolidin-1-yl)pyrazolo[1,5- <br> a]pyrimidin-3-yl)(piperidin-1- <br> yl)methanone | $\begin{aligned} & \text { LCMS (apci) } \\ & m / z=395.1 \\ & (\mathrm{M}+\mathrm{H}) \end{aligned}$ |
| 138 |  | 5-((R)-2-(5-fluoropyridin-3- <br> yl)pyrrolidin-1-yl)-N-((2R,3S,4S)-3-(hydroxymethyl)bicyclo[2.2.1]heptan2 -yl)pyrazolo[1,5-a]pyrimidine-3carboxamide | $\begin{aligned} & \text { LCMS (apci) } \\ & \mathrm{m} / \mathrm{z}=451.2 \\ & (\mathrm{M}+\mathrm{H}) \end{aligned}$ |

## Example 139


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

3-yl)(3-hydroxyazetidin-1-yl)methanone
[00589] To a DMF ( 0.4 mL ) solution of (R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (Preparation K, $30 \mathrm{mg}, 0.084$ mmol ) was added HATU ( $38 \mathrm{mg}, 0.10 \mathrm{mmol}$ ) and azetidin-3-ol hydrochloride ( $11 \mathrm{mg}, 0.10$ mmol ) at ambient temperature, followed by dropwise addition of DIEA ( $0.044 \mathrm{ml}, 0.25$ mmol ) at $0^{\circ} \mathrm{C}$. After stirring for 20 minutes at ambient temperature, the reaction was directly purified by reverse-phase chromatography ( 5 to $50 \%$ acetonitrile/water) to yield the final product as white solid ( $26 \mathrm{mg}, 75 \%$ ). LCMS (apci) $\mathrm{m} / \mathrm{z}=413.1(\mathrm{M}+\mathrm{H})$.

Example 140


5-((R)-2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-((trans)-4-
hydroxycyclohexyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide
[00590] To a solution of (R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1yl)pyrazolo [1,5-a]pyrimidine-3-carboxylic acid (Preparation K, $30 \mathrm{mg}, 0.084 \mathrm{mmol}$ ) in anhydrous $\mathrm{CH}_{2} \mathrm{Cl}_{2}(2 \mathrm{~mL})$ was added $\mathrm{HOBt}(34 \mathrm{mg}, 0.25 \mathrm{mmol})$ followed by EDCI ( 48 mg , 0.25 mmol ). The solution was stirred for 30 minutes, then treated with (trans)-4aminocyclohexanol ( $29 \mathrm{mg}, 0.25 \mathrm{mmol}$ ) followed by triethylamine ( $35 \mu \mathrm{~L}, 0.25 \mathrm{mmol}$ ). After stirring at ambient temperature for 5 hours, the reaction mixture was diluted with EtOAc, washed with saturated $\mathrm{NH}_{4} \mathrm{Cl}(20 \mathrm{~mL})$, saturated $\mathrm{NaHCO}_{3}$, and brine, then dried $\left(\mathrm{Na}_{2} \mathrm{SO}_{4}\right)$, filtered and concentrated. The crude material was purified by silica chromatography $\left(4 \% \mathrm{MeOH} / \mathrm{CH}_{2} \mathrm{Cl}_{2}\right)$ to yield the final product as white solid ( $23 \mathrm{mg}, 60 \%$ ). LCMS (apci) m/z $=455.1(\mathrm{M}+\mathrm{H})$.

## Example 141


(R)-tert-butyl 3-(5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamido)propylcarbamate
[00591] To a mixture of (R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (Preparation K, $200 \mathrm{mg}, 0.560 \mathrm{mmol}$ ) and HATU ( $255 \mathrm{mg}, 0.672 \mathrm{mmol}$ ) in DMF ( 2 mL ) was added DIEA ( $292 \mu \mathrm{~L}, 1.68 \mathrm{mmol}$ ), followed by dropwise addition of tert-butyl 3-aminopropylcarbamate ( $117 \mathrm{mg}, 0.672 \mathrm{mmol}$ ) at ambient temperature. After stirring for 3 hours, the reaction was directly purified by reverse-phase chromatography ( 5 to $70 \%$ acetonitrile/water) to yield the final product as white solid ( $250 \mathrm{mg}, 87 \%$ ). LCMS (apci) $\mathrm{m} / \mathrm{z}=414.1$ ( $\mathrm{M}+\mathrm{H}-\mathrm{Boc}$ ).

## Example 142



## (R)-N-(3-aminopropyl)-5-(2-(5-fluoro-2-oxo-1,2-dihydropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide

[00592] A mixture of (R)-tert-butyl 3-(5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamido)propylcarbamate (Example 141, $70 \mathrm{mg}, 0.14 \mathrm{mmol})$ and $\mathrm{HCl}(4 \mathrm{~N}$ dioxane, $1.7 \mathrm{~mL}, 6.8 \mathrm{mmol})$ in a pressure reaction tube was heated at $85^{\circ} \mathrm{C}$ for 12 hours then concentrated under reduced pressure. The crude material was purified by reverse-phase chromatography ( 5 to $40 \%$ acetonitrile/water) to yield the final product as white solid. LCMS (apci) $\mathrm{m} / \mathrm{z}=400.1(\mathrm{M}+\mathrm{H})$.

## Example 143



## N-((S)-2,3-dihydroxypropyl)-5-((R)-2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide

[00593] Step A: Preparation of N -(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-5-((R)-2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3carboxamide. Prepared according to the method described in Example 140, replacing (trans)-4-aminocyclohexanol with (S)-(2,2-dimethyl-1,3-dioxolan-4-yl)methanamine. LCMS (apci) $\mathrm{m} / \mathrm{z}=471.0(\mathrm{M}+\mathrm{H}-\mathrm{Boc})$.
[00594] Step B: Preparation of N -((S)-2,3-dihydroxypropyl)-5-((R)-2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide. To a solution of N -(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-5-((R)-2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (36 mg, $0.077 \mathrm{mmol})$ in THF ( 2 mL ) was added $\mathrm{HCl}(3 \mathrm{~N} \mathrm{aq)}$. ) at ambient temperature. The resulting mixture was stirred for 5 hours. The reaction was diluted with EtOAc, washed with saturated $\mathrm{NH}_{4} \mathrm{Cl}$ and brine, then dried $\left(\mathrm{MgSO}_{4}\right)$, filtered and concentrated. The crude material was rinsed with ether to yield the final product as white solid ( $30 \mathrm{mg}, 91 \%$ ). LCMS (apci) $\mathrm{m} / \mathrm{z}=$ $431.1(\mathrm{M}+\mathrm{H})$.

## Example 144



N-((S)-3-chloro-2-hydroxypropyl)-5-((R)-2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide
[00595] Step A: Preparation of (S)-1-amino-3-chloropropan-2-ol hydrochloride. To a solution of benzaldehyde ( $4.50 \mathrm{~g}, 42.4 \mathrm{mmol}$ ) in $\mathrm{EtOH}(12 \mathrm{~mL})$ was added aqueous ammonia $(4.01 \mathrm{~g}, 65.9 \mathrm{mmol})$ in several portions. After stirring for 10 minutes, ( S )-2(chloromethyl)oxirane ( $3.81 \mathrm{~g}, 41.2 \mathrm{mmol}$ ) was added and the reaction mixture was stirred for 2 hours at ambient temperature. The reaction mixture was then heated at $35-40^{\circ} \mathrm{C}$ with a heating mantle for 6 hours, followed by stirring at ambient temperature for 18 hours. The reaction was concentrated to 5 mL and toluene ( 5 mL ) was added. The mixture was heated to $36^{\circ} \mathrm{C}$ and a solution of concentrated $\mathrm{HCl}(6.09 \mathrm{~g}, 61.8 \mathrm{mmol})$ and water $(5.9 \mathrm{~mL})$ was added slowly over 5 minutes to maintain an internal reaction temperature range of $36-41^{\circ} \mathrm{C}$. The biphasic mixture was heated at $42-45^{\circ} \mathrm{C}$ for 3 hours. The organic phase was separated and
washed with water ( 10 mL ). The aqueous phases were combined and ethanol ( 10 mL ) was added. The mixture was concentrated to 10 mL , and ethanol ( $6 \times 10 \mathrm{~mL}$ ) was added, concentrating after each addition. After the last concentration step, the slurry was warmed to reflux, cooled to ambient temperature, and then placed at $-20^{\circ} \mathrm{C}$ for 18 hours. The product was collected by vacuum filtration, washed with cold ethanol, and vacuum-dried, to provide the product as white solid ( $3.58 \mathrm{~g}, 60 \%$ yield).
[00596] Step B: Preparation of N-((S)-3-chloro-2-hydroxypropyl)-5-((R)-2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide. Prepared by the method described in Example 139, replacing azetidin-3-ol hydrochloride with (S)-1-amino-3-chloropropan-2-ol hydrochloride. LCMS (apci) m/z $=449.0(\mathrm{M}+\mathrm{H})$

## Example 145



N-((R)-3-chloro-2-hydroxypropyl)-5-((R)-2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide
[00597] Step A: Preparation of (R)-1-amino-3-chloropropan-2-ol hydrochloride. Prepared by the method described in Example 144, Step A, replacing (S)-2(chloromethyl)oxirane with (R)-2-(chloromethyl)oxirane.
[00598] Step B: Preparation of N-((R)-3-chloro-2-hydroxypropyl)-5-((R)-2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide. Prepared by the method described in Example 139, replacing azetidin-3-ol hydrochloride with (R)-1-amino-3-chloropropan-2-ol hydrochloride. LCMS (apci) m/z $=449.0(\mathrm{M}+\mathrm{H})$


## (R)-N-(2-chloroethoxy)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide

[00599] Step A: Preparation of 2-(2-chloroethoxy)isoindoline-1,3-dione. A 1 L round-bottomed flask was charged 2-hydroxyisoindoline-1,3-dione ( $16.6 \mathrm{~g}, 98.71 \mathrm{mmol}$ ), followed by DMF ( 100 mL ), then 1-bromo-2-chloroethane ( $25.2 \mathrm{~mL}, 296.1 \mathrm{mmol}$ ), and then
triethylamine ( $42.1 \mathrm{~mL}, 296.1 \mathrm{mmol}$ ). After stirring at ambient temperature overnight, the reaction mixture was filtered $(\mathrm{GF} / \mathrm{F})$ and rinsed with DMF . The filtrate $(250 \mathrm{~mL})$ was poured into ice-water ( 2 L ) while stirring, and the resulting precipitate was filtered, rinsed with water, and dried, yielding the crude product as a white solid ( 21 g ). The crude product was triturated with heptane $(3 \times 400 \mathrm{~mL})$, filtered and air-dried, giving the product as white solid (17.6 g, 79\%).
[00600] Step B: Preparation of O-(2-chloroethyl)hydroxylamine hydrochloride. A 1 L three-necked round-bottomed flask was charged $\mathrm{HCl}(6 \mathrm{M}$ aq., $295 \mathrm{~mL}, 1773 \mathrm{mmol}$ ), followed by 2-(2-chloroethoxy)isoindoline-1,3-dione ( $10 \mathrm{~g}, 44.3 \mathrm{mmol}$ ) with stirring. A water condenser was attached and the reaction was refluxed at $100^{\circ} \mathrm{C}$ for 2 hours, then stirred at ambient temperature overnight. The reaction mixture was filtered. Absolute EtOH was added to the filtrate and filtrate was concentrated. The crude material was triturated from hot EtOH to yield the first crop of product as white solid $(2.2 \mathrm{~g})$. The mother liquor was concentrated and triturated as described, yielding a second crop of product (1.7) g.
[00601] Step C: Preparation of (R)-N-(2-chloroethoxy)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide. Prepared by the method described in Example 139, replacing azetidin-3-ol hydrochloride with O-(2chloroethyl)hydroxylamine hydrochloride. LCMS (apci) m/z=434.9(M+H)
[00602] The compounds listed in Table B were prepared according to the method described in Example 139 or Example 140, by reacting (R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (Preparation K) with an appropriate amine starting material in the presence of an amide coupling reagent (e.g. HATU, EDCI/HOBt) and an organic base (e.g. DIEA, TEA) in an appropriate solvent (e.g. DMF, DCM).

Table B

| Ex. \# | Structure | Chemical Name | Data |
| :---: | :---: | :--- | :--- |
| 147 |  | (R)-(5-(2-(5-fluoro-2- <br> methoxypyridin-3-yl)pyrrolidin-1- <br> yl)pyrazolo[1,5-a]pyrimidin-3- <br> yl)(3-hydroxy-3-methylazetidin-1- <br> yl)methanone | LCMS (apci) <br> $\mathrm{m} / \mathrm{z}=427.1$ <br> $(\mathrm{M}+\mathrm{H})$ |

142

| Ex. \# | Structure | Chemical Name | Data |
| :---: | :---: | :---: | :---: |
| 148 |  | (R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-(3- <br> hydroxypropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide | $\begin{aligned} & \text { LCMS (apci) } \\ & \mathrm{m} / \mathrm{z}=415.1 \\ & (\mathrm{M}+\mathrm{H}) \end{aligned}$ |
| 149 |  | N-(2,3-dihydroxypropyl)-5-((R)-2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide | $\begin{aligned} & \text { LCMS (apci) } \\ & \mathrm{m} / \mathrm{z}=431.1 \\ & (\mathrm{M}+\mathrm{H}) \end{aligned}$ |
| 150 |  | N-((R)-2,3-dihydroxypropyl)-5- <br> ((R)-2-(5-fluoro-2-methoxypyridin- <br> 3-yl)pyrrolidin-1-yl)pyrazolo[1,5- <br> a]pyrimidine-3-carboxamide | $\begin{aligned} & \text { LCMS (apci) } \\ & \mathrm{m} / \mathrm{z}=431.0 \\ & (\mathrm{M}+\mathrm{H}) \end{aligned}$ |
| 151 |  | (R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-(4- <br> hydroxybutyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide | $\begin{aligned} & \text { LCMS (apci) } \\ & \mathrm{m} / \mathrm{z}=429.1 \\ & (\mathrm{M}+\mathrm{H}) \end{aligned}$ |
| 152 |  | (R)-N-(2-tert-butoxyethoxy)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide | $\begin{aligned} & \text { LCMS (apci) } \\ & \mathrm{m} / \mathrm{z}=473.0 \\ & (\mathrm{M}+\mathrm{H}) \end{aligned}$ |
| 153 |  | (R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-methylpyrazolo[1,5-a]pyrimidine-3-carboxamide | $\begin{aligned} & \mathrm{MS}(\mathrm{apci}) \mathrm{m} / \mathrm{z}= \\ & 371.1(\mathrm{M}+\mathrm{H}) \end{aligned}$ |
| 154 |  | 5-((R)-2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-((1S,3S)-3- <br> hydroxycyclopentyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide | $\begin{aligned} & \text { MS (apci) } \mathrm{m} / \mathrm{z}= \\ & 441.1(\mathrm{M}+\mathrm{H}) \end{aligned}$ |
| 155 |  | (R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-(2- <br> hydroxyethyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide | $\begin{aligned} & \mathrm{MS}(\mathrm{apci}) \mathrm{m} / \mathrm{z}= \\ & 401.1(\mathrm{M}+\mathrm{H}) \end{aligned}$ |

143
Ex.\#

| Ex. \# | Structure | Chemical Name | Data |
| :---: | :---: | :--- | :--- |
| 164 |  | (R)-N-(2-bromoethoxy)-5-(2-(5- <br> fluoro-2-methoxypyridin-3- <br> yl)pyrrolidin-1-yl)pyrazolo[1,5- <br> a]pyrimidine-3-carboxamide | LCMS (apci) <br> $\mathrm{m} / \mathrm{z}=479.0$ <br> $(\mathrm{M}+\mathrm{H})$ |

[00603] The compounds listed Table C were prepared by the method described in Examples 1, 139 or 140, by reacting (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (Preparation C) with an appropriate amine starting material in the presence of an amide coupling reagent (e.g. HATU, EDCI/HOBt) and an organic base (e.g. DIEA, TEA) in an appropriate solvent (e.g. DMF, DCM).

## Table C

| Ex. \# | Structure | Chemical Name | Data |
| :---: | :---: | :---: | :---: |
| 165 |  | 5-(2-(2,5-difluorophenyl)pyrrolidin- <br> 1-yl)-N-(2- <br> hydroxyethyl)pyrazolo[1,5- <br> a]pyrimidine-3-carboxamide | $\begin{aligned} & \text { LCMS (apci) } \\ & \mathrm{m} / \mathrm{z}=388.1 \\ & (\mathrm{M}+\mathrm{H}) \end{aligned}$ |
| 166 |  | 5-((R)-2-(2,5- <br> difluorophenyl)pyrrolidin-1-yl)-N-(2- <br> hydroxypropyl)pyrazolo[1,5- <br> a]pyrimidine-3-carboxamide | $\begin{aligned} & \text { LCMS (apci) } \\ & \mathrm{m} / \mathrm{z}=402.1 \\ & (\mathrm{M}+\mathrm{H}) \end{aligned}$ |
| 167 |  | 5-((R)-2-(2,5- <br> difluorophenyl)pyrrolidin-1-yl)-N-(2- <br> hydroxypropyl)pyrazolo[1,5- <br> a]pyrimidine-3-carboxamide | $\begin{aligned} & \text { LCMS (apci) } \\ & \mathrm{m} / \mathrm{z}=402.1 \\ & (\mathrm{M}+\mathrm{H}) \end{aligned}$ |
| 168 |  | 5-((R)-2-(2,5- <br> difluorophenyl)pyrrolidin-1-yl)-N-(3- <br> hydroxy-2,2- <br> dimethylpropyl)pyrazolo[ $1,5-$ <br> a]pyrimidine-3-carboxamide | $\begin{aligned} & \operatorname{LCMS}(\text { apci }) \\ & \mathrm{m} / \mathrm{z}=430.2 \\ & (\mathrm{M}+\mathrm{H}) \end{aligned}$ |
| 169 |  | 5-((R)-2-(2,5- <br> difluorophenyl)pyrrolidin-1-yl)-N((1S, 3S)-3- <br> hydroxycyclopentyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide | $\begin{aligned} & \text { LCMS (apci) } \\ & \mathrm{m} / \mathrm{z}=428.1 \\ & (\mathrm{M}+\mathrm{H}) \end{aligned}$ |


| Ex. \# | Structure | Chemical Name | Data |
| :---: | :---: | :---: | :---: |
| 170 |  | 5-((R)-2-(2,5- <br> difluorophenyl)pyrrolidin-1-yl)-N-(2- <br> (4-hydroxypiperidin-1- <br> yl)ethyl)pyrazolo[1,5-a]pyrimidine-3carboxamide | $\begin{aligned} & \text { LCMS (apci) } \\ & \mathrm{m} / \mathrm{z}=471.2 \\ & (\mathrm{M}+\mathrm{H}) \end{aligned}$ |
| 171 |  | 5-((R)-2-(2,5- <br> difluorophenyl)pyrrolidin-1-yl)-N-(2- <br> (4-methylpiperazin-1- <br> yl)ethyl)pyrazolo[1,5-a]pyrimidine-3- <br> carboxamide | LCMS (apci) <br> $\mathrm{m} / \mathrm{z}=470.2$ <br> (M+H) |
| 172 |  | 5-((R)-2-(2,5- <br> difluorophenyl)pyrrolidin-1-yl)-N-(2- <br> methoxyethyl)pyrazolo[1,5- <br> a]pyrimidine-3-carboxamide | $\begin{gathered} \text { LCMS (apci) } \\ \mathrm{m} / \mathrm{z}=402.1 \\ (\mathrm{M}+\mathrm{H}) \end{gathered}$ |
| 173 |  | $\begin{aligned} & \text { 5-((R)-2-(2,5- } \\ & \text { difluorophenyl)pyrrolidin-1-yl)-N- } \\ & \text { (1,3-dihydroxypropan-2- } \\ & \text { yl)pyrazolo[1,5-a]pyrimidine-3- } \\ & \text { carboxamide } \end{aligned}$ | $\begin{gathered} \text { LCMS (apci) } \\ \mathrm{m} / \mathrm{z}=418.1 \\ (\mathrm{M}+\mathrm{H}) \end{gathered}$ |
| 174 |  | 5-((R)-2-(2,5- <br> difluorophenyl)pyrrolidin-1-yl)-N-((2S,3R)-1,3-dihydroxybutan-2-yl)pyrazolo[1,5-a]pyrimidine-3carboxamide | $\begin{gathered} \text { LCMS (apci) } \\ \mathrm{m} / \mathrm{z}=432.1 \\ (\mathrm{M}+\mathrm{H}) \end{gathered}$ |
| 175 |  | 5-((R)-2-(2,5- <br> difluorophenyl)pyrrolidin-1-yl)-N-((2S,3S)-1,3-dihydroxybutan-2-yl)pyrazolo[1,5-a]pyrimidine-3carboxamide | $\begin{gathered} \text { LCMS (apci) } \\ \mathrm{m} / \mathrm{z}=432.1 \\ (\mathrm{M}+\mathrm{H}) \end{gathered}$ |
| 176 |  | $5-((\mathrm{R})-2-(2,5-$ <br> difluorophenyl)pyrrolidin-1-yl)-N-((2R,3S)-1,3-dihydroxybutan-2-yl)pyrazolo[1,5-a]pyrimidine-3carboxamide | $\begin{gathered} \text { LCMS (apci) } \\ \mathrm{m} / \mathrm{z}=432.1 \\ (\mathrm{M}+\mathrm{H}) \end{gathered}$ |
| 177 |  | 5-((R)-2-(2,5- <br> difluorophenyl)pyrrolidin-1-yl)-N- <br> ((S)-1-hydroxypropan-2- <br> yl)pyrazolo[1,5-a]pyrimidine-3carboxamide | $\begin{gathered} \text { LCMS (apci) } \\ \mathrm{m} / \mathrm{z}=402.1 \\ (\mathrm{M}+\mathrm{H}) \end{gathered}$ |


| Ex. \# | Structure | Chemical Name | Data |
| :---: | :---: | :---: | :---: |
| 178 |  | $\begin{aligned} & \text { 5-((R)-2-(2,5- } \\ & \text { difluorophenyl)pyrrolidin-1-yl)-N- } \\ & \text { ((S)-1-hydroxybutan-2- } \\ & \text { yl)pyrazolo[1,5-a]pyrimidine-3- } \\ & \text { carboxamide } \end{aligned}$ | $\begin{gathered} \text { LCMS (apci) } \\ \mathrm{m} / \mathrm{z}=416.1 \\ (\mathrm{M}+\mathrm{H}) \end{gathered}$ |
| 179 |  | 5-((R)-2-(2,5- <br> difluorophenyl)pyrrolidin-1-yl)-N-((S)-1-hydroxy-3-methylbutan-2-yl)pyrazolo[1,5-a]pyrimidine-3carboxamide | $\begin{gathered} \text { LCMS (apci) } \\ \mathrm{m} / \mathrm{z}=430.1 \\ (\mathrm{M}+\mathrm{H}) \end{gathered}$ |
| 180 |  | 5-((R)-2-(2,5- <br> difluorophenyl)pyrrolidin-1-yl)-N-((S)-1-hydroxy-3,3-dimethylbutan-2-yl)pyrazolo[1,5-a]pyrimidine-3carboxamide | $\begin{gathered} \text { LCMS (apci) } \\ \mathrm{m} / \mathrm{z}=444.2 \\ (\mathrm{M}+\mathrm{H}) \end{gathered}$ |

## Example 181



N-cyclopropyl-5-(2-(5-fluoro-2-methylpyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide
[00604] To a solution of (R)-5-(2-(5-fluoro-2-methylpyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (Preparation O, $50 \mathrm{mg}, 0.15 \mathrm{mmol}$ ) in DCM $(2 \mathrm{~mL})$ was added HOBt ( $40 \mathrm{mg}, 0.29 \mathrm{mmol}$ ) followed by EDCI ( $84 \mathrm{mg}, 0.44 \mathrm{mmol}$ ). The solution was stirred at ambient temperature for 15 minutes, then treated with triethylamine ( $61 \mu \mathrm{~L}, 0.44 \mathrm{mmol}$ ) followed by cyclopropylamine ( $31 \mu \mathrm{~L}, 0.44 \mathrm{mmol}$ ). After stirring for 16 hours the mixture was partitioned between saturated $\mathrm{NH}_{4} \mathrm{Cl}$ solution ( 20 mL ) and DCM (20 $\mathrm{mL})$ and the aqueous layer was extracted with DCM $(2 \times 10 \mathrm{~mL})$. The combined organic phases were washed with brine ( 10 mL ), dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and concentrated. The residue was purified by silica gel column chromatography, eluting with $2-4 \% \mathrm{MeOH} / \mathrm{DCM}$, to afford the title product as white solid ( $44 \mathrm{mg}, 79 \%$ ). MS (apci) $\mathrm{m} / \mathrm{z}=381.1(\mathrm{M}+\mathrm{H})$.

## Example 182



N-cyclopropyl-5-(2-(2-ethyl-5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-

## 3-carboxamide

[00605] Prepared according to the method of Example 181, substituting (R)-5-(2-(5-fluoro-2-methylpyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid with (R)-5-(2-(2-ethyl-5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3carboxylic acid (Preparation Q). MS (apci) m/z $=395.1(\mathrm{M}+\mathrm{H})$.
[00606] The compounds listed in Table D were prepared by the method described in Example 181 or 182, by reacting (R)-5-(2-(5-fluoro-2-methylpyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (Preparation O) or (R)-5-(2-(2-ethyl-5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (Preparation Q) with an appropriate amine starting material in the presence of an amide coupling reagent (e.g. $\mathrm{EDCI} / \mathrm{HOBt}$ ) and an organic base (e.g. TEA) in an appropriate solvent (e.g. DCM).

Table D
Ex. \#

148
Ex. \#

149
Ex. \#

## Example 202


(R)-N-tert-butyl-5-(2-(5-fluoro-2-oxo-1,2-dihydropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide.
[00607] A pressure flask was charged with (R)-N-tert-butyl-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (Example 80, $10 \mathrm{mg}, 0.024 \mathrm{mmol})$, dioxane ( 0.7 mL ) and $2 \mathrm{M} \mathrm{HCl}(0.100 \mathrm{~mL}, 0.200 \mathrm{mmol})$. The flask was sealed and the reaction mixture was stirred at $80^{\circ} \mathrm{C}$ for 5 days. The mixture was cooled to ambient temperature and concentrated. The residue was purified by reverse-phase column chromatography ( $0-50 \%$ acetonitrile/water) to afford the title compound ( $8.2 \mathrm{mg}, 85 \%$ ). MS (apci) $\mathrm{m} / \mathrm{z}=399.1(\mathrm{M}+\mathrm{H})$.

## Example 203


(R)-N-(2-chloroethyl)-5-(2-(5-fluoro-2-oxo-1,2-dihydropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide
[00608] Prepared by the method described in Example 202, replacing (R)-N-tert-butyl-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-
carboxamide with (R)-N-(2-chloroethyl)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (Example 163, $100 \mathrm{mg}, 0.239 \mathrm{mmol}$ ), replacing 2 M HCl with 4 M HCl dioxane solution, and reaction was conducted at $100{ }^{\circ} \mathrm{C}$ for 90 minutes. LCMS (apci) m/z $=405.0(\mathrm{M}+\mathrm{H})$.

## Example 204



N-cyclopropyl-5-((2R)-2-(2-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)-5-
fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide
[00609] Step A: Preparation of ethyl 5-((2R)-2-(2-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylate. A mixture of (R)-ethyl 5-(2-(5-fluoro-2-hydroxyphenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylate (Example 86, Step C, $140 \mathrm{mg}, 0.378 \mathrm{mmol}$ ), 4-(chloromethyl)-2,2-dimethyl-1,3-dioxolane ( $114 \mathrm{mg}, 0.756 \mathrm{mmol}$ ), potassium carbonate ( $261 \mathrm{mg}, 1.89$ mmol ) and sodium bromide ( $77.8 \mathrm{mg}, 0.756 \mathrm{mmol}$ ) in dry DMF ( 5 mL ) was heated at $100^{\circ} \mathrm{C}$ for 14 days. The mixture was concentrated and the residue purified by chromatography to afford the title compound ( $45 \mathrm{mg}, 25 \%$ yield). MS (apci) $\mathrm{m} / \mathrm{z}=485.0(\mathrm{M}+\mathrm{H})$.
[00610] Step B: Preparation of 5-((2R)-2-(2-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid. The compound was prepared according to the method of Example 86, Step E, using ethyl 5-((2R)-2-(2-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylate ( $47 \mathrm{mg}, 100 \%$ ). MS (apci) m/z $=457.0(\mathrm{M}+\mathrm{H})$.
[00611] Step C: Preparation of N-cyclopropyl-5-((2R)-2-(2-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3carboxamide. Prepared according to the method of Example 86, Step F, using 5-((2R)-2-(2-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid and cyclopropyl amine to yield the title compound as a white solid ( $33.0 \mathrm{mg}, 99 \%$ yield.). MS (apci) m/z $=496.1(\mathrm{M}+\mathrm{H})$.

## Example 205



## 5-((2R)-2-(2-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide

[00612] Prepared according to the procedure described in Example 204 using ammonium chloride in place of cyclopropyl amine in Step C (white solid, $13 \mathrm{mg}, 85 \%$ yield.). MS (apci) $\mathrm{m} / \mathrm{z}=456.0(\mathrm{M}+\mathrm{H})$.

## Example 206



N-cyclopropyl-5-((2R)-2-(3-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)-5-
fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide
[00613] Prepared according to the method of Example 204 using (R)-ethyl 5-(2-(3-fluoro-5-hydroxyphenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylate (Example 76 , Step C) in Step A ( $36 \mathrm{mg}, 82 \%$ yield). MS (apci) m/z $=496.1(\mathrm{M}+\mathrm{H})$.

## Example 207



5-((2R)-2-(3-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide
[00614] Prepared according to the method of Example 204, using (R)-ethyl 5-(2-(3-fluoro-5-hydroxyphenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylate (Example 76, Step C) in Step A and ammonium chloride in Step C to yield the title compound as a white solid ( $19 \mathrm{mg}, 55 \%$ yield.). MS (apci) $\mathrm{m} / \mathrm{z}=456.0(\mathrm{M}+\mathrm{H})$.

Example 208


N-cyclopropyl-5-((2R)-2-(3-(2,3-dihydroxypropoxy)-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide
[00615] A solution of N-cyclopropyl-5-((2R)-2-(3-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (Example 206, $30 \mathrm{mg}, 0.061 \mathrm{mmol}$ ) in dioxane ( 0.5 mL ) was charged with two drops of 6 N HCl and shaken for two minutes. DIEA ( 5 drops) was added and the mixture directly
purified by reverse phase column chromatography ( $0-50 \%$ acetonitrile/water) to afford N -cyclopropyl-5-((2R)-2-(3-(2,3-dihydroxypropoxy)-5-fluorophenyl)pyrrolidin-1-
yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide ( $23 \mathrm{mg}, 83 \%$ yield) as a clear film. MS (apci) $\mathrm{m} / \mathrm{z}=456.1(\mathrm{M}+\mathrm{H})$.

## Example 209



## 5-((2R)-2-(3-(2,3-dihydroxypropoxy)-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-

 a]pyrimidine-3-carboxamide[00616] Prepared from 5-((2R)-2-(3-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (Example 207) according to the procedure of Example $208(8.5 \mathrm{mg}, 55 \%$ yield). MS (apci) $\mathrm{m} / \mathrm{z}=416.0$ $(\mathrm{M}+\mathrm{H})$.

## Example 210



N-cyclopropyl-5-((2R)-2-(2-(2,3-dihydroxypropoxy)-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide
[00617] Prepared from N-cyclopropyl-5-((2R)-2-(2-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (Example 204) using the procedure of Example 208 ( $19 \mathrm{mg}, 65 \%$ yield). MS (apci) $\mathrm{m} / \mathrm{z}=$ $456.1(\mathrm{M}+\mathrm{H})$.

## Example 211



## 5-((2R)-2-(2-(2,3-dihydroxypropoxy)-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-

a]pyrimidine-3-carboxamide
[00618] Prepared from 5-((2R)-2-(3-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (Example 205) using the procedure of Example $208(10 \mathrm{mg}, 95 \%$ yield $)$. MS (apci) m/z $=416.0(\mathrm{M}+\mathrm{H})$.

## Example 212



## 5-((2R,5S)-2-(5-fluoropyridin-3-yl)-5-(hydroxymethyl)pyrrolidin-1-yl)-N-((R)-1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide.

[00619] Step A: Preparation of (S)-ethyl 2-(tert-butoxycarbonylamino)-5-(5-fluoropyridin-3-yl)-5-oxopentanoate. A solution of 3-bromo-5-fluoropyridine ( $4.28 \mathrm{~g}, 24.3$ mmol ) in dry THF ( 25 mL ) was cooled to -40 to $-50^{\circ} \mathrm{C}$ and 2 M isopropylmagnesium chloride in THF ( $10.2 \mathrm{~mL}, 20.4 \mathrm{mmol}$ ) was added. The mixture was allowed to warm to $0{ }^{\circ} \mathrm{C}$ and was stirred for 30 minutes. The mixture was cooled to $-20^{\circ} \mathrm{C}$ and a solution of (S)-1-tert-butyl 2-ethyl 5-oxopyrrolidine-1,2-dicarboxylate ( $5.00 \mathrm{~g}, 19.4 \mathrm{mmol}$ ) in dry THF ( 15 mL ) was added. The mixture was allowed to reach ambient temperature over 30 minutes and was stirred at ambient temperature for 30 minutes. The reaction was slowly quenched with $2 \mathrm{M} \mathrm{HCl}(10 \mathrm{~mL}, 20.0 \mathrm{mmol})$ followed by $10 \%$ aqueous $\mathrm{NH}_{4} \mathrm{Cl}(10 \mathrm{~mL})$. The mixture was stirred for 10 minutes and was transferred to a separatory funnel using MTBE rinses ( 10 mL ). Heptane ( 15 mL ) was added and the organic layer was removed. The organic layer was washed $10 \%$ aqueous $\mathrm{NH}_{4} \mathrm{Cl}(25 \mathrm{~mL})$ and DI $\mathrm{H}_{2} \mathrm{O}(25 \mathrm{~mL})$. The organic layer was concentrated to provide the crude product as a yellow oil ( $7.03 \mathrm{~g}, 102 \%$ ).
[00620] Step B: Preparation of (2S,5R)-ethyl 5-(5-fluoropyridin-3-yl)pyrrolidine-2carboxylate. (S)-ethyl 2-(tert-butoxycarbonylamino)-5-(5-fluoropyridin-3-yl)-5oxopentanoate $(4.80 \mathrm{~g}, 13.55 \mathrm{mmol})$ was treated with TFA ( 24 mL ) and the mixture was stirred at ambient temperature for 45 minutes. The mixture was concentrated and the residue was dissolved in $\mathrm{H}_{2} \mathrm{O}(10 \mathrm{~mL})$ and $\mathrm{EtOAc}(50 \mathrm{~mL})$ was added. The mixture was treated slowly with saturated aqueous $\mathrm{K}_{2} \mathrm{CO}_{3}(15 \mathrm{~mL})$. The aqueous layer was separated and the organic layer was washed with $10 \%$ aqueous $\mathrm{NH}_{4} \mathrm{Cl}$. The EtOAc layer was concentrated to
give crude (S)-ethyl 5-(5-fluoropyridin-3-yl)-3,4-dihydro-2H-pyrrole-2-carboxylate as an amber oil ( $2.67 \mathrm{~g}, 83 \%$ yield). The oil was dissolved in isopropyl alcohol ( 20 mL ) and was treated with $10 \% \mathrm{Pd} / \mathrm{C}(0.266 \mathrm{~g}, 0.250 \mathrm{mmol})$. The reaction vessel was purged with hydrogen gas (3X) and mixture was stirred at ambient temperature under 1 atm of hydrogen for 16 hours. The reaction was purged with nitrogen and filtered through a Celite pad. The filtrate was concentrated to furnish the title compound as an amber oil that began to solidify upon standing ( $2.58 \mathrm{~g}, 96 \%$ ).
[00621] Step C: Preparation of ((2S,5R)-5-(5-fluoropyridin-3-yl)pyrrolidin-2yl)methanol. To a solution of (2S,5R)-ethyl 5-(5-fluoropyridin-3-yl)pyrrolidine-2carboxylate $(1.10 \mathrm{~g}, 4.62 \mathrm{mmol})$ in dry THF $(20 \mathrm{~mL})$ was added $2 \mathrm{M}_{\mathrm{LiAlH}}^{4}$ in THF $(3.00$ $\mathrm{mL}, 6.00 \mathrm{mmol})$. The reaction was stirred at ambient temperature for 30 minutes and $\mathrm{Na}_{2} \mathrm{SO}_{4}$ $10 \mathrm{H}_{2} \mathrm{O}(3.00 \mathrm{~g}, 9.31 \mathrm{mmol})$ was added in small portions. The mixture was stirred for 3 hours at ambient temperature and was filtered. The collected solid was washed with EtOAc and the washes combined with the filtrate. The solution was concentrated to provide crude ( $(2 \mathrm{~S}, 5 \mathrm{R})$ -5-(5-fluoropyridin-3-yl)pyrrolidin-2-yl)methanol ( $0.95 \mathrm{~g}, 105 \%$ yield) that was used directly in the next step. MS (apci) m/z=197.1(M+H).
[00622] Step D: Preparation of ethyl 5-((2R,5S)-2-(5-fluoropyridin-3-yl)-5-(hydroxymethyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylate. A mixture of ((2S,5R)-5-(5-fluoropyridin-3-yl)pyrrolidin-2-yl)methanol ( $0.910 \mathrm{~g}, 4.64 \mathrm{mmol}$ ), ethyl 5-chloropyrazolo[1,5-a]pyrimidine-3-carboxylate (Preparation B, $1.05 \mathrm{~g}, 4.64 \mathrm{mmol}$ ) and DIEA $(1.10 \mathrm{~mL}, 6.00 \mathrm{mmol})$ in isopropyl alcohol $(1.0 \mathrm{~mL})$ was heated at $90^{\circ} \mathrm{C}$ for 16 hours. The reaction mixture was concentrated and the residue was purified by reverse phase column chromatography ( $0-50 \%$ acetonitrile/water) followed by normal phase column chromatography ( $2-5 \% \mathrm{MeOH} / \mathrm{DCM}$ ) to afford ethyl 5-((2R,5S)-2-(5-fluoropyridin-3-yl)-5-(hydroxymethyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylate ( $0.250 \mathrm{~g}, 14 \%$ yield) as a viscous, clear oil. MS (apci) m/z $=386.0(\mathrm{M}+\mathrm{H})$.
[00623] Step E: Preparation of 5-((2R,5S)-2-(5-fluoropyridin-3-yl)-5-(hydroxymethyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid. A mixture of ethyl 5-((2R,5S)-2-(5-fluoropyridin-3-yl)-5-(hydroxymethyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylate $(0.250 \mathrm{~g}, 0.649 \mathrm{mmol})$ and 2 M sodium hydroxide ( $3.24 \mathrm{~mL}, 6.48$ $\mathrm{mmol})$ in $\mathrm{MeOH}(10 \mathrm{~mL})$ was stirred at ambient temperature for 4 days followed by $50{ }^{\circ} \mathrm{C}$ for 5 hours. The reaction was cooled to ambient temperature and 4 M HCl in dioxane $(1.78$ $\mathrm{mL}, 7.14 \mathrm{mmol}$ ) was added. The mixture was concentrated and the residue was purified by
reverse phase column chromatography ( $0-40 \%$ acetonitrile/water) to afford 5-((2R,5S)-2-(5-fluoropyridin-3-yl)-5-(hydroxymethyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3carboxylic acid ( $210 \mathrm{mg}, 90 \%$ yield) as a white solid. MS (apci) $\mathrm{m} / \mathrm{z}=358.0(\mathrm{M}+\mathrm{H})$.
[00624] Step F: Preparation of 5-((2R,5S)-2-(5-fluoropyridin-3-yl)-5-(hydroxymethyl)pyrrolidin-1-yl)-N-((R)-1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide. To a mixture of 5-((2R,5S)-2-(5-fluoropyridin-3-yl)-5-(hydroxymethyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid ( $10.0 \mathrm{mg}, 0.028$ mmol ), (R)-1,1,1-trifluoropropan-2-amine ( $6.33 \mathrm{mg}, 0.056 \mathrm{mmol}$ ) and HATU ( 10.5 mg , 0.045 mmol ) in dry DMF ( 0.2 mL ) was added DIEA ( $15.0 \mu \mathrm{~L}, 0.084 \mathrm{mmol}$ ). The reaction vessel was flushed with nitrogen, sealed, and the reaction stirred at ambient temperature for 16 hours. The reaction mixture was directly purified by reverse phase column chromatography ( $0-50 \% \mathrm{CH}_{3} \mathrm{CN} / \mathrm{H}_{2} \mathrm{O}$ ) to provide the title compound ( $6.50 \mathrm{mg}, 51 \%$ yield) as a white solid. MS (apci) $\mathrm{m} / \mathrm{z}=453.0(\mathrm{M}+\mathrm{H})$.

## Example 213



5-((2R,5S)-2-(5-fluoropyridin-3-yl)-5-(hydroxymethyl)pyrrolidin-1-yl)-N-((S)-1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide
[00625] Prepared according to the method of Example 212, Step F, using (S)-1,1,1-trifluoropropan-2-amine (white solid; $5.5 \mathrm{mg}, 43 \%$ ). MS (apci) m/z $=453.0(\mathrm{M}+\mathrm{H})$.

## Example 214



5-((2R,5S)-2-(5-fluoropyridin-3-yl)-5-(hydroxymethyl)pyrrolidin-1-yl)-N-(1-methylcyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide
[00626] Prepared according to the method of Example 212, Step F, using 1methylcyclopropane amine (white solid; $2.5 \mathrm{mg}, 22 \%$ ). MS (apci) $\mathrm{m} / \mathrm{z}=411.1(\mathrm{M}+\mathrm{H})$.

## Example 215



## 5-((2R,5S)-2-(5-fluoropyridin-3-yl)-5-(hydroxymethyl)pyrrolidin-1-yl)-Nisopropylpyrazolo [1,5-a]pyrimidine-3-carboxamide

[00627] Prepared according to the method of Example 212, Step F, using isopropyl amine (white solid; $2.5 \mathrm{mg}, 12 \%$ ). MS (apci) m/z = $399.1(\mathrm{M}+\mathrm{H})$.

Example 216


## 5-((2R,4S)-2-(3-fluorophenyl)-4-hydroxypyrrolidin-1-yl)-N-((S)-1,1,1-trifluoropropan-2-

yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide
[00628] Step A: Preparation of (ethyl 5-((2R,4S)-4-acetoxy-2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylate. To a mixture of ethyl 5-((2R,4R)-2-(3-fluorophenyl)-4-hydroxypyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3carboxylate (Example 41, Step E, $260 \mathrm{mg}, 0.702 \mathrm{mmol}$ ) and $\mathrm{PPh}_{3}(460 \mathrm{mg}, 1.75 \mathrm{mmol})$ in THF ( 10.0 mL ) was added DIAD ( $276 \mu \mathrm{~L}, 1.40 \mathrm{mmol}$ ) followed by acetic acid ( $80.4 \mu \mathrm{~L}$, $1.40 \mathrm{mmol})$. The reaction was stirred at ambient temperature for 48 hours and then concentrated. The residue was purified by reverse phase column chromatography ( $0-70 \%$ acetonitrile/water) to afford ethyl 5-((2R,4S)-4-acetoxy-2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylate ( $228 \mathrm{mg}, 79 \%$ yield). MS (apci) $\mathrm{m} / \mathrm{z}=413.0$ $(\mathrm{M}+\mathrm{H})$.
[00629] Step B: Preparation of 5-((2R,4S)-2-(3-fluorophenyl)-4-hydroxypyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid. A mixture of ethyl 5-((2R,4S)-4-acetoxy-2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylate ( $225 \mathrm{mg}, 0.546$ mmol ) and $\mathrm{NaOH}(131 \mathrm{mg}, 1.64 \mathrm{mmol})$ in $\mathrm{MeOH}(1.0 \mathrm{~mL})$ was stirred at ambient temperature for 60 hours followed by 3 hours at $60^{\circ} \mathrm{C}$. The mixture was cooled to ambient temperature and 4 M HCl in dioxane ( 1 mL ) was added. The mixture was concentrated and
the residue was treated with DCM. The mixture was filtered through Celite and concentrated to afford 5-((2R,4S)-2-(3-fluorophenyl)-4-hydroxypyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid ( $188 \mathrm{mg}, 10 \%$ yield) as a white solid. MS (apci) m/z $=343.0(\mathrm{M}+\mathrm{H})$.
[00630] Step C: Preparation of 5-((2R,4S)-2-(3-fluorophenyl)-4-hydroxypyrrolidin-1-yl)-N-((S)-1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide. Prepared according to the method of Example 212, Step F, using 5-((2R,4S)-2-(3-fluorophenyl)-4-hydroxypyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid and (S)-1,1,1-trifluoropropan-2-amine (white solid; $2.1 \mathrm{mg}, 16 \%$ yield). MS (apci) m/z $=438.0(\mathrm{M}+\mathrm{H})$.

## Example 217



5-((2R,4S)-2-(3-fluorophenyl)-4-hydroxypyrrolidin-1-yl)-N-isopropylpyrazolo[1,5-a]pyrimidine-3-carboxamide
[00631] Prepared according to the method of Example 212, Step F, using 5-((2R,4S)-2-(3-fluorophenyl)-4-hydroxypyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (Example 216, Step B) and isopropyl amine. The title compound was obtained as a white solid ( $5.5 \mathrm{mg}, 49 \%$ yield). MS (apci) m/z $=384.1(\mathrm{M}+\mathrm{H})$.

## Example 218



5-((2R,4S)-2-(3-fluorophenyl)-4-hydroxypyrrolidin-1-yl)-N-methylpyrazolo[1,5-
a]pyrimidine-3-carboxamide
[00632] Prepared according to the method of Example 212, Step F, using 5-((2R,4S)-2-(3-fluorophenyl)-4-hydroxypyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (Example 216, Step B) and methyl amine. The title compound was obtained as a white solid ( $6.1 \mathrm{mg}, 29 \%$ yield). MS (apci) m/z $=356.1(\mathrm{M}+\mathrm{H})$.

## Example 219



5-((2S,5R)-5-(5-fluoropyridin-3-yl)-2-(hydroxymethyl)-2-methylpyrrolidin-1-yl)-N-isopropylpyrazolo[1,5-a]pyrimidine-3-carboxamide
[00633] Step A: Preparation of (2S,5R)-1-tert-butyl 2-ethyl 5-(5-fluoropyridin-3-yl)pyrrolidine-1,2-dicarboxylate. A mixture of (2S,5R)-ethyl 5-(5-fluoropyridin-3-yl)pyrrolidine-2-carboxylate (Example 212, Step B, $1.00 \mathrm{~g}, 4.20 \mathrm{mmol}$ ), di-tert-butyl dicarbonate ( $0.962 \mathrm{~g}, 4.41 \mathrm{mmol}$ ) and PS-DMAP ( $0.210 \mathrm{~g}, 0.210 \mathrm{mmol}, 1.00 \mathrm{mmol} / \mathrm{g} \mathrm{load}$ ) in dry DCM ( 20 mL ) was mixed at ambient temperature for 18 hours. The reaction mixture was filtered and the filtrate was concentrated. The residue was purified on a silica gel column (2$10 \% \mathrm{MeOH} / \mathrm{DCM}$ ) to afford (2S,5R)-1-tert-butyl 2-ethyl 5-(5-fluoropyridin-3-yl)pyrrolidine-1,2-dicarboxylate ( $1.36 \mathrm{~g}, 96 \%$ yield) as a yellow oil. MS (apci) m/z $=339.0(\mathrm{M}+\mathrm{H})$.
[00634] Step B: Preparation of (2S,5R)-1-tert-butyl 2-ethyl 5-(5-fluoropyridin-3-yl)-2-methylpyrrolidine-1,2-dicarboxylate. A solution of (2S,5R)-1-tert-butyl 2-ethyl 5-(5-fluoropyridin-3-yl)pyrrolidine-1,2-dicarboxylate ( $250 \mathrm{mg}, 0.739 \mathrm{mmol}$ ) in THF ( 10 mL ) was cooled to $-78^{\circ} \mathrm{C}$ and 0.5 M KHMDS in toluene ( $1.77 \mathrm{~mL}, 0.885 \mathrm{mmol}$ ) was added dropwise. The reaction was stirred for 1 hour at $-78^{\circ} \mathrm{C}$ and $\operatorname{MeI}(59.9 \mu \mathrm{~L}, 0.960 \mathrm{mmol})$ was added. The reaction was allowed to warm to ambient temperature and saturated aqueous $\mathrm{NaCl}(20 \mathrm{~mL})$ was added. The mixture was extracted with EtOAc $(2 \times 50 \mathrm{~mL})$ and the combined organic extracts were filtered and concentrated to afford (2S,5R)-1-tert-butyl 2-ethyl 5-(5-fluoropyridin-3-yl)-2-methylpyrrolidine-1,2-dicarboxylate ( $255 \mathrm{mg}, 98 \%$ yield) as a clear oil. $\mathrm{MS}($ apci $) \mathrm{m} / \mathrm{z}=353.1(\mathrm{M}+\mathrm{H})$.
[00635] Step C: Preparation of (2S,5R)-tert-butyl 5-(5-fluoropyridin-3-yl)-2-(hydroxymethyl)-2-methylpyrrolidine-1-carboxylate. A solution of (2S,5R)-1-tert-butyl 2ethyl 5-(5-fluoropyridin-3-yl)-2-methylpyrrolidine-1,2-dicarboxylate ( $240 \mathrm{mg}, 0.681 \mathrm{mmol}$ ) in THF ( 10 mL ) was cooled to $-78{ }^{\circ} \mathrm{C}$ and 1 M LiAlH 44 in THF ( $1.50 \mathrm{~mL}, 1.50 \mathrm{mmol}$ ) was added dropwise. The reaction was allowed to warm to $0{ }^{\circ} \mathrm{C}$ and was quenched with small portions of $\mathrm{Na}_{2} \mathrm{SO}_{4}-10 \mathrm{H}_{2} \mathrm{O}(967 \mathrm{mg}, 6.81 \mathrm{mmol})$. The mixture was filtered and concentrated
to afford (2S,5R)-tert-butyl 5-(5-fluoropyridin-3-yl)-2-(hydroxymethyl)-2-methylpyrrolidine-1-carboxylate ( $200 \mathrm{mg}, 95 \%$ yield). MS (apci) $\mathrm{m} / \mathrm{z}=311.1(\mathrm{M}+\mathrm{H})$.
[00636] Step D: Preparation of ((2S,5R)-5-(5-fluoropyridin-3-yl)-2-methylpyrrolidin-2-yl)methanol hydrochloride. To a solution of (2S,5R)-tert-butyl 5-(5-fluoropyridin-3-yl)-2-(hydroxymethyl)-2-methylpyrrolidine-1-carboxylate ( $200 \mathrm{mg}, 0.644 \mathrm{mmol}$ ) in DCM ( 5 mL ) was added 4 M HCl in dioxane ( $1.61 \mathrm{~mL}, 6.44 \mathrm{mmol}$ ). The reaction was stirred at ambient temperature for 16 hours and then concentrated to afford ((2S,5R)-5-(5-fluoropyridin-3-yl)-2-methylpyrrolidin-2-yl)methanol hydrochloride ( $130 \mathrm{mg}, 96 \%$ yield). MS (apci) m/z $=211.1$ ( $\mathrm{M}+\mathrm{H}$ ).
[00637] Step E: Preparation of ethyl 5-((2S,5R)-5-(5-fluoropyridin-3-yl)-2-(hydroxymethyl)-2-methylpyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylate. A sealed reaction vessel was charged with ((2S,5R)-5-(5-fluoropyridin-3-yl)-2-methylpyrrolidin-2-yl)methanol hydrochloride $(0.135 \mathrm{~g}, 0.547 \mathrm{mmol})$, ethyl 5 -chloropyrazolo[1,5-a]pyrimidine-3-carboxylate (Preparation B, $0.136 \mathrm{~g}, 0.602 \mathrm{mmol}$ ), DIEA ( $0.124 \mathrm{~mL}, 0.711 \mathrm{mmol}$ ) and isopropyl alcohol ( 1 mL ). The vessel was sealed and the mixture was heated at $190^{\circ} \mathrm{C}$ for 48 hours. The reaction was cooled to ambient temperature and concentrated. The residue was purified by reverse phase column chromatography ( 0 $50 \%$ acetonitrile/water) to afford ethyl 5-((2S,5R)-5-(5-fluoropyridin-3-yl)-2-(hydroxymethyl)-2-methylpyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylate ( 55 mg , $25 \%$ yield) as a viscous clear oil. MS (apci) $\mathrm{m} / \mathrm{z}=400.1(\mathrm{M}+\mathrm{H})$.
[00638] Step F: Preparation of 5-((2S,5R)-5-(5-fluoropyridin-3-yl)-2-(hydroxymethyl)-2-methylpyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid. A mixture of ethyl 5-((2S,5R)-5-(5-fluoropyridin-3-yl)-2-(hydroxymethyl)-2-methylpyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylate ( $52.0 \mathrm{mg}, 0.130 \mathrm{mmol}$ ) and $\mathrm{NaOH}(26.0 \mathrm{mg}$, $0.325 \mathrm{mmol})$ in $\mathrm{MeOH}(1.0 \mathrm{~mL})$ was stirred at ambient temperature for 60 hours. The reaction was treated with $\mathrm{HCl}(4 \mathrm{~N}$ dioxane, $163 \mu \mathrm{~L}, 0.651 \mathrm{mmol})$ and concentrated. The residue was treated with DCM and filtered through Celite. The solution was concentrated to afford $\quad 5$-((2S,5R)-5-(5-fluoropyridin-3-yl)-2-(hydroxymethyl)-2-methylpyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid ( $29 \mathrm{mg}, 60 \%$ yield) as a white solid. MS (apci) $\mathrm{m} / \mathrm{z}=372.0(\mathrm{M}+\mathrm{H})$.
[00639] Step G: Preparation of 5-((2S,5R)-5-(5-fluoropyridin-3-yl)-2-(hydroxymethyl)-2-methylpyrrolidin-1-yl)-N-isopropylpyrazolo[1,5-a]pyrimidine-3carboxamide. Prepared according to the method of Example 212, Step F, using 5-((2S,5R)-5-
(5-fluoropyridin-3-yl)-2-(hydroxymethyl)-2-methylpyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid and isopropyl amine. The title compound was obtained as a white solid ( $7.2 \mathrm{mg}, 46 \%$ yield). MS (apci) $\mathrm{m} / \mathrm{z}=413.1(\mathrm{M}+\mathrm{H})$.

## Example 220



5-((2S,5R)-5-(5-fluoropyridin-3-yl)-2-(hydroxymethyl)-2-methylpyrrolidin-1-yl)-N-((S)-

## 1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide

[00640] Prepared according to the method of Example 212, Step F, using 5-((2S,5R)-5-(5-fluoropyridin-3-yl)-2-(hydroxymethyl)-2-methylpyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (Example 219, Step F) and (S)-1,1,1-trifluoropropan-2-amine. The title compound was obtained as a white solid ( $5.4 \mathrm{mg}, 31 \%$ yield). MS (apci) $\mathrm{m} / \mathrm{z}=$ $467.1(\mathrm{M}+\mathrm{H})$.

## Example 221


(R)-(5-(2-(2-amino-5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-
yl)(azetidin-1-yl)methanone
[00641] A mixture of (R)-N-(3-aminopropyl)-5-(2-(5-fluoro-2-oxo-1,2-dihydropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide hydrochloride (Example 142, $83 \mathrm{mg}, 0.190 \mathrm{mmol}$ ) and $\mathrm{POCl}_{3}(697 \mu \mathrm{~L}, 7.62 \mathrm{mmol}$ ) was sealed and heated at $100{ }^{\circ} \mathrm{C}$ for 5 minutes. The reaction mixture was diluted with 1 mL heptane and azeotroped twice to yield the crude product. The crude material was purified by reverse-phase chromatography ( 5 to $40 \%$ acetonitrile/water) to yield the title product as white solid ( 2 mg , $3 \%$ ). LCMS (apci) m/z = $382.3(\mathrm{M}+\mathrm{H})$.

## Example 222


(R)-tert-butyl 3-(5-(2-(2-chloro-5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-
a]pyrimidine-3-carboxamido)propylcarbamate
[00642] Step A: Preparation of (R)-tert-butyl 2-(2-chloro-5-fluoropyridin-3-yl)pyrrolidine-1-carboxylate: A solution of tert-butyl pyrrolidine-1-carboxylate ( 1 mL 5.70 mmol ) and (-)-sparteine ( $1.31 \mathrm{~mL}, 5.70 \mathrm{mmol}$ ) in anhydrous MTBE ( 30 mL ) was first cooled to $-78{ }^{\circ} \mathrm{C}$ under nitrogen, followed by addition of sec-butyl lithium ( $4.07 \mathrm{~mL}, 1.4 \mathrm{M}, 5.70$ mmol ) drop-wise over 15 minutes with a syringe, maintaining the temperature below $-75^{\circ} \mathrm{C}$. The pale yellowish solution was stirred at $-78{ }^{\circ} \mathrm{C}$ for 3 hours before being treated with zinc chloride ( $3.80 \mathrm{~mL}, 1.0 \mathrm{M}, 3.80 \mathrm{mmol}$ ) dropwise over 15 minutes while maintaining the temperature below $-73^{\circ} \mathrm{C}$. The mixture was stirred at $-78^{\circ} \mathrm{C}$ for 30 minutes, then placed into an ambient temperature water bath and stirred for another hour. At this point a large amount of white precipitate was present. The mixture was treated with 3-bromo-2-chloro-5fluoropyridine ( $1.00 \mathrm{~g}, 4.75 \mathrm{mmol}$ ) in MTBE ( 5 mL ), followed by addition of palladium acetate ( $53 \mathrm{mg}, 0.24 \mathrm{mmol}$ ) and tri-t-butylphosphine tetrafluoroborate ( $83 \mathrm{mg}, 0.28 \mathrm{mmol}$ ). The mixture was allowed to stir at ambient temperature overnight to reach completion. The mixture was treated with $\mathrm{NH}_{4} \mathrm{OH}(1 \mathrm{~mL})$, stirred for 30 minutes and filtered through GF/F paper, washing with MTBE. The filtrate was washed with $10 \%$ citric acid ( 30 mL ) and the aqueous layer was back-washed with MTBE $(2 \times 30 \mathrm{~mL})$. The combined organic phases were washed with brine ( 20 mL ), dried $\left(\mathrm{MgSO}_{4}\right)$, and concentrated to afford the crude product as dark yellowish oil. This crude material was purified on a silica 50 g Biotage SNAP cartridge eluting with $10 \%$ EtOAc in hexanes to afford the desired product as colorless oil ( $0.5 \mathrm{~g}, 35 \%$ ). MS (apci pos) $\mathrm{m} / \mathrm{z}=201.1$ ( $\mathrm{M}+\mathrm{H}-\mathrm{Boc}$ ).
[00643] Step B: Preparation of (R)-2-chloro-5-fluoro-3-(pyrrolidin-2-yl)pyridine dihydrochloride: To a dioxane ( 5 mL ) solution of (R)-tert-butyl 2-(2-chloro-5-fluoropyridin-3-yl)pyrrolidine-1-carboxylate ( $500 \mathrm{mg}, 1.66 \mathrm{mmol}$ ) was added $\mathrm{HCl}(4 \mathrm{~N}$ dioxane, 20 mL ), followed by stirring at ambient temperature overnight. The mixture was concentrated and treated with $\mathrm{Et}_{2} \mathrm{O}$, then vacuum-dried, to provide the product as a white solid $(0.36 \mathrm{~g}, 80 \%)$.

MS (apci pos) $\mathrm{m} / \mathrm{z}=201.1(\mathrm{M}+\mathrm{H})$. The enantiomeric excess (ee\%) of the product was determined to be $>92 \%$ according to the method described in Preparation A.
[00644] Step C: Preparation of (R)-ethyl 5-(2-(2-chloro-5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylate: To a solution of ethyl 5-hydroxypyrazolo[1,5-a]pyrimidine-3-carboxylate (Preparation B, Step A, $275 \mathrm{mg}, 1.33$ mmol ) in anhydrous DMF ( 5 mL ) was added (Benzotriazol-1yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP) ( $646 \mathrm{mg}, 1.46 \mathrm{mmol}$ ). The heterogeneous mixture was stirred for 10 minutes before adding DIEA ( $1.16 \mathrm{~mL}, 6.6$ mmol ), followed by addition of (R)-2-chloro-5-fluoro-3-(pyrrolidin-2-yl)pyridine dihydrochloride ( $363 \mathrm{mg}, 1.33 \mathrm{mmol}$ ). The reaction was stirred at ambient temperature overnight to reach completion. The mixture was partitioned between $10 \%$ citric acid ( 30 mL ) and EtOAc ( 30 mL ), and the aqueous layer was extracted with EtOAc ( $2 \times 20 \mathrm{~mL}$ ). The combined organic phases were washed successively with water ( 20 mL ), saturated $\mathrm{NaHCO}_{3}$ $(20 \mathrm{~mL})$, water $(20 \mathrm{~mL})$ and brine $(3 \times 20 \mathrm{~mL})$, then dried $\left(\mathrm{Na}_{2} \mathrm{SO}_{4}\right)$ and concentrated to afford the crude product as an orange foam. The crude material was purified on a 25 g Biotage SNAP silica cartridge eluting with $1 \% \mathrm{MeOH} / \mathrm{DCM}$ to afford the desired product as cream-colored foam ( $0.35 \mathrm{~g}, 68 \%$ ). MS (apci pos) m/z $=390.0(\mathrm{M}+\mathrm{H})$.
[00645] Step D: Preparation of (R)-5-(2-(2-chloro-5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid. Prepared by the method described in Preparation C, Step B, replacing (R)-ethyl 5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylate with (R)-ethyl 5-(2-(2-chloro-5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylate. MS (apci pos) m/z = 361.9 ( $\mathrm{M}+\mathrm{H}$ ).
[00646] Step E: Preparation of (R)-tert-butyl 3-(5-(2-(2-chloro-5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamido)propylcarbamate. Prepared according to the method described in Example 141, replacing (R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid with (R)-5-(2-(2-chloro-5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid to yield the title product as white solid. LCMS (apci pos) $\mathrm{m} / \mathrm{z}=418.2(\mathrm{M}+\mathrm{H}-\mathrm{Boc})$.

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## Example 223


(R)-N-(3-aminopropyl)-5-(2-(2-chloro-5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-
a]pyrimidine-3-carboxamide
[00647] A mixture of (R)-tert-butyl 3-(5-(2-(2-chloro-5-fluoropyridin-3-yl)pyrrolidin1 -yl)pyrazolo[1,5-a]pyrimidine-3-carboxamido)propylcarbamate (Example 222, $6 \mathrm{mg}, 0.012$ $\mathrm{mmol})$ and $\mathrm{HCl}(4 \mathrm{~N}$ dioxane, $145 \mu \mathrm{~L}, 0.58 \mathrm{mmol})$ was stirred at ambient temperature for 2 hours and concentrated to yield the product as white solid. LCMS (apci pos) $\mathrm{m} / \mathrm{z}=418.1$ $(\mathrm{M}+\mathrm{H})$.

## Example 224


(R)-N-(2-tert-butoxyethoxy)-5-(2-(2-chloro-5-fluoropyridin-3-yl)pyrrolidin-1-
yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide
[00648] Prepared according to the method described in Example 222, Step E, replacing tert-butyl 3-aminopropylcarbamate with O -(2-tert-butoxyethyl)hydroxylamine hydrochloride to yield the title product as white solid ( $58 \mathrm{mg}, 87 \%$ ). LCMS (apci) m/z $=476.9(\mathrm{M}+\mathrm{H})$.

## Example 225


(R)-5-(2-(2-chloro-5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(2-hydroxyethoxy)pyrazolo[1,5-a]pyrimidine-3-carboxamide
[00649] (R)-N-(2-tert-butoxyethoxy)-5-(2-(2-chloro-5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (Example 224, $57 \mathrm{mg}, 0.120 \mathrm{mmol}$ ) was treated with $\mathrm{HCl}(4 \mathrm{~N}$ dioxane, $1.49 \mathrm{~mL}, 5.98 \mathrm{mmol})$, followed by two drops of MeOH to make a clear colorless solution. After stirring 30 minutes at ambient temperature, the reaction was
concentrated and dried to yield the title product as white solid, assuming quantitative yield. LCMS (apci) m/z $=421.0(\mathrm{M}+\mathrm{H})$

## Example 226



## (R)-N-tert-butyl-5-(2-(5-fluoro-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide

[00650] Prepared by the method described in Example 140, using (R)-5-(2-(5-fluoro-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3carboxylic acid (Preparation R) and 2-methylpropan-2-amine. The residue was purified by silica column chromatography, eluting with $3 \% \mathrm{MeOH} / \mathrm{DCM}$ to yield the title compound ( 26 $\mathrm{mg}, 75 \%$ yield). MS (apci) $\mathrm{m} / \mathrm{z}=413.1(\mathrm{M}+\mathrm{H})$.
[00651] The compounds listed in the following Table were also prepared according to the method described in Example 140, by reacting (R)-5-(2-(5-fluoro-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (Preparation R) with the appropriate amine starting material in the presence of an amide coupling reagent (e.g. EDCI/HOBt), an organic base (for example, TEA) in a solvent (for example, DCM).

Table E

| Ex. \# | Structure | Chemical Name | Data |
| :---: | :---: | :---: | :---: |
| 227 |  | (R)-5-(2-(5-fluoro-1-methyl-2-oxo- <br> 1,2-dihydropyridin-3-yl)pyrrolidin-1- <br> yl)-N-isopropylpyrazolo[1,5- <br> a]pyrimidine-3-carboxamide | $\begin{aligned} & \text { MS (apci) m/z } \\ & =399.1 \\ & (\mathrm{M}+\mathrm{H}) \end{aligned}$ |
| 228 |  | (R)-N-cyclopropyl-5-(2-(5-fluoro-1-methyl-2-oxo-1,2-dihydropyridin-3- <br> yl)pyrrolidin-1-yl)pyrazolo[1,5- <br> a]pyrimidine-3-carboxamide | $\begin{aligned} & \text { MS (apci) m/z } \\ & =397.1 \\ & (\mathrm{M}+\mathrm{H}) \end{aligned}$ |


| Ex. \# | Structure | Chemical Name | Data |
| :---: | :---: | :---: | :---: |
| 229 |  | (R)-5-(2-(5-fluoro-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)pyrrolidin-1- <br> yl)-N-(6-methylpyridin-3- <br> yl)pyrazolo[1,5-a]pyrimidine-3carboxamide | $\begin{aligned} & \text { MS (apci) m/z } \\ & =448.1 \\ & (\mathrm{M}+\mathrm{H}) \end{aligned}$ |
| 230 |  | (R)-N-cyclobutyl-5-(2-(5-fluoro-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide | $\begin{aligned} & \text { MS (apci) m/z } \\ & =411.1 \\ & (\mathrm{M}+\mathrm{H}) \end{aligned}$ |
| 231 |  | (R)-5-(2-(5-fluoro-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)pyrrolidin-1-yl)-N-(pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide | $\begin{aligned} & \text { MS (apci) m/z } \\ & =434.1 \\ & (\mathrm{M}+\mathrm{H}) \end{aligned}$ |
| 232 |  | (R)-N-(cyclopropylmethyl)-5-(2-(5- <br> fluoro-1-methyl-2-oxo-1,2- <br> dihydropyridin-3-yl)pyrrolidin-1- <br> yl)pyrazolo[1,5-a]pyrimidine-3- <br> carboxamide | $\begin{aligned} & \text { MS (apci) m/z } \\ & =411.1 \\ & (\mathrm{M}+\mathrm{H}) \end{aligned}$ |
| 233 |  | 5-((R)-2-(5-fluoro-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)pyrrolidin-1-yl)-N-((S)-1-hydroxy-3,3-dimethylbutan-2-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide | $\begin{aligned} & \text { MS (apci) m/z } \\ & =457.1 \\ & (\mathrm{M}+\mathrm{H}) \end{aligned}$ |
| 234 |  | 5-((R)-2-(5-fluoro-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)pyrrolidin-1-yl)-N-((1R,2R)-2- <br> hydroxycyclohexyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide | $\begin{aligned} & \text { MS (apci) m/z } \\ & =455.1 \\ & (\mathrm{M}+\mathrm{H}) \end{aligned}$ |
| 235 |  | N-((R)-1-cyclopropylethyl)-5-((R)-2-(5-fluoro-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3carboxamide | $\begin{aligned} & \text { MS (apci) m/z } \\ & =425.1 \\ & (\mathrm{M}+\mathrm{H}) \end{aligned}$ |
| 236 |  | N-((S)-1-cyclopropylethyl)-5-((R)-2-(5-fluoro-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3carboxamide | $\begin{aligned} & \text { MS (apci) m/z } \\ & =425.1 \\ & (\mathrm{M}+\mathrm{H}) \end{aligned}$ |

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| Ex. \# | Structure | Chemical Name | Data |
| :---: | :---: | :---: | :---: |
| 237 |  | (R)-5-(2-(5-fluoro-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)pyrrolidin-1-yl)-N-(1-methylcyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide | $\begin{aligned} & \text { MS (apci) } \mathrm{m} / \mathrm{z} \\ & =411.1 \\ & (\mathrm{M}+\mathrm{H}) \end{aligned}$ |
| 238 |  | 5-((R)-2-(5-fluoro-1-methyl-2-oxo- <br> 1,2-dihydropyridin-3-yl)pyrrolidin-1- <br> yl)-N-((trans)-4- <br> hydroxycyclohexyl)pyrazolo[1,5- <br> a]pyrimidine-3-carboxamide | $\begin{aligned} & \text { MS (apci) m/z } \\ & =455.1 \\ & (\mathrm{M}+\mathrm{H}) \end{aligned}$ |
| 239 |  | (R)-5-(2-(5-fluoro-1-methyl-2-oxo- <br> 1,2-dihydropyridin-3-yl)pyrrolidin-1- <br> yl)-N-(5-fluoropyridin-2- <br> yl)pyrazolo[1,5-a]pyrimidine-3- <br> carboxamide | $\begin{aligned} & \text { MS (apci) } \mathrm{m} / \mathrm{z} \\ & =452.1 \\ & (\mathrm{M}+\mathrm{H}) \end{aligned}$ |

## Example 240


(R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-(3-methyl-1H-pyrazol-5-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide
[00652] To a suspension of (R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (Preparation K, $101 \mathrm{mg}, 0.283 \mathrm{mmol}$ ) in THF ( 5 mL ) was added triethylamine ( $34.3 \mathrm{mg}, 0.339 \mathrm{mmol}$ ), followed by the addition of 2,4,6trichlorobenzoyl chloride ( $75.8 \mathrm{mg}, 0.311 \mathrm{mmol}$ ). The suspension was stirred for 2 hours and then 3-methyl-1H-pyrazol-5-amine ( $35.7 \mathrm{mg}, 0.367 \mathrm{mmol}$ ) was introduced. The reaction was heated at $60^{\circ} \mathrm{C}$ for 3 hours. After cooling to room temperature, the reaction was partitioned between EtOAc ( 20 mL ) and saturated aqueous $\mathrm{NaHCO}_{3}(10 \mathrm{~mL})$. After phase-separation, the aqueous layer was extracted with EtOAc $(2 \times 10 \mathrm{~mL})$. The combined organics were dried $\left(\mathrm{Na}_{2} \mathrm{SO}_{4}\right)$, filtered and concentrated. The residue was purified via silica chromatography
(EtOAc/MeOH 20:1) to yield the title product ( $23 \mathrm{mg}, 19 \%$ ). LCMS (apci) $\mathrm{m} / \mathrm{z}=437.0$ ( $\mathrm{M}+\mathrm{H}$ ).
[00653] The compounds listed in Table F were also prepared according to the method described in Example 240, using (R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid, Preparation $K$ ) and an appropriate amine.

Table F
Ex. \#
[00654] The compounds in Table G can also be prepared according to the method of Example 240.

Table G

| Ex. \# | Structure | Name |
| :---: | :---: | :---: |
| 245 |  | (R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-(2-methyl-1H-imidazol-4-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide |
| 246 |  | (R)-N-(1,2-dimethyl-1H-imidazol-4-yl)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide |

What is claimed is:

1. A compound having the general formula $\mathbf{I}$


I
or a salt thereof, wherein:
$\mathrm{R}^{1}$ is H or (1-6C alkyl);
$\mathrm{R}^{2}$ is $\mathrm{H},(1-6 \mathrm{C})$ alkyl, $-(1-6 \mathrm{C})$ fluoroalkyl, $-(1-6 \mathrm{C})$ difluoroalkyl, $-(1-6 \mathrm{C})$ trifluoroalkyl, -(1-6C)chloroalkyl, -(2-6C)chlorofluoroalkyl, $\quad-(2-6 \mathrm{C})$ difluorochloroalkyl, $\quad-(2-$ $6 \mathrm{C})$ chlorohydroxyalkyl, $\quad-(1-6 \mathrm{C})$ hydroxyalkyl, $-(2-6 \mathrm{C})$ dihydroxyalkyl, $-(1-6 \mathrm{C}$ alkyl) CN , -(1-6C alkyl) $\mathrm{SO}_{2} \mathrm{NH}_{2}$, -(1-6C alkyl) $\mathrm{NHSO}_{2}\left(1-3 \mathrm{C}\right.$ alkyl), $-(1-6 \mathrm{C}$ alkyl $) \mathrm{NH}_{2},-(1-6 \mathrm{C}$ alkyl) $\mathrm{NH}(1-4 \mathrm{C}$ alkyl $),-(1-6 \mathrm{C}$ alkyl $) \mathrm{N}(1-4 \mathrm{C} \text { alkyl })_{2}, \quad-(1-6 \mathrm{C}$ alkyl $) \mathrm{NHC}(=\mathrm{O}) \mathrm{O}(1-4 \mathrm{C}$ alkyl $),-$ (1-6C alkyl)hetCyc ${ }^{1}$, $-\left(1-6 \mathrm{C}\right.$ alkyl)het $\mathrm{Ar}^{1}$, het $\mathrm{Ar}^{2}$, hetCyc ${ }^{2}$, $-\mathrm{O}(1-6 \mathrm{C}$ alkyl) which is optionally substituted with halogen, OH or (1-4C)alkoxy, $-\mathrm{O}\left(3-6 \mathrm{C}\right.$ cycloalkyl), $\mathrm{Cyc}^{1}$, $-(1-6 \mathrm{C}$ alkyl)(3-6C cycloalkyl), -(1-6Calkyl)(1-4C alkoxy), -(1-6C hydroxyalkyl)(1-4C alkoxy), a bridged 7 -membered cycloalkyl ring optionally substituted with (1-6C)hydroxyalkyl, or a bridged 7-8 membered heterocyclic ring having 1-2 ring nitrogen atoms;
or $N R^{1} \mathrm{R}^{2}$ forms a 4-6 membered azacyclic ring optionally substituted with one or more substituents independently selected from (1-6C)alkyl, $\mathrm{OH}, \mathrm{CO}_{2} \mathrm{H},\left(1-3 \mathrm{C}\right.$ alkyl) $\mathrm{CO}_{2} \mathrm{H}$, -O(1-6C alkyl) and (1-6C)hydroxyalkyl;
hetCyc ${ }^{1}$ is a 5-6 membered heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O , wherein hetCyc ${ }^{1}$ is optionally substituted with oxo, OH , halogen or ( $1-6 \mathrm{C}$ )alkyl;
hetCyc ${ }^{2}$ is a 6 membered carbon-linked heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O , wherein het $\mathrm{Cyc}^{2}$ is optionally substituted with F , $\mathrm{SO}_{2} \mathrm{NH}_{2}, \mathrm{SO}_{2}(1-3 \mathrm{C}$ alkyl) or halogen;
het $\mathrm{Ar}^{1}$ is a 5 -membered heteroaryl ring having 1-2 ring heteroatoms independently selected from N and O and optionally substituted with (1-4C)alkyl;
het $A r^{2}$ is a 5-6 membered heteroaryl ring having 1-2 ring nitrogen atoms and optionally substituted with one or more substituents independently selected from (1-4C)alkyl, (3-6C)cycloalkyl, halogen and OH;
$\mathrm{Cyc}^{1}$ is a 3-6 membered cycloalkyl ring which is optionally substituted with one or more substituents independently selected from -(1-4C alkyl), $-\mathrm{OH},-\mathrm{OMe},-\mathrm{CO}_{2} \mathrm{H},-(1-4 \mathrm{C}$ alkyl)OH, halogen and $\mathrm{CF}_{3}$;

Y is (i) phenyl optionally substituted with one or more substituents independently selected from halogen, (1-4C)alkoxy, $-\mathrm{CF}_{3}-\mathrm{CHF}_{2},-\mathrm{O}\left(1-4 \mathrm{C}\right.$ alkyl)hetCyc ${ }^{3}$, -(1-4C alkyl)hetCyc ${ }^{3},-\mathrm{O}(1-4 \mathrm{C}$ alkyl $) \mathrm{O}(1-3 \mathrm{C}$ alkyl) and $-\mathrm{O}(3-6 \mathrm{C}$ dihydroxyalkyl), 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 substituents independently selected from halogen, $-\mathrm{O}\left(1-4 \mathrm{C}\right.$ alkyl), (1-4C)alkyl and $\mathrm{NH}_{2}$, or (iii) a pyrid-2-on-3-yl ring optionally substituted with one or more substituents independently selected from halogen and (1-4C)alkyl;
hetCyc ${ }^{3}$ is a 5-6 membered heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O and optionally substituted with (1-6C)alkyl;

X is $-\mathrm{CH}_{2}-,-\mathrm{CH}_{2} \mathrm{CH}_{2}$-, $-\mathrm{CH}_{2} \mathrm{O}$ - or $-\mathrm{CH}_{2} \mathrm{NR}^{\mathrm{d}}$-;
$\mathrm{R}^{\mathrm{d}}$ is H or $-(1-4 \mathrm{C}$ alkyl);
$\mathrm{R}^{3}$ is H or -( $1-4 \mathrm{C}$ alkyl);
each $\mathrm{R}^{4}$ is independently selected from halogen, -(1-4C)alkyl, $-\mathrm{OH},-(1-4 \mathrm{C})$ alkoxy, -$\mathrm{NH}_{2},-\mathrm{NH}\left(1-4 \mathrm{C}\right.$ alkyl) and $-\mathrm{CH}_{2} \mathrm{OH}$; and
n is $0,1,2,3,4,5$ or 6 .
2. A compound of claim 1 , wherein:
$\mathrm{R}^{1}$ is H or $-(1-6 \mathrm{C}$ alkyl);
$\mathrm{R}^{2} \quad$ is $\mathrm{H}, \quad-(1-6 \mathrm{C})$ alkyl, $\quad-(1-6 \mathrm{C}) f l u o r o a l k y l, \quad-(1-6 \mathrm{C})$ hydroxyalkyl, $\quad-(2-$ $6 \mathrm{C})$ dihydroxyalkyl, $-\left(1-6 \mathrm{C}\right.$ alkyl) CN , -(1-6C alkyl) $\mathrm{SO}_{2} \mathrm{NH}_{2}$, -(1-6C alkyl) $\mathrm{NHSO}_{2}(1-3 \mathrm{C}$ alkyl), -(1-6C alkyl) $\mathrm{NH}_{2}$, -(1-6C alkyl)NH(1-4C alkyl), -(1-6C alkyl)N(1-4C alkyl) $)_{2}$, -(16 C alkyl)hetCyc ${ }^{1},-(1-6 \mathrm{C}$ alkyl $)$ het $\mathrm{Ar}^{1}$, het $\mathrm{Ar}^{2}$, hetCyc ${ }^{2},-\mathrm{O}(1-6 \mathrm{C}$ alkyl), $-\mathrm{O}(3-6 \mathrm{C}$ cycloalkyl $)$, $\mathrm{Cyc}^{1}$, or a bridged 7 -membered cycloalkyl ring,
or $N R^{1} \mathrm{R}^{2}$ forms a 4-6 membered azacyclic ring optionally substituted with one or more substituents independently selected from -(1-6C)alkyl, $-\mathrm{OH},-\mathrm{CO}_{2} \mathrm{H}$ and $-(1-3 \mathrm{C}$ alkyl) $\mathrm{CO}_{2} \mathrm{H}$;
hetCyc ${ }^{1}$ is a 5-6 membered heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O , wherein hetCyc ${ }^{1}$ is optionally substituted with oxo;
hetCyc ${ }^{2}$ is a 6 membered carbon-linked heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O , wherein hetCyc ${ }^{2}$ is optionally substituted with F , $\mathrm{SO}_{2} \mathrm{NH}_{2}$, or $\mathrm{SO}_{2}$ (1-3C alkyl);
het $\mathrm{Ar}^{1}$ is a 5 -membered heteroaryl ring having 1-2 ring heteroatoms independently selected from N and O and optionally substituted with -(1-4C)alkyl;
het $\mathrm{Ar}^{2}$ is a 5-6 membered heteroaryl ring having 1-2 ring nitrogen atoms and optionally substituted with one or more substituents independently selected from -(14C)alkyl;
$\mathrm{Cyc}^{1}$ is 3-6 membered cycloalkyl ring which is optionally substituted with one or more substituents independently selected from -(1-4C alkyl), $-\mathrm{OH},-\mathrm{OMe},-\mathrm{CO}_{2} \mathrm{H}$ and $-(1-4 \mathrm{C}$ alkyl)OH;

Y is (i) phenyl optionally substituted with one or more substituents independently selected from halogen, $-(1-4 \mathrm{C})$ alkoxy, $-\mathrm{CF}_{3}-\mathrm{CHF}_{2},-\mathrm{O}\left(1-4 \mathrm{C}\right.$ alkyl)hetCyc ${ }^{3}$ and $-\mathrm{O}(1-4 \mathrm{C}$ alkyl) O (1-3C alkyl), 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 substituents independently selected from halogen, $-\mathrm{O}(1-4 \mathrm{C}$ alkyl) and (1-4C)alkyl;
hetCyc ${ }^{3}$ is a 5-6 membered heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O ;

X is $-\mathrm{CH}_{2}-,-\mathrm{CH}_{2} \mathrm{CH}_{2}-,-\mathrm{CH}_{2} \mathrm{O}$ - or $-\mathrm{CH}_{2} \mathrm{NR}^{\mathrm{d}}$-;
$\mathrm{R}^{\mathrm{d}}$ is H or $-(1-4 \mathrm{C}$ alkyl);
$\mathrm{R}^{3}$ is H or $-(1-4 \mathrm{C}$ alkyl);
each $\mathrm{R}^{4}$ is independently selected from halogen, -(1-4C)alkyl, $-\mathrm{OH},-(1-4 \mathrm{C})$ alkoxy, $\mathrm{NH}_{2}, \mathrm{NH}\left(1-4 \mathrm{C}\right.$ alkyl) and $\mathrm{CH}_{2} \mathrm{OH}$; and
n is $0,1,2,3,4,5$ or 6 .
3. A compound according to claims 1 or 2 , wherein:
$\mathrm{R}^{1}$ is H or $-(1-6 \mathrm{C}$ alkyl); and
$\mathrm{R}^{2} \quad$ is $\mathrm{H}, \quad-(1-6 \mathrm{C})$ alkyl, $\quad-(1-6 \mathrm{C})$ fluoroalkyl, $\quad-(1-6 \mathrm{C})$ hydroxyalkyl, $\quad-(2-$ $6 \mathrm{C})$ dihydroxyalkyl, $-\left(1-6 \mathrm{C}\right.$ alkyl) CN , -(1-6C alkyl) $\mathrm{SO}_{2} \mathrm{NH}_{2}$, -(1-6C alkyl) $\mathrm{NHSO}_{2}(1-3 \mathrm{C}$ alkyl), -(1-6C alkyl) $\mathrm{NH}_{2}$, -(1-6C alkyl) $\mathrm{NH}\left(1-4 \mathrm{C}\right.$ alkyl), $-\left(1-6 \mathrm{C}\right.$ alkyl) $\mathrm{N}(1-4 \mathrm{C} \text { alkyl })_{2}$, $-(1-$ 6 C alkyl)hetCyc ${ }^{1},-\left(1-6 \mathrm{C}\right.$ alkyl)hetAr ${ }^{1}$, het $\mathrm{Ar}^{2}$, $-\mathrm{O}(1-6 \mathrm{C}$ alkyl $),-\mathrm{O}(3-6 \mathrm{C}$ cycloalkyl), or a 3, 4 or 5 membered cycloalkyl ring optionally substituted with one or more substituents independently selected from -(1-4C alkyl), $-\mathrm{OH},-\mathrm{OMe},-\mathrm{CO}_{2} \mathrm{H}$ and $-(1-4 \mathrm{C}$ alkyl $) \mathrm{OH}$,
or $N R^{1} \mathrm{R}^{2}$ forms a 4-6 membered azacyclic ring optionally substituted with one or more substituents independently selected from -(1-6C)alkyl, $-\mathrm{OH},-\mathrm{CO}_{2} \mathrm{H}$ and $-(1-3 \mathrm{C}$ alkyl) $\mathrm{CO}_{2} \mathrm{H}$.
4. A compound according to claims 1 or 2, wherein:
$\mathrm{R}^{1}$ is H or $-(1-6 \mathrm{C}$ alkyl);
$\mathrm{R}^{2} \quad$ is $\mathrm{H}, \quad-(1-6 \mathrm{C})$ alkyl, $\quad-(1-6 \mathrm{C})$ fluoroalkyl, $\quad-(1-6 \mathrm{C})$ hydroxyalkyl, $\quad-(2-$ $6 \mathrm{C})$ dihydroxyalkyl, $-\left(1-6 \mathrm{C}\right.$ alkyl) CN , -(1-6C alkyl) $\mathrm{SO}_{2} \mathrm{NH}_{2}$, -(1-6C alkyl) $\mathrm{NHSO}_{2}(1-3 \mathrm{C}$ alkyl), -(1-6C alkyl) $\mathrm{NH}_{2}$, -(1-6C alkyl)NH(1-4C alkyl), $-(1-6 \mathrm{C}$ alkyl $) \mathrm{N}(1-4 \mathrm{C} \text { alkyl })_{2},-(1-$ 6 C alkyl)hetCyc ${ }^{1},-(1-6 \mathrm{C}$ alkyl $)$ het $\mathrm{Ar}^{1}$, het $\mathrm{Ar}^{2}$, hetCyc ${ }^{2},-\mathrm{O}(1-6 \mathrm{C}$ alkyl), $-\mathrm{O}(3-6 \mathrm{C}$ cycloalkyl $)$, or a bridged 7-membered cycloalkyl ring,
or $N R^{1} \mathrm{R}^{2}$ forms a 4-6 membered azacyclic ring optionally substituted with one or more substituents independently selected from -(1-6C)alkyl, $-\mathrm{OH},-\mathrm{CO}_{2} \mathrm{H}$ and $-(1-3 \mathrm{C}$ alkyl) $\mathrm{CO}_{2} \mathrm{H}$.
5. A compound according to any of claims $1-4$, wherein $\mathrm{R}^{2}$ is H or $-(1-6 \mathrm{C})$ alkyl.
6. A compound of claim 5 , wherein $R^{2}$ is $-(1-6 C)$ alkyl.
7. A compound of claim 6 , wherein $R^{2}$ is methyl, ethyl, isopropyl or tert-butyl.
8. A compound of claim 5, wherein $\mathrm{R}^{2}$ is H .
9. A compound according to any of claims 1-4, wherein $R^{2}$ is $-(1-$ 6 C)hydroxyalkyl or -(2-6C)dihydroxyalkyl.
10. A compound of claim 9, wherein $\mathrm{R}^{2}$ is $\mathrm{CH}_{2} \mathrm{CH}_{2} \mathrm{OH}, \mathrm{CH}_{2} \mathrm{CH}(\mathrm{OH}) \mathrm{CH}_{2} \mathrm{OH}$ or $\mathrm{C}\left(\mathrm{CH}_{3}\right)\left(\mathrm{CH}_{2} \mathrm{OH}\right)_{2}$.
11. A compound of claim 1 or 2, wherein $\mathrm{R}^{2}$ is $\mathrm{Cyc}^{1}$ or a bridged 7-membered cycloalkyl ring.
12. A compound according to claim 11 , wherein $\mathrm{R}^{2}$ is $\mathrm{Cyc}^{1}$ optionally substituted with optionally substituted with one or two substituents independently selected from methyl, $-\mathrm{OH},-\mathrm{CH}_{2} \mathrm{OH}$ and $-\mathrm{CO}_{2} \mathrm{H}$.
13. A compound according to claim 12 , wherein $R^{2}$ is cyclopropyl.
14. A compound of claim 1 or 2 , wherein $\mathrm{Cyc}^{1}$ is a 3,4 or 5 membered cycloalkyl ring which is optionally substituted with one or more substituents independently selected from -( $1-4 \mathrm{C}$ alkyl), $-\mathrm{OH},-\mathrm{OMe},-\mathrm{CO}_{2} \mathrm{H}$ and $-(1-4 \mathrm{C}$ alkyl) OH .
15. A compound of claim 1, wherein $\mathrm{Cyc}^{1}$ is a 3, 4 or 5 membered cycloalkyl ring which is optionally substituted with one or more substituents independently selected from -(1-4C alkyl), $-\mathrm{OH},-\mathrm{OMe},-\mathrm{CO}_{2} \mathrm{H},-\left(1-4 \mathrm{C}\right.$ alkyl) OH , halogen and $\mathrm{CF}_{3}$.
16. A compound according to claim 1 or 2 , wherein $R^{2}$ is a 3,4 or 5 membered cycloalkyl ring which is optionally substituted with one or more substituents independently selected from -( $1-4 \mathrm{C}$ alkyl), $-\mathrm{OH},-\mathrm{OMe},-\mathrm{CO}_{2} \mathrm{H}$ and $-(1-4 \mathrm{C}$ alkyl) OH .
17. A compound according to claim 16 , wherein $\mathrm{R}^{2}$ is cyclopropyl optionally substituted with one or more substituents independently selected from methyl, $-\mathrm{CO}_{2} \mathrm{H}$, or $-\mathrm{CH}_{2} \mathrm{OH}$.
18. A compound of claim 1 or 2 , wherein $\mathrm{R}^{2}$ is $-\mathrm{O}(1-6 \mathrm{C}$ alkyl) or $-\mathrm{O}(3-6 \mathrm{C}$ cycloalkyl).
19. A compound of claim 18 , wherein $\mathrm{R}^{2}$ is selected from -OMe, -OEt and cyclopropoxy.
20. A compound of claim 1 or 2 , wherein $R^{2}$ is selected from -(1-6C)fluoroalkyl, $-\left(1-6 \mathrm{C}\right.$ alkyl) $\mathrm{CN},-(1-6 \mathrm{C}$ alkyl $) \mathrm{SO}_{2} \mathrm{NH}_{2}$, and $-\left(1-6 \mathrm{C}\right.$ alkyl) $\mathrm{NHSO}_{2}(1-3 \mathrm{C}$ alkyl).
21. A compound of claim 20, wherein $\mathrm{R}^{2}$ is selected from $-\mathrm{C}\left(\mathrm{CH}_{3}\right)_{2} \mathrm{CH}_{2} \mathrm{~F}$, $-\mathrm{C}\left(\mathrm{CH}_{3}\right)_{2} \mathrm{CH}_{2} \mathrm{OH}, \quad \mathrm{CH}_{2} \mathrm{C}\left(\mathrm{CH}_{3}\right)_{2} \mathrm{OH}, \quad-\mathrm{CH}_{2} \mathrm{CN}, \quad-\mathrm{C}\left(\mathrm{CH}_{3}\right)_{2} \mathrm{CN}, \quad-\mathrm{CH}_{2} \mathrm{CH}_{2} \mathrm{SO}_{2} \mathrm{NH}_{2}$, $-\mathrm{CH}_{2} \mathrm{CH}_{2} \mathrm{NHSO}_{2} \mathrm{CH}_{3}$ and $-\mathrm{C}\left(\mathrm{CH}_{3}\right)_{2} \mathrm{CH}_{2} \mathrm{NHSO}_{2} \mathrm{CH}_{3}$.
22. A compound of claim 1 or 2 , wherein $\mathrm{R}^{2}$ is selected from $-(1-6 \mathrm{C}$ alkyl $) \mathrm{NH}_{2}$, $-(1-6 \mathrm{C}$ alkyl $) \mathrm{NH}\left(1-4 \mathrm{C}\right.$ alkyl) and $-\left(1-6 \mathrm{C}\right.$ alkyl) $\mathrm{N}(1-4 \mathrm{C} \text { alkyl })_{2}$.
23. A compound of claim 22, wherein $\mathrm{R}^{2}$ is selected from $-\mathrm{CH}_{2} \mathrm{C}\left(\mathrm{CH}_{3}\right)_{2} \mathrm{NH}_{2}$, $-\mathrm{C}\left(\mathrm{CH}_{3}\right)_{2} \mathrm{NHCH}_{3}$ and $-(1-6 \mathrm{C}$ alkyl $) \mathrm{NMe}_{2}$.
24. A compound of claim 1 or 2 , wherein $R^{2}$ is selected from -(1-6C alkyl)hetCyc ${ }^{1}$ and -(1-6C alkyl)hetAr ${ }^{1}$.
25. A compound of claim 1 or 2 , wherein $R^{2}$ is selected from -(1-6C alkyl)hetAr ${ }^{1}$ and het $\mathrm{Ar}^{2}$.
26. A compound according to any of claims 1-25, wherein $R^{1}$ is $H$.

27 A compound of claim 1 , wherein $N R^{1} R^{2}$ forms a 4-6 membered azacyclic ring optionally substituted with one or more substituents independently selected from -(1$6 \mathrm{C}) \mathrm{alkyl},-\mathrm{OH},-\mathrm{CO}_{2} \mathrm{H}$ and $-\left(1-3 \mathrm{C}\right.$ alkyl) $\mathrm{CO}_{2} \mathrm{H}$.
28. A compound according to any of claims 1-27, wherein X is $-\mathrm{CH}_{2}-$ or $-\mathrm{CH}_{2} \mathrm{CH}_{2}$-.
29. A compound of claim 28 wherein X is $-\mathrm{CH}_{2}$ -
30. A compound according to any of claims 1-27, wherein X is $-\mathrm{CH}_{2} \mathrm{O}$.
31. A compound according to any of claims 1-27, wherein X is $-\mathrm{CH}_{2} \mathrm{NR}^{\mathrm{d}}$ -
32. A compound according to any of claims 1-31, wherein Y is phenyl optionally substituted with one or more substituents independently selected from halogen, $-(1-4 \mathrm{C})$ alkoxy, $\mathrm{CF}_{3}, \mathrm{CHF}_{2}, \quad-\mathrm{O}\left(1-4 \mathrm{C}\right.$ alkyl)hetCyc ${ }^{3}$, $-(1-4 \mathrm{C}$ alkyl $)$ hetCyc ${ }^{3}$ and $-\mathrm{O}(1-4 \mathrm{C}$ alkyl) $\mathrm{O}(1-3 \mathrm{C}$ alkyl).
33. A compound of claim 32 , wherein Y is phenyl optionally substituted with one or more substituents independently selected from $-\mathrm{F},-\mathrm{Cl},-\mathrm{OMe},-\mathrm{CF}_{3},-\mathrm{CHF}_{2}$, morpholinylethoxy, morpholinylethyl and $-\mathrm{OCH}_{2} \mathrm{CH}_{2} \mathrm{OMe}$.
34. A compound of claim 33, wherein Y is phenyl, 3-fluorophenyl, 2,5difluorophenyl, 2-chloro-5-fluorophenyl, 2-methoxyphenyl, 2-methoxy-5-fluorophenyl, 2-trifluoromethyl-5-fluorophenyl, 2-difluoromethyl-5-fluorophenyl, 3-chloro-5-fluorophenyl, 3-fluoro-5-(2-morpholinylethoxy)phenyl, 3-fluoro-5-(2-morpholinylethyl)phenyl, 5-fluoro-2-(2-morpholinylethyl)phenyl, 3-fluoro-5-methoxyethoxyphenyl or 5-fluoro-2methoxyethoxyphenyl.
35. A compound according to any of claims 1-31, wherein Y is fluorophenyl optionally substituted with a substituent selected from - $\mathrm{O}\left(1-4 \mathrm{C}\right.$ alkyl)hetCyc ${ }^{3},-\mathrm{O}(1-4 \mathrm{C}$ alkyl)O(1-3C alkyl) and -O(3-6C dihydroxyalkyl).
36. A compound of claim 35, wherein Y is fluorophenyl substituted with a substituent selected from morpholinylethoxy, $-\mathrm{OCH}_{2} \mathrm{CH}_{2} \mathrm{OMe}$, 2,3-dihydroxypropoxy and 2,2-dimethyl-1,3-dioxolanyl.
37. A compound of claim 34 , wherein Y is 2,5 -difluorophenyl.
38. A compound according to any of claims $1-31$, 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 substituents independently selected from halogen, -O(1-4C alkyl) and (1-4C)alkyl.
39. A compound of claim 38 , wherein Y is pyridyl optionally substituted with one or more substituents independently selected from $\mathrm{F},-\mathrm{OMe}$ and Me .
40. A compound of claim 39, wherein Y is pyrid-2-yl, pyrid-3-yl, 5-fluoropyrid-3yl, 2-methoxy-5-fluoropyridy-3-yl or 2-methyl-5-fluoropyridy-3-yl.
41. A compound according to any of claims $1-31$, wherein Y is a $5-6$ membered heteroaryl ring having a ring heteroatom selected from N and S , wherein said ring is substituted with one or more substituents independently selected from halogen and (14C)alkyl.
42. A compound of claim 41, wherein Y is pyridyl substituted with one or more substituents independently selected from F , methyl and ethyl.
43. A compound of claim 42, wherein Y is 5-fluoropyrid-3-yl, 2-methyl-5-fluoropyrid-3-yl or 2-ethyl-5-fluoropyrid-3-yl.
44. A compound of claim 40 or 43 , wherein Y is 5 -fluoropyrid-3-yl.
45. A compound according to any of claims 1-31, wherein Y is a pyrid-2-on-3-yl ring optionally substituted with one or more substituents independently selected form halogen and ( $1-4 \mathrm{C}$ )alkyl.
46. A compound of claim 45 , wherein Y is 5 -fluoropyridin- $2(1 \mathrm{H})$-one optionally substituted with ( $1-4 \mathrm{C}$ )alkyl.
47. A compound of claim 1, wherein:
$\mathrm{R}^{1}$ is H or $-(1-6 \mathrm{C}$ alkyl);
$\mathrm{R}^{2} \quad$ is $\quad \mathrm{H}, \quad-(1-6 \mathrm{C})$ alkyl, $\quad-(1-6 \mathrm{C})$ fluoroalkyl, $\quad-(1-6 \mathrm{C})$ hydroxyalkyl, $\quad$-(2$6 \mathrm{C})$ dihydroxyalkyl, $-\left(1-6 \mathrm{C}\right.$ alkyl) CN , $-\left(1-6 \mathrm{C}\right.$ alkyl) $\mathrm{SO}_{2} \mathrm{NH}_{2}$, -(1-6C alkyl) $\mathrm{NHSO}_{2}(1-3 \mathrm{C}$ alkyl), -(1-6C alkyl) $\mathrm{NH}_{2}$, -(1-6C alkyl)NH(1-4C alkyl), $-(1-6 \mathrm{C}$ alkyl $) \mathrm{N}(1-4 \mathrm{C} \text { alkyl })_{2}$, $-(1-$ 6 C alkyl)hetCyc ${ }^{1},-(1-6 \mathrm{C}$ alkyl $)$ het $\mathrm{Ar}^{1}$, het $\mathrm{Ar}^{2}$, hetCyc ${ }^{2},-\mathrm{O}(1-6 \mathrm{C}$ alkyl), $-\mathrm{O}(3-6 \mathrm{C}$ cycloalkyl $)$, or $\mathrm{Cyc}^{1}$;
or $N R^{1} \mathrm{R}^{2}$ forms a 4-6 membered azacyclic ring optionally substituted with one or more substituents independently selected from -(1-6C)alkyl, $-\mathrm{OH},-\mathrm{CO}_{2} \mathrm{H}$ and $-(1-3 \mathrm{C}$ alkyl) $\mathrm{CO}_{2} \mathrm{H}$;
$\mathrm{Cyc}^{1}$ is a 3,4 or 5 membered cycloalkyl ring which is optionally substituted with one or more substituents independently selected from -(1-4C alkyl), $-\mathrm{OH},-\mathrm{OMe},-\mathrm{CO}_{2} \mathrm{H}$ and $-(1-$ 4C alkyl)OH.

X is $\mathrm{CH}_{2}$; and
Y is (i) fluorophenyl optionally substituted with a substituent selected from $-\mathrm{O}(1-4 \mathrm{C}$ alkyl)hetCyc ${ }^{3}$, $-\left(1-4 \mathrm{C}\right.$ alkyl)hetCyc ${ }^{3},-\mathrm{O}(1-4 \mathrm{C}$ alkyl $) \mathrm{O}(1-3 \mathrm{C}$ alkyl) and $-\mathrm{O}(3-6 \mathrm{C}$ dihydroxyalkyl), (ii) pyridyl substituted with one or more substituents independently selected from F, methyl and ethyl, or (iii) 5-fluoropyridin-2(1H)-one optionally substituted with (14C)alkyl.
48. A compound of claim 47, wherein Y is fluorophenyl optionally substituted with a substituent selected from - $\mathrm{O}\left(1-4 \mathrm{C}\right.$ alkyl)hetCyc ${ }^{3}$, $-(1-4 \mathrm{C}$ alkyl $)$ hetCyc ${ }^{3},-\mathrm{O}(1-4 \mathrm{C}$ alkyl)O(1-3C alkyl) and -O(3-6C dihydroxyalkyl).
49. A compound of claim 47, wherein Y is pyridyl substituted with one or more substituents independently selected from F , methyl and ethyl.
50. A compound of claim 47, wherein Y is 5 -fluoropyridin-2(1H)-one optionally substituted with ( $1-4 \mathrm{C}$ )alkyl.
51. A compound according to any of claims $47-50$, wherein $R^{2}$ is a 3,4 or 5 membered cycloalkyl ring which is optionally substituted with one or more substituents independently selected from -(1-4C)alkyl, $-\mathrm{OH},-\mathrm{OMe},-\mathrm{CH}_{2} \mathrm{OH}$ and $-(1-4 \mathrm{C}) \mathrm{alkylOH}$.
52. A compound according to claim 51 , wherein $\mathrm{R}^{4}$ is $\mathrm{OH}, \mathrm{F}$, methyl, or $\mathrm{CH}_{2} \mathrm{OH}$.
53. A compound according to claim 52 , wherein $n$ is 0,1 or 2 .
54. A compound according to claim 53 , wherein $\mathrm{R}^{3}$ is hydrogen.
55. A compound according to any of claims 1-54, wherein Y has the absolute configuration of Figure Ia:


Ia
56. A compound according to any of claims 1-55, wherein $\mathrm{R}^{3}$ is H .
57. A compound according to any of claims $1-56$, wherein $n$ is $0-2$ and $R^{4}$ is $F$ or Me.
58. A compound according to claim 57 , wherein n is 0 .
59. A pharmaceutical composition, which comprises a compound of Formula I as defined in any one of claims 1 to 58 , or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable diluent or carrier.
60. A method for treating a disease or disorder selected from 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 as defined in any one of claims 1 to 58 , or a pharmaceutically acceptable salt thereof.
61. The method of claim 60 , wherein the disease or disorder is pain.
62. A compound of Formula $\mathbf{I}$ as defined in any one of claims 1 to 58 , or a pharmaceutically acceptable salt thereof, for use in the treatment of pain, cancer, inflammation, neurodegenerative disease or Trypanosoma cruzi infection.
63. A process for the preparation of a compound of claim 1, which comprises:
(a) reacting a corresponding compound of Formula II


II or a reactive derivative thereof with an amine having the formula $\mathrm{HNR}^{1} \mathrm{R}^{2}$; or
(b) for compounds of Formula I where $\mathrm{R}^{1}$ and $\mathrm{R}^{2}$ are each hydrogen, reacting a compound of Formula III


III
with an inorganic acid; or
(c) for a compound of Formula $\mathbf{I}$ where $\mathrm{R}^{2}$ is (alkyl) $\mathrm{NHSO}_{2}((1-3 \mathrm{C}$ alkyl), reacting a compound having the formula IV


IV
with ( $1-3 \mathrm{C}$ alkyl) $\mathrm{SO}_{2} \mathrm{Cl}$; or
(d) for compounds of Formula I wherein Y is 5 -fluoropyridin-2(1H)-one, treating a corresponding compound having the formula VIII


VIII
with an acid at elevated temperatures; or
(e) for a compound of Formula $\mathbf{I}$ wherein $\mathrm{R}^{2}$ is $\mathrm{CH}_{2} \mathrm{CH}(\mathrm{OH}) \mathrm{CH}_{2} \mathrm{OH}$, treating a corresponding compound having the formula IX


IX
with an acid; or
(f) for a compound of Formula I wherein Y is fluorophenyl substituted with - $\mathrm{OCH}_{2} \mathrm{CH}(\mathrm{OH}) \mathrm{CH}_{2} \mathrm{OH}$, treating a corresponding compound having the formula $\mathbf{X}$

with an acid; and
removing or adding any protecting groups if desired, and forming a salt if desired.

