SUBSTITUTED PICOLINAMIDE KINASE INHIBITORS

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] This application claims priority under 35 U.S.C. 119(e) from U.S. Provisional Applications No. 61/663,510 filed on June 22, 2012 and Nonprovisional U.S. Application No. 13/841,867 filed March 15, 2013, which is herein incorporated in its entirety by reference.

FIELD OF THE INVENTION

[0002] Provided are picolinamide compounds which act as inhibitors of Spleen tyrosine kinase (Syk). Pharmaceutical compositions containing these compounds, methods for their use to treat a condition mediated at least in part by syk activity, and methods for their preparation are also provided.

BACKGROUND OF THE INVENTION

[0003] Protein kinases constitute a large family of structurally related enzymes that are responsible for the control of a variety of signal transduction processes within cells (see, e.g., Hardie and Hanks, The Protein Kinase Facts Book, I and II, Academic Press, San Diego, Calif., 1995). Protein kinases are thought to have evolved from a common ancestral gene due to the conservation of their structure and catalytic function. Almost all kinases contain a similar 250-300 amino acid catalytic domain. The kinases can be categorized into families by the substrates they phosphorylate (e.g., protein-tyrosine, protein-serine/threonine, lipids, etc.). Sequence motifs have been identified that generally correspond to each of these families (see, e.g., Hanks & Hunter, (1995), FASEB J. 9:576-596; Knighton *et al.*, (1991), Science 253:407-414; Hiles *et al.*, (1992), Cell 70:419-429; Kunz *et al.*, (1993), Cell 73:585-596; Garcia-Bustos *et al.*, (1994), EMBO J. 13:2352-2361).

[0004] Many diseases are associated with abnormal cellular responses triggered by protein kinase-mediated events. These diseases include autoimmune diseases, inflammatory diseases, bone diseases, metabolic diseases, neurological and neurodegenerative diseases, cancer, cardiovascular diseases, allergies, asthma, alzheimer's disease and hormone-related diseases. As

a consequence, there has been substantial efforts in medicinal chemistry to find inhibitors of protein kinases for use as therapeutic agents.

[0005] Immunoreceptor tyrosine activation motif (ITAM)-mediated signaling has emerged as a primary event in signaling pathways responsible for human pathologies. ITAM-mediated signaling is responsible for relaying activation signals initiated at classical immune receptors such as T-cell receptors, B-cell receptors, Fc receptors in immune cells and at GPVI and FcγRIIa in platelets to downstream intracellular molecules such as Syk and ZAP-70 (Underhill, D.M and Goodridge, H. S., *Trends Immunol.*, 28:66-73, 2007).

[0006] The binding of a ligand to an ITAM-containing receptor triggers signaling events which allows for the recruitment of proteins from a family of nonreceptor tyrosine kinases called the Src family. These kinases phosphorylate tyrosine residues within the ITAM sequence, a region with which the tandem SH2 domains on either Syk or ZAP-70 interact.

[0007] Syk, along with Zap-70, is a member of the Syk family of protein tyrosine kinases. The interaction of Syk or ZAP-70 with diphosphorylated ITAM sequences induces a conformation change in the kinases that allows for tyrosine phosphorylation of the kinase itself. Phosphorylated Syk family members activate a multitude of downstream signaling pathway proteins which include Src homology 2 (SH2) domain containing leukocyte-specific phosphoprotein of 76 kDa (SLP-76), Linker of Activation of T-cells (LAT) and PLC (phospholipase C)γ2.

[0008] Human pathologies attributed to dysfunctional ITAM-mediated signaling include autoimmune diseases such as rheumatoid arthritis, systemic lupus, multiple sclerosis, hemolytic anemia, immune-thrombocytopenia purpura, and heparin-induced thrombocytopenia and arteriosclerosis. Interestingly, many of the above mentioned diseases are thought to occur through crosslinking of Fc receptors by antibodies which, via Syk, activate a signaling cascade in mast, basophil and other immune cells that result in the release of cell mediators responsible for inflammatory reactions. The release of mediators and the production of cytokines in IgE stimulation-dependent allergic and inflammatory reactions from mast cells and basophiles can be controlled by inhibiting the tyrosine kinase activity of Syk (Rossi, A.B. *et al.*, *J Allergy Clin Immunol.*, 118:749-755, 2006). In immune-thrombocytopenia, antibody bound platelets are cleared by the spleen by an Fc receptor/ITAM/Syk-mediated process (Crow, A.R. *et al.*, *Blood*,

106:abstract 2165, 2005). Drug-induced thrombocytopenia, caused by heparin- platelet factor 4 immune complexes that activate platelet FcγRIIa, also involve Syk signaling downstream of receptor engagement (Reilly, M.P., *Blood*, 98:2442-2447, 2001).

[0009] Platelet agonists induce inside-out integrin signaling resulting in fibrinogen binding and platelet aggregation. This initiates outside-in signaling which produces further stimulation of platelets. Syk is activated during both phases of integrin signaling, and inhibition of Syk is shown to inhibit platelet adhesion to immobilized proteins (Law, D.A. *et al.*, *Blood*, 93:2645-2652, 1999). Release of arachidonic acid and serotonin and platelet aggregation induced by collagen are markedly inhibited in platelets derived from Syk deficient mouse (Poole, A. *et al.*, *EMBO J.*, 16:2333-2341, 1997). Thus Syk inhibitors may also possess anticoagulation action.

[0010] Because of the role Syk plays in Ig-induced platelet activation, it is likely to be important in arteriosclerosis and restenosis. Arteriosclerosis is a class of diseases characterized by the thickening and hardening of the arterial walls of blood vessels. Although all blood vessels are susceptible to this serious degenerative condition, the aorta and the coronary arteries serving the heart are most often affected. Arteriosclerosis is of profound clinical importance since it can increase the risk of heart attacks, myocardial infarctions, strokes, and aneurysms.

[0011] The traditional treatment for arteriosclerosis includes vascular recanalization procedures for less-serious blockages and coronary bypass surgery for major blockages. A serious shortcoming of intravascular procedures is that, in a significant number of treated individuals, some or all of the treated vessels restenose (*i.e.*, re-narrow). For example, restenosis of an atherosclerotic coronary artery after PTCA (Percutaeous Transluminal Coronary Angioplasty) occurs in 10-50% of patients undergoing this procedure and subsequently requires either further angioplasty or a coronary artery bypass graft. Furthermore, restenosis of an atherosclerotic coronary artery after stenting occurs in 10-20% of patients undergoing this procedure and subsequently requires repeat treatments to maintain adequate blood flow through the affected artery. Restenosis generally occurs in a relatively brief time period, *e.g.*, roughly less than six months, after treatment.

[0012] While the exact hormonal and cellular processes promoting restenosis have not been determined, restenosis is thought to be due in part to mechanical injury to the walls of the blood vessels caused by the balloon catheter or other intravascular device. For example, the process of

PTCA, in addition to opening the obstructed artery, also injures resident coronary arterial smooth muscle cells (SMCs). In response to this injury, adhering platelets, infiltrating macrophages, leukocytes, or the smooth muscle cells themselves release cell-derived growth factors such as platelet-derived growth factor (PDGF), with subsequent proliferation and migration of medial SMCs through the internal elastic lamina to the area of the vessel intima. Further proliferation and hyperplasia of intimal SMCs and, most significantly, production of large amounts of extracellular matrix over a period of three to six months results in the filling in and narrowing of the vascular space sufficient to significantly obstruct blood flow.

[0013] In addition to the role Syk plays in Ig-induced platelet activations, Syk plays a very important role in collagen-mediated signaling. The primary adhesive protein responsible for platelet adhesion and activation is collagen. Collagen is a filamentous protein contained within the fibrotic caps of atheromas which becomes exposed to blood during plaque rupture. Collagen functions initially by binding von Willebrand factor which tethers platelets through binding platelet membrane GPIb. Collagen functions secondarily by engaging the two collagen receptors on platelets, GPVI and integrin $\alpha 2\beta 1$.

[0014] GPVI exists in platelet membranes as a complex with FcRγ, an interaction required for the expression of GPVI. Activation of FcγRIIa on platelets results in platelet shape change, secretion and thrombosis. Signaling by the GPVI/FcRγ complex is initiated by tyrosine phosphorylation of the ITAM domain of FCRγ followed by the recruitment of Syk. Activation of GPVI leads to induction of multiple platelet functions including: activation of integrins $\alpha 2\beta 1$ to achieve firm platelet adhesion, and GP IIb-IIIa which mediates platelet aggregation and thrombosis growth; platelet secretion, allowing for the delivery of inflammatory proteins such as CD40L, RANTES and TGFβ to the vessel wall; and the expression of P-selectin which allows for the recruitment of leukocytes. Therefore, it is believed that Syk inhibitors can inhibit thrombotic events mediated by platelet adhesion, activation and aggregation.

[0015] It has been reported that the tyrosine phosphorylation of intracellular protein (activation) induced by stimulation of a receptor for IgG antibody, FcγR, and the phagocytosis mediated by FcγR are considerably inhibited in macrophages derived from Syk deficient mouse (Crowley, M.T. *et al.*, *J. Exp. Med.*, 186:1027-1039, 1997). This suggests that Syk has a markedly important role in the FcγR-mediated phagocytosis of macrophages.

[0016] It has also been reported that an antisense oligonucleotide of Syk suppresses the apoptosis inhibition of eosinophils induced by GM-CSF (Yousefi, S. *et al., J. E. Med.*, 183:1407-1414, 1996), showing that Syk is essential for the life extending signal of eosinophils caused by GM-CSF and the like. Since life extension of eosinophils is closely related to the transition of diseases into a chronic state in allergic disorders, such as asthma, Syk inhibitors can also serve as therapeutic agents for chronic eosinophilic inflammation.

[0017] Syk is important for the activation of B-cells via a B-cell antigen receptor and is involved in the phosphatidylinositol metabolism and increase in the intracellular calcium concentration caused by the antigen receptor stimulation (Hutchcroft, J E. *et al., J. Biol. Chem.*, 267:8613-8619, 1992; and Takata, M. *et al., EMBO J.*, 13:1341-1349, 1994). Thus, Syk inhibitors may be used to control the function of B-cells and are, therefore, expected to serve as therapeutic agents for antibody-related diseases.

[0018] Syk binds to a T-cell antigen receptor, quickly undergoes tyrosine phosphorylation through crosslinking of the receptor and synergistically acts upon intracellular signals mediated by Src tyrosine kinases such as Lck (Couture, C. *et al., Proc. Natl. Acad. Sci. USA,* 91:5301-5305, 1994; and Couture, C. *et al., Mol. Cell. Biol.,* 14:5249-5258, 1994). Syk is present in mature T-cell populations, such as intraepithelial γδ T-cells and naïve αβ T-cells, and has been reported to be capable of phosphorylation of multiple components of the TCR signaling cascade (Latour, S. *et. al., Mol Cell Biol.*, 17:4434-4441, 1997). As a consequence, Syk inhibitors may serve as agents for inhibiting cellular immunity mediated by T-cell antigen receptor.

[0019] Recent comparative genomic hybridization studies have identied Syk as another gene important in the pathogenesis of Mantle Cell Lymphoma (MCL) (Chen, R. *et al. Journal of Clinical Oncology*, 2007 ASCO Annual Meeting Proceedings (Post-Meeting Edition).Vol 25, No 18S (June 20 Supplement), 2007: 8056). MCL represents 5–10% of all non-Hodgkins lymphomas and it is a difficult form of lymphoma to treat. It has the worst prognosis among the B cell lymphomas with median survival of three years. It has been reported that Syk is overexpressed in MCL (Rinaldi, A, *et.al, Br. J. Haematol.,* 2006; 132:303–316) and that Syk mediates mTOR (mammalian target of Rapamycin) survival signals in follicular, mantel cell, Burkitt's, and diffuse large B-cell non-Hodgkin's lymphomas (Leseux, L., et. al, Blood, 2006; 108:4156-4162).

[0020] Several lines of evidence suggest that many B-cell lymphomas depend upon B-cell receptor (BCR)-mediated survival signals. BCR signaling induces receptor oligomerization and phosphorylation of Igα and β immunoreceptor tyrosine-based activated motifs by SRC family kinases. ITAM phosphorylation results in the recruitment and activation of Syk that initiates downstream events and amplifies the original BCR signal. Given the role of tonic BCR signaling in normal B cell and Syk-dependent survival of non-Hodgkins lymphoma cell lines in vitro (Chen, L., *et.al*, *Blood*, 2006; 108:3428–3433), Syk inhibition is a promising rational treatment target for certain B-cell lymphomas and chronic lymphocytic leukemia (CLL) (Stefania Gobessi, Luca Laurenti, Pablo Longo, Laura Carsetti, Giuseppe Leone, Dimitar G. Efremov, Constitutive activation of the protein tyrosine kinase Syk in Chronic Lymphocytic Leukemia B-cells, Blood, 2007, 110, Abstract 1123). Recent data shows that administration of a multikinase inhibitor which inhibits Syk, may have significant clinical activity in CLL patients (Friedberg JW *et al*, Blood 2010; 115(13),).

[0021] The oncogenic potential of the spleen tyrosine kinase (Syk) has been described in a number of different settings. Clinically, Syk over-expression is reported in Mantle Cell Lymphoma (Rinaldi, A, *et.al*, *Br. J. Haematol.*, 2006; 132:303–316) and the TEL-Syk fusion protein (Translocated ETS Leukemia) generated by a chromosomal translocation (t(9;12)(q22;p12)) leads to increased Syk activity and is associated with myelodysplastic syndrome (Kuno, Y., *et.al*, *Blood*, 2001; 97:1050–1055). Leukemia is induced in mice by adoptively transferring bone marrow cells that express human TEL-Syk (Wossning, T., JEM, 2006; 203:2829-2840). Further, in mouse primary bone marrow cells, over-expression of Syk results in IL-7 independent growth in culture (Wossning, T., *et.al*, JEM, 2006; 203:2829-2840). Additional recent studies also suggest that Syk-dependant survival signals may play a role in B-cell malignancies, including DLBCL(Diffuse Large B-Cell Lymphoma), mantle cell lymphoma and follicular lymphoma (Gururajan, Jennings *et al.* 2006; Irish, Czerwinski *et al.* J Immunol 176(10): 5715-9 (2006). Given the role of tonic BCR signaling in normal B cells and Syk-dependent survival of NHL cell lines in vitro, the specific inhibition of Syk may prove promising for the treatment of certain B-cell lymphomas.

[0022] Interestingly, Syk signaling appears to be required for B-cell development and survival in humans and mouse. Inducible loss of the B-cell receptor (Lam, K., *et.al*, Cell, 1997; 90:1073-

1083) or Igα (Kraus, M., *et.al*, Cell, 2004; 117:787-800) results in loss of peripheral B-cells in mice. Over-expression of the protein tyrosine phosphatase PTP-RO, which is known to negatively regulate Syk activity, inhibits proliferation and induces apoptosis in cell lines derived from non-Hodgkin's lymphomas (Chen, L., *et.al*, *Blood*, 2006; 108:3428–3433). Finally, B-cell lymphomas rarely exhibit loss of BCR expression, and anti-idiotype therapy rarely leads to resistance (Kuppers, R. Nat Rev Cancer, 2005; 5:251-262).

[0023] Engagement of the antigen-specific B cell receptor (BCR) activates multiple signaling pathways that ultimately regulate the cells activation status, promoting survival and clonal expansion. Signaling through the BCR is made possible by its association with two other members of the immunoglobulin super-family; Igα and Igβ, each bearing an immuno-tyrosine based activation motif (ITAM) (Jumaa, Hendriks *et al.* Annu Rev Immunol 23: 415-45 (2005). The ITAM domain is directly phosphorylated by Src family kinases in response to BCR engagement. The spleen tyrosine kinase (Syk) docks with and phosphorylates the ITAM, a process that enhances its kinase activity, resulting in Syk autophosphorylation and tyrosine phosphorylation of multiple downstream substrates (Rolli, Gallwitz *et al.* Mol Cell 10(5): 1057-69 (2002). This signaling pathway is active in B cells beginning at the transition from pro- to pre-B cell stage of development, when the newly formed pre-BCR is expressed. In fact, B cell development arrests at the pro-B cell stage in Syk knockout mice (Cheng, Rowley *et al.* 1995; Turner, Mee *et al.* Nature 378(6554): 303-6 (1995). Inducible loss of the B cell receptor (Lam, Kuhn *et al.* Cell 90(6): 1073-83 (1997) or Igα (Kraus, Alimzhanov *et al.* Cell 117(6): 787-800 (2004) results in loss of peripheral B cells in mice. Human B cells also appear to require Syk for proliferation and survival. Over-expression of the protein tyrosine phosphatase PTP-RO, a negative regulator of Syk activity, inhibits proliferation and induces apoptosis in cell lines derived from non-Hodgkin's lymphomas (NHL) (Chen, Juszczynski *et al.* Blood 108(10): 3428-33 (2006). Knock down of Syk by siRNA in the NHL line SUDHL-4 led to a block in the G1/S transition of the cell cycle (Gururajan, Dasu *et al.* J Immunol 178(1): 111-21 (2007). Together, these data suggest that Syk signaling is required for the development, proliferation, and even survival of human and mouse B cells.

[0024] Recently, R406 (Rigel Pharmaceuticals) was reported to inhibit ITAM signaling in response to various stimuli, including FcεR1 and BCR induced Syk activation (Braselmann,

Taylor *et al.* J Pharmacol Exp Ther 319(3): 998-1008(2006). Interestingly, this ATP-competitive inhibitor of Syk was also active against Flt3, cKit, and JAK kinases, but not against Src kinsase (Braselmann, Taylor *et al.* 2006). Activating mutations to Flt3 are associated with AML (Acute Myeloid Leukemia) and inhibition of this kinase is currently under clinical development (Burnett and Knapper Hematology Am Soc Hematol Educ Program 2007: 429-34 (2007). Over-activation of the tyrosine kinase cKit is also associated with hematologic malignancies, and a target for cancer therapy (Heinrich, Griffith *et al.* Blood 96(3): 925-32 (2000). Similarly, JAK3 signaling is implicated in leukemias and lymphomas, and is currently exploited as a potential therapeutic target (Heinrich, Griffith *et al.* 2000). Importantly, the multi-kinase inhibitory activity of R406 attenuates BCR signaling in lymphoma cell lines and primary human lymphoma samples, resulting in apoptosis of the former (Chen, Monti *et al.* Blood 111(4): 2230-7 (2008). Further, a phase II clinical trial reported favorable results by this compound in refractory NHL and chronic lymphocytic leukemia (Friedberg JW *et al*, Blood 2010; 115(13)). Although the precise mechanism of action is unclear for R406, the data suggest that inhibition of kinases that mediate survival signaling in lymphocytes is clinically beneficial.

[0025] Additional recent studies also suggest that Syk-dependant survival signals may play a role in B-cell malignancies, including DLBCL, mantle cell lymphoma and follicular lymphoma (see e.g., S. Linfengshen *et al. Blood*, Feb. 2008; 111: 2230-2237; J. M. Irish *et al. Blood*, 2006; 108: 3135-3142; A. Renaldi *et al. Brit J. Haematology*, 2006; 132: 303-316; M. Guruoajan *et al. J. Immunol*, 2006; 176: 5715-5719; L. Laseux *et al. Blood*, 2006; 108: 4156-4162.

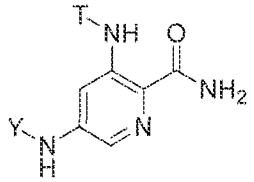
[0026] While progress has been made in this field, there remains a need in the art for compounds that inhibit Syk kinase, as well as for methods for treating conditions in a patient, such as restenosis, and/or inflammation that can benefit from such inhibition. Moreover, the availability of compounds that selectively inhibit one of these kinases as compared to other kinases would also be desirable. The present invention satisfies this and other needs.

BRIEF SUMMARY OF THE INVENTION

[0027] The present invention provides in one group of embodiments novel compounds having activity as inhibitors of Syk activity (also referred to herein as "Syk inhibitors"). In other groups

of embodiments, provided are methods for their preparation and use, and to pharmaceutical compositions containing the same.

[0028] In one group of embodiments, provided is a compound of Formula (I):



(I)

or a tautomer or a pharmaceutically acceptable salt thereof, wherein T and Y are described below.

[0029] In another group of embodiments, provided is a pharmaceutical composition comprising a therapeutically effective amount of a compound provided herein, or a pharmaceutical acceptable salt thereof, and a pharmaceutically acceptable carrier and/or diluent.

[0030] The compounds disclosed herein have utility over a wide range of therapeutic applications, and may be used to treat a variety of conditions, mediated at least in part by Syk activity, in both men and women, as well as a mammal in general (also referred to herein as a "subject"). For example, such conditions include, but are not limited to, those associated with cardiovascular disease, inflammatory disease, or autoimmune disease. More specifically, the compounds of the present invention have utility for treating conditions or disorders including, but not limited to: restenosis, inflammation, heparin induced thrombocytopenia, dilated cardiomyopathy, sickle cell disease, atherosclerosis, myocardial infarction, vascular inflammation, unstable angina, acute coronary syndromes, allergy, asthma, rheumatoid arthritis, B-cell mediated diseases such as Non-Hodgkin's lymphoma, Crohn's disease, anti-phospholipid syndrome, lupus, psoriasis, multiple sclerosis, and chronic lymphocytic leukemia. Thus, in one embodiment, methods are disclosed which include the administration of an effective amount of a compound provided herein, typically in the form of a pharmaceutical composition, to a subject in need thereof.

[0031] In one group of embodiments, provided is a method for inhibiting the Syk activity of a blood sample comprising contacting said sample with a compound of the present invention.

[0032] The group of embodiments, provided are compounds in purified forms, as well as chemical intermediates.

[0033] These and other embodiments, objects, features, and advantages of the invention will be apparent upon reference to the following detailed description. To this end, various references are set forth herein which describe in more detail certain background information, procedures, compounds and/or compositions, and are each hereby incorporated by reference in their entirety.

DETAILED DESCRIPTION OF THE INVENTION

[0034] These and other aspects, objects, features and advantages of the invention will be apparent upon reference to the following detailed description.

[0035] The abbreviations used herein are conventional, unless otherwise defined. ACN = acetonitrile, AcOH = acetic acid, AIBN = azobisisobutyronitrile (also azobisisobutylonitrile), aq. = aqueous, Ar = argon, Boc = t-butylcarboxy, Bz - benzoyl, Bn = benzyl, BOP = benzotriazol-1-yloxytris(dimethylamino)-phosphonium hexafluorophosphate, BPO = benzoyl peroxide, nBuOH = n-butanol, °C = degrees celcius, CBr_4 = tetrabromomethane, Cbz = benzyloxycarbonyl, mCPBA = m-chloroperoxybenzoic acid, CH_2Cl_2 or DCM = dichloromethane, Cs_2CO_3 = cesium carbonate, $CuCl_2$ = copper chloride; DIBAL = diisobutylaluminum hydride, DIEA = Hunig's base or diisopropyl ethylamine, DME = dimethoxy-ethane, DMF = dimethyl formamide, DMSO = dimethyl sulfoxide, DPPA = diphenyl phosphoryl azide, EDC = 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide, Et_3N = triethylamine, EtOAc = ethyl acetate, g = gram, HATU = 2-(1H 7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate, HOBT = hydroxybenzotriazole, H_2 = hydrogen; H_2O = water; HBr = hydrogen bromide; HCl = hydrogen chloride, HIV = human immunodeficiency virus, HPLC = high pressure liquid chromatography, h = hour, IgE = immunoglobulin E, IC_{50} = The concentration of an inhibitor that is required for 50% inhibition of an enzyme in vitro, IPA = isopropyl alcohol, kg = kilogram, KCN = potassium cyanide, KOH = potassium hydroxide, K_2PO_4 = potassium phosphate, LDA = lithium diisopropylamide, $LiAlH_4$ = lithium aluminum hydride = LiOH: lithium hydroxide; MeCN = acetonitrile; MS = Mass Spec, m/z = mass to charge ratio, Ms = methanesulfonyl, MHz = Mega Hertz, MeOH = methanol, MTBE = methyl tert-butyl ether, μM = micromolar, μL = microliter, mg = milligram, mm = millimeter, mM = millimolar, mmol = millimole, mL = milliliter, mOD/min = millioptical density units per minute, min = minute, M =

molar, Na_2CO_3 = sodium carbonate, ng = nanogram, $NaHCO_3$ = sodium bicarbonate; $NaNO_2$ = sodium nitrite; NaOH = sodium hydroxide; $Na_2S_2O_3$ = sodium thiosulfate; Na_2SO_4 = sodium sulfate; NBS = N-bromosuccinimide; NH_4Cl = ammonium chloride; NH_4OAc = ammonium acetate; NaSMe = sodium methylthiolate, NBS = N-bromosuccinamide, n-BuLi = n-butyl lithium, nm = nanometer, nM = nanomolar, N = Normal, NMP = N-methylpyrrolidone, NMR = nuclear magnetic resonance, Pd/C = palladium on carbon, $Pd(PPh_3)_4$ = Tetrakis-(triphenyl-phosphine)-palladium, pM = picomolar, Pin = pinacolato, PEG = polyethylene glycol, PMB = paramethoxybenzyl, PPh_3 or Ph_3P = triphenyl phosphine, psi = pound per square inch, pTSA= para-toluenesulphonic acid, RLV = Raucher leukemia virus, Ra-Ni = Rainey Nickel, rp = reverse phase, sat = saturated, $SOCl_2$ = thionyl chloride, RT = room temperature, TEA = triethylamine, THF = tetrahydrofuran, TFA = trifluoroacetic acid, TLC = thin layer chromatography, TMS = trimethylsilyl, Tf = trifluoromethylsulfonyl and TSC = trisodium citrate.

[0036] It is noted here that as used in this specification and the appended claims, the singular forms "a," "an," and "the" include plural reference unless the context clearly dictates otherwise.

[0037] "Alkoxy" refers to –O(alkyl) where alkyl as defined herein. Representative examples of alkoxy groups include methoxy, ethoxy, *t*-butoxy, and the like.

[0038] "Alkyl," by itself or as part of another substituent, means, unless otherwise stated, a straight or branched chain, fully saturated aliphatic hydrocarbon radical having the number of carbon atoms designated. For example, "C_{1-8}alkyl" refers to a hydrocarbon radical straight or branched, containing from 1 to 8 carbon atoms that is derived by the removal of one hydrogen atom from a single carbon atom of a parent alkane. Alkyl includes branched chain isomers of straight chain alkyl groups such as isopropyl, t-butyl, isobutyl, sec-butyl, and the like. Representative alkyl groups include straight and branched chain alkyl groups having 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 carbon atoms. Further representative alkyl groups include straight and branched chain alkyl groups having 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms.

[0039] "Alkenyl" refers to a linear monovalent hydrocarbon radical or a branched monovalent hydrocarbon radical having the number of carbon atoms indicated in the prefix and containing at least one double bond, but no more than three double bonds. For example, C_{2-8}alkenyl is meant to include, ethenyl, propenyl, 1,3-butadienyl and the like.

[0040] "Alkynyl" means a linear monovalent hydrocarbon radical or a branched monovalent hydrocarbon radical containing at least one triple bond and having the number of carbon atoms indicated in the prefix. The term "alkynyl" is also meant to include those alkyl groups having one triple bond and one double bond. For example, C_{2-8}alkynyl is meant to include ethynyl, propynyl and the like.

[0041] "Amino" refers to a monovalent radical $-NH_2$.

[0042] "Aryl" by itself or as part of another substituent refers to a polyunsaturated, aromatic, hydrocarbon group containing from 6 to 14 carbon atoms, which can be a single ring or multiple rings (up to three rings) which are fused together or linked covalently. Aryl groups include aromatic ring(s) fused to non-aromatic cycloalkyl groups and where the point of attachment to the remainder of the molecule can be through any suitable ring atom of any ring. Thus the phrase includes, but is not limited to, groups such as phenyl, biphenyl, anthracenyl, naphthyl by way of example. Non-limiting examples of aryl groups include phenyl, 1-naphthyl, 2-naphthyl and 4-biphenyl.

[0043] "Bond" when used as an element in a Markush group means that the corresponding group does not exist, and the groups of both sides are directly linked.

[0044] "Cycloalkyl" refers to a saturated or partially saturated cyclic group of from 3 to 14 carbon atoms and no ring heteroatoms and having a single ring or multiple rings including fused, bridged, and spiro ring systems. The term "cycloalkyl" includes cycloalkenyl groups, a partially saturated cycloalkyl ring having at least one site of >C=C< ring unsaturation. Examples of cycloalkyl groups include, for instance, adamantyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclooctyl, and cyclohexenyl. "$C_{u'-v'}$cycloalkyl" refers to cycloalkyl groups having u' to v' carbon atoms as ring members. "$C_{u'-v'}$cycloalkenyl" refers to cycloalkenyl groups having u' to v' carbon atoms as ring members.

[0045] "Heteroaryl" refers to a cyclic or polycyclic radical having at least one aromatic ring and from one to five ring heteroatom selected from N, O, and S, and optionally one or more oxo (=O) substituents attached to one or more carbon ring atoms, and wherein the nitrogen and sulfur ring atoms are optionally oxidized. A heteroaryl group can be attached to the remainder of the molecule through a heteroatom or through a carbon atom and can contain 5 to 10 carbon atoms.

Heteroaryl groups include polycyclic aromatic ring(s) fused to non-aromatic cycloalkyl or heterocycloalkyl groups, and where the point of attachment to the remainder of the molecule can be through any suitable ring atom of any ring. In a polycyclic heteroaryl group, the ring heteroatom(s) can be in either an aromatic or non-aromatic ring or both. The term "aromatic ring" include any ring having at least one planar resonance structure where 2n+2 pi electrons are delocalized about the ring. Non-limiting examples of heteroaryl groups include xanthine, hypoxanthine, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, benzopyrazolyl, 5-indolyl, azaindole, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxalinyl, 5-quinoxalinyl, 3-quinolyl, 6-quinolyl 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 1-pyrazolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl and 4-pyrimidyl. "Monocyclic heteroaryl" refers to a heteroaryl radical that contains one ring. "Bicyclic heteroaryl" refers to a heteroaryl radical that contains two rings.

[0046] The term "heterocycloalkyl" or "heterocyclyl" refers to a cycloalkyl group containing at least one ring heteroatom and optionally one or more oxo substituents. As used herein, the term "heteroatom" is meant to include oxygen (O), nitrogen (N), and sulfur (S), wherein the heteroatoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. Each heterocycle can be attached at any available ring carbon or heteroatom. Each heterocycle may have one or more rings. When multiple rings are present, they can be fused together. Each heterocycle typically contains 1, 2, 3, 4 or 5, independently selected heteroatoms. Preferably, these groups contain 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms, 0, 1, 2, 3, 4 or 5 nitrogen atoms, 0, 1 or 2 sulfur atoms and 0, 1 or 2 oxygen atoms. More preferably, these groups contain 1, 2 or 3 nitrogen atoms, 0-1 sulfur atoms and 0-1 oxygen atoms. Non-limiting examples of heterocycle groups include morpholin-3-one, piperazine-2-one, piperazin-1-oxide, piperidine, morpholine, piperazine, isoxazoline, pyrazoline, imidazoline, pyrrolidine, and the like.

[0047] "Halo" or "halogen" by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Additionally, terms such as "haloalkyl", are meant to include alkyl in which one or more hydrogen is substituted with halogen atoms which can be the same or different, in a number ranging from one up to the maximum number of halogens permitted e.g. for alkyl, (2m'+1), where m' is the total number of

carbon atoms in the alkyl group. For example, the term "halo$C_{1\text{-}8}$alkyl" is meant to include difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like. The term "haloalkenyl", and "haloalkynyl" refers to alkenyl and alkynyl radicals having one or more halogen atoms. Additionally, term "haloalkoxy" refers to an alkoxy radical substituted with one or more halogen atoms. In one group of embodiments, the haloakyl, haloalkenyl, haloalkynyl, and haloalkoxy groups have from one to 5 or from one to 3 halo atoms. Examples of haloalkoxy groups include difluoromethoxy and trifluoromethoxy. In one group of embodiments, the halo atoms of the haloalkenyl and haloalkynyl groups are attached to the aliphatic portions of these groups.

[0048] The terms "optional" or "optionally" as used throughout the specification means that the subsequently described event or circumstance may but need not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, "heteroaryl group optionally substituted with an alkyl group means that the alkyl may but need not be present, and the description includes situations where the heteroaryl group is substituted with an alkyl group and situations where the heteroaryl group is not substituted with the alkyl group.

[0049] The term "oxo" includes a mono $-O^-$ or divalent $=O$ oxygen atom.

[0050] In each of the above embodiments designating a number of atoms e.g. "$C_{1\text{-}8}$" is meant to include all possible embodiments that have one fewer atom. Non-limiting examples include $C_{1\text{-}4}$, $C_{1\text{-}5}$, $C_{1\text{-}6}$, $C_{1\text{-}7}$, $C_{2\text{-}8}$, $C_{2\text{-}7}$, $C_{3\text{-}8}$, $C_{3\text{-}7}$ and the like.

[0051] The term "pharmaceutically acceptable salts" is meant to include salts of the active compounds which are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds of the present invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of salts derived from pharmaceutically-acceptable inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic, manganous, potassium, sodium, zinc and the like. Salts derived from pharmaceutically-acceptable organic bases include salts of primary, secondary and tertiary amines, including substituted amines, cyclic amines, naturally-occurring amines and the like,

such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like. When compounds of the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, malonic, benzoic, succinic, suberic, fumaric, mandelic, phthalic, benzenesulfonic, *p*-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (see, e.g., Berge, S.M. *et al.*, "Pharmaceutical Salts," *Journal of Pharmaceutical Science*, 66:1-19, 1977). Certain specific compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

[0052] The neutral forms of the compounds may be regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents, but otherwise the salts are equivalent to the parent form of the compound for the purposes of the present invention.

[0053] The term "pharmaceutically acceptable carrier or excipient" means a carrier or excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes a carrier or excipient that is acceptable for veterinary use as well as human pharmaceutical use. A "pharmaceutically acceptable carrier or excipient" as used in the specification and claims includes both one and more than one such carrier or excipient.

[0054] The terms "pharmaceutically effective amount", "therapeutically effective amount" or "therapeutically effective dose" refers to the amount of the subject compound that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician. The term "therapeutically effective amount" includes that amount of a compound that, when administered, is sufficient to prevent development of, or alleviate to some extent, one or more of the symptoms of the condition or disorder being treated. The therapeutically effective amount will vary depending on the compound, the disorder or condition and its severity and the age, weight, etc., of the mammal to be treated.

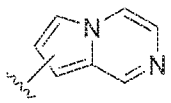
[0055] "Protecting group" refers to a group of atoms that, when attached to a reactive functional group in a molecule, mask, reduce or prevent the reactivity of the functional group. Typically, a protecting group may be selectively removed as desired during the course of a synthesis. Examples of protecting groups can be found in Greene and Wuts, Protective Groups in Organic Chemistry, 3rd Ed., 1999, John Wiley & Sons, NY and Harrison *et al.*, Compendium of Synthetic Organic Methods, Vols. 1-8, 1971-1996, John Wiley & Sons, NY. Representative amino protecting groups include, but are not limited to, formyl, acetyl, trifluoroacetyl, benzyl, benzyloxycarbonyl ("CBZ"), tert-butoxycarbonyl ("Boc"), trimethylsilyl ("TMS"), 2-trimethylsilyl-ethanesulfonyl ("TES"), trityl and substituted trityl groups, allyloxycarbonyl, 9-fluorenylmethyloxycarbonyl ("FMOC"), nitro-veratryloxycarbonyl ("NVOC") and the like. Representative hydroxy protecting groups include, but are not limited to, those where the hydroxy group is either acylated or alkylated such as benzyl and trityl ethers, as well as alkyl ethers, tetrahydropyranyl ethers, trialkylsilyl ethers (e.g., TMS or TIPPS groups) and allyl ethers.

[0056] "Tautomer" refers to alternate forms of a molecule that differ in the position of a proton, such as enol-keto and imine-enamine tautomers, or the tautomeric forms of heteroaryl groups containing a -N=C(H)-NH- ring atom arrangement, such as pyrazoles, imidazoles, benzimidazoles, triazoles, and tetrazoles. A person of ordinary skill in the art would recognize that other tautomeric ring atom arrangements are possible.

[0057] The terms "treat", "treating", "treatment" and grammatical variations thereof as used herein, includes partially or completely delaying, alleviating, mitigating or reducing the intensity, progression, or worsening of one or more attendant symptoms of a disorder or condition and/or

alleviating, mitigating or impeding one or more causes of a disorder or condition. Treatments according to the invention may be applied preventively, prophylactically, pallatively or remedially.

[0058] The term "wavy line" signifies the point of attachment of the substituent to the remainder of the molecule, such as to the part of the molecule containing the picolinamide core. When the wavy line is not depicted as being specifically appended to a specific ring atom, the point of attachment can be to any suitable atom of the substituent. For example, the wavy line in the following structure:



is intended to include, as the point of attachment, any of the six substitutable carbon atoms.

[0059] Compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed "isomers". Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers". "Stereoisomer" and "stereoisomers" refer to compounds that exist in different stereoisomeric forms if they possess one or more asymmetric centers or a double bond with asymmetric substitution and, therefore, can be produced as individual stereoisomers or as mixtures. Stereoisomers include enantiomers and diastereomers. Stereoisomers that are not mirror images of one another are termed "diastereomers" and those that are non-superimposable mirror images of each other are termed "enantiomers". When a compound has an asymmetric center, for example, it is bonded to four different groups, a pair of enantiomers is possible. An enantiomer can be characterized by the absolute configuration of its asymmetric center and is described by the R- and S-sequencing rules of Cahn and Prelog, or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or levorotatory (*i.e.*, as (+) or (-)-isomers respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is called a "racemic mixture". Unless otherwise indicated, the description is intended to include individual stereoisomers as well as mixtures. The methods for the determination of stereochemistry and the separation of stereoisomers are well-known in the art (*see* discussion in Chapter 4 of ADVANCED

ORGANIC CHEMISTRY, 4th edition J. March, John Wiley and Sons, New York, 1992) differ in the chirality of one or more stereocenters.

[0060] The compounds of the present invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with isotopes, such as for example deuterium (^{2}H), tritium (^{3}H), iodine-125 (^{125}I) or carbon-14 (^{14}C). 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.

[0061] Unless indicated otherwise, the nomenclature of substituents that are not explicitly defined herein are arrived at by naming the terminal portion of the functionality followed by the adjacent functionality toward the point of attachment. For example, the substituent "alkoxyalkyl" refers to an akyl group that is substituted with alkoxy, "hydoxyalkyl" refers to an akyl group that is substituted with hydroxyl, and (phenyl)C_{1-8}alkyl refers to an akyl group that is substituted with phenyl. For these substituents, the point of attachment is at the alkyl group.

[0062] It is understood that the definitions and formulas provided herein are not intended to include impermissible substitution patterns (*e.g.*, methyl substituted with 5 fluoro groups). Such impermissible substitution patterns are well known to the skilled artisan.

[0063] An "antagonist" or "inhibitor" refers to an agent or molecule that inhibits or binds to, partially or totally blocks stimulation or activity, decreases, closes, prevents, delays activation or enzymatic activity, inactivates, desensitizes, or down regulates the activity of a receptor of the invention. As used herein, "antagonist" also includes a reverse or inverse agonist.

[0064] As used herein, the term "condition or disorder responsive to modulation of Syk " and related terms and phrases refer to a condition or disorder associated with inappropriate, e.g., less than or greater than normal, activity of Syk and at least partially responsive to or affected by modulation of Syk (e.g., Syk antagonist or agonist results in some improvement in patient well-being in at least some patients). Inappropriate functional activity of Syk might arise as the result of expression of Syk in cells which normally do not express the receptor, greater than normal production of Syk, or slower than normal metabolic inactivation or elimination of Syk or its active metabolites, increased expression of Syk or degree of intracellular activation (leading

to, e.g., inflammatory and immune-related disorders and conditions) or decreased expression of Syk. A condition or disorder associated with Syk may include a " Syk -mediated condition or disorder".

[0065] As used herein, the phrases "a condition or disorder mediated at least in part by Syk kinase activity", and related phrases and terms refer to a condition or disorder characterized by inappropriate, e.g., greater than normal, Syk activity. Inappropriate Syk functional activity might arise as the result of Syk expression in cells which normally do not express Syk or increased Syk expression or degree of intracellular activation (leading to, e.g., inflammatory and immune-related disorders and conditions). A condition or disorder mediated at least in part by Syk or JAK kinase activity may be completely or partially mediated by inappropriate Syk functional activity. However, a condition or disorder mediated at least in part by Syk kinase activity is one in which modulation of Syk results in some effect on the underlying condition or disorder (e.g., an Syk antagonist results in some improvement in patient well-being in at least some patients).

[0066] The term "inflammation" as used herein refers to infiltration of white blood cells (*e.g.,* leukocytes, monocytes, *etc.*) into the area being treated for restenosis.

[0067] The term "intervention" refers to an action that produces an effect or that is intended to alter the course of a disease process. For example, "vascular intervention" refers to the use of an intravascular procedure such as angioplasty or a stent to open an obstructed blood vessel.

[0068] The term "intravascular device" refers to a device useful for a vascular recanalization procedure to restore blood flow through an obstructed blood vessel. Examples of intravascular devices include, without limitation, stents, balloon catheters, autologous venous/arterial grafts, prosthetic venous/arterial grafts, vascular catheters, and vascular shunts.

[0069] The term "leukocyte" refers to any of the various blood cells that have a nucleus and cytoplasm, separate into a thin white layer when whole blood is centrifuged, and help protect the body from infection and disease. Examples of leukocytes include, without limitation, neutrophils, eosinophils, basophils, lymphocytes, and monocytes.

[0070] The terms "modulate", "modulation" and the like refer to the ability of a compound to increase or decrease the function and/or expression of Syk, where such function may include

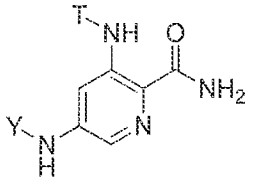
transcription regulatory activity and/or protein-binding. Modulation may occur *in vitro* or *in vivo*. Modulation, as described herein, includes the inhibition, antagonism, partial antagonism, activation, agonism or partial agonism of a function or characteristic associated with Syk, either directly or indirectly, and/or the upregulation or downregulation of the expression of Syk, either directly or indirectly. In a preferred embodiment, the modulation is direct. Inhibitors or antagonists are compounds that, e.g., bind to, partially or totally block stimulation, decrease, prevent, inhibit, delay activation, inactivate, desensitize, or downregulate signal transduction. Activators or agonists are compounds that, e.g., bind to, stimulate, increase, open, activate, facilitate, enhance activation, activate, sensitize or upregulate signal transduction. The ability of a compound to inhibit the function of Syk can be demonstrated in a biochemical assay, e.g., binding assay, or a cell-based assay, e.g., a transient transfection assay.

[0071] "Modulators" of activity are used to refer to "ligands", "antagonists" and "agonists" identified using *in vitro* and *in vivo* assays for activity and their homologs and mimetics. Modulators include naturally occurring and synthetic ligands, antagonists, agonists, molecules and the like. Assays to identify antagonists and agonists include, e.g., applying putative modulator compounds to cells, in the presence or absence of a receptor of the invention and then determining the functional effects on a receptor of the invention activity. Samples or assays comprising a receptor of the invention that are treated with a potential activator, inhibitor, or modulator are compared to control samples without the inhibitor, activator, or modulator to examine the extent of effect. Control samples (untreated with modulators) are assigned a relative activity value of 100%. Inhibition is achieved when the activity value of a receptor of the invention relative to the control is about 80%, optionally 50% or 25-1%. Activation is achieved when the activity value of a receptor of the invention relative to the control is 110%, optionally 150%, optionally 200-500%, or 1000-3000% higher.

[0072] "Subject" refers to human and non-human animals, especially mammals. Examples of subjects include, but are not limited to, humans, cows, dogs, cats, goats, sheep, pigs and rabbits.

Kinase inhibitors

[0073] In one group of embodiments, provided is a compound of Formula (I):



(I)

or a tautomer or a pharmaceutically acceptable salt thereof, wherein

T is $(CH_2)_d(X^1)$ where X^1 is selected from the group consisting of aryl and monocyclic or bicyclic heteroaryl comprising 1-4 heteroatoms selected from S, O and N, wherein the aryl and heteroaryl are optionally substituted with 1 to 5 R^1 and d is 0 or 1;

each R^1 is independently selected from the group consisting of halo, C_{1-8}alkyl, C_{2-8}alkenyl, haloC_{1-8}alkyl, $(CH_2)_nSR^{1a}$, $(CH_2)_nOR^{1a}$, $O(CH_2)_jOR^{1a}$, $(CH_2)_nNR^{1b}R^{1c}$, $(CH_2)_nCOR^{1e}$, $(CH_2)_nCONR^{1b}R^{1c}$, $(CH_2)_nNR^{1b}COR^{1e}$, $(CH_2)_nCONR^{1b}(OR^{1a})$, $(CH_2)_nCO_2R^{1a}$, $O(CH_2)_nCO_2R^{1a}$, $(CH_2)_nNR^{1b}CO_2R^{1a}$, $(CH)_nSO_2NR^{1b}R^{1c}$, $(CH_2)_nNR^{1b}SO_2R^{1e}$, $(CH_2)_nSOR^{1e}$, $(CH_2)_nSO_2R^{1e}$, oxo, $(CH_2)_nCN$, N_3, NO_2, and –L-W, where n is 0, 1, 2, 3, 4, 5, or 6 and j is 1, 2, 3, 4, 5, or 6;

L is selected from the group consisting of $-O(CH_2)_b-$, -SO-, $-SO_2-$, -CO-, $-NR^{1d}-$, $-CONR^{1d}(CH_2)_b-$, $-NR^{1d}CO-$, $-NR^{1d}SO_2-$, $-SO_2NR^{1d}-$, a bond, and $-(CH_2)_z-$ where b is 0, 1, 2, 3, 4, or 5 and z is 1, 2, 3, 4, or 5;

W is selected from the group consisting of aryl, monocyclic or bicyclic heteroaryl comprising 1-4 heteroatoms selected from S, O and N, C_{3-8}cycloalkyl, and 3-8 membered heterocyclyl comprising 1-4 heteroatoms selected from S, O and N, each optionally substituted with 1 to 3 R^2;

each R^2 is independently selected from the group consisting of halo, C_{1-8}alkyl, C_{2-8}alkenyl, haloC_{1-8}alkyl, $(CH_2)_mSR^{2a}$, $(CH_2)_mOR^{2a}$, $O(CH_2)_kOR^{2a}$, $(CH_2)_mNR^{2b}R^{2c}$, $(CH_2)_mCOR^{2e}$, $(CH_2)_mCONR^{2b}R^{2c}$, $(CH_2)_mNR^{2b}COR^{2e}$, $(CH_2)_mCONR^{2b}(OR^{2a})$, $(CH_2)_mCO_2R^{2a}$, $O(CH_2)_mCO_2R^{2a}$, $(CH_2)_mNR^{2b}CO_2R^{2a}$, $(CH)_mSO_2NR^{2b}R^{2c}$, $(CH_2)_mNR^{2b}SO_2R^{2e}$, $(CH_2)_mSOR^{2e}$, $(CH_2)_mSO_2R^{2e}$, oxo, $(CH_2)_mCN$, N_3, and NO_2, where m is 0, 1, 2, 3, 4, 5, or 6 and k is 1, 2, 3, 4, 5, or 6;

R^{1a}, R^{1b}, R^{1c}, R^{1d}, R^{2a}, R^{2b}, and R^{2c} are independently selected from the group consisting of H, C_{1-8}alkyl, C_{2-8}alkenyl, and haloC_{1-8}alkyl;

R^{1e} and R^{2e} are independently selected from the group consisting of C_{1-8}alkyl, C_{2-8}alkenyl, and haloC_{1-8}alkyl;

Y is  or $(CH_2)_v(X^2)$, wherein

v is 0, 1, 2, or 3;

X^2 is selected from the group consisting of CH_2CH_3, $(CH_2)_3NH_2$, C_{3-8}cycloalkyl, 3-8 membered heterocyclyl comprising 1-4 heteroatoms selected from S, O and N, aryl, and monocyclic or bicyclic heteroaryl comprising 1-4 heteroatoms selected from S, O and N, wherein cycloalkyl, heterocyclyl, aryl, and heteroaryl are each optionally substituted with 1 to 3 R^{10};

R^4 is selected from the group consisting of H, halo, C_{1-8}alkyl, C_{2-8}alkenyl, haloC_{1-8}alkyl, $(CH_2)_pSR^{4a}$, $(CH_2)_pSOR^{4a}$, $(CH_2)_pSO_2R^{4a}$, $(CH_2)_pOR^{4a}$, $(CH_2)_pNR^{4b}R^{4c}$, $(CH_2)_fCONR^{4b}R^{4c}$, $(CH_2)_pNR^{4b}COR^{4d}$, $(CH_2)_fCO_2R^{4a}$, $(CH_2)_pNR^{4b}CO_2R^{4a}$, $(CH_2)_f$ C_{3-8}cycloalkyl, $(CH_2)_p(O)$ C_{3-8}cycloalkyl, $(CH_2)_p(S)$ C_{3-8}cycloalkyl, $(CH)_pSO_2NR^{4b}R^{4c}$, $(CH_2)_pNH$ C_{3-8}cycloalkyl, $(CH_2)_fCN$, $(CH_2)_f$(aryl), $(CH_2)_f$(monocyclic or bicyclic heteroaryl comprising 1-4 heteroatoms selected from S, O and N), $(CH_2)_f$(aryl)(monocyclic or bicyclic heteroaryl comprising 1-4 heteroatoms selected from S, O and N), $(CH_2)_f$(3-8 membered heterocyclyl comprising 1-4 heteroatoms selected from S, O and N), $(CH_2)_p(O)(CH_2)_f$(aryl), $(CH_2)_p(O)(CH_2)_f$(monocyclic or bicyclic heteroaryl comprising 1-4 heteroatoms selected from S, O and N), $(CH_2)_p(O)(CH_2)_fC_{3-8}$cycloalkyl, and $(CH_2)_p(O)(CH_2)_f$(3-8 membered heterocyclyl comprising 1-4 heteroatoms selected from S, O and N), where aryl, heteroaryl, cycloalkyl, and heterocyclyl are each optionally substituted with 1 to 3 R^{11a}, f is 0, 1, 2, 3, 4, 5, or 6, and p is 1, 2, 3, 4, 5, or 6; or R^4 and R^5 together form =O or a 3 to 8 membered carbocyclic or heterocyclic ring optionally substituted with 1 to 3 R^{11a};

R^5 is selected from the group consisting of H and C_{1-8}alkyl;

R^6 is selected from the group consisting of H, C_{1-8}alkyl, OH, O(C_{1-8}alkyl), CO_2R^{6a}, $CO(NR^{6a}R^{6b})$, and C_{3-8}cycloalkyl; or R^6 together with R^7 and the atoms to which they are attached to form a heterocyclyl ring optionally substituted with 1 to 3 R^{11b};

R^7 is selected from the group consisting of H, C_{1-8}alkyl, and cycloalkyl;

R^8 is selected from the group consisting of H, C_{1-8}alkyl, $(CH_2)_uNR^{8b}R^{8c}$, $(CH_2)_gCONR^{8b}R^{8c}$, $(CH_2)_gCO(CH_2)_uNR^{8b}R^{8c}$, $(CH_2)_gCO_2R^{8a}$, $(CH_2)_uOR^{8a}$,

$CH(C_{1-8}alkyl)OR^{8a}$, $(CH_2)_g$ C_{3-8}cycloalkyl, (CH_2) 3-8 membered heterocyclyl comprising 1-4 heteroatoms selected from S, O and N, $(CH_2)_g$aryl, (CH_2) monocyclic or bicyclic heteroaryl comprising 1-4 heteroatoms selected from S, O and N, and $(CH_2)_u(O)$(aryl), where aryl, cycloalkyl, heteroaryl, and heterocyclyl are each optionally substituted with 1 to 3 R^{11c}, g is 0, 1, 2, 3, 4, 5, or 6 and u is 1, 2, 3, 4, 5, or 6; or R^8 together with R^9 and the atoms to which they are attached to form =O, =S, or a cycloalkyl or heterocyclyl ring optionally substituted with R^{11c};

R^9 is H or alkyl;

R^{10} is independently selected from the group consisting of halo, C_{1-8}alkyl, C_{2-8}alkenyl, haloC_{1-8}alkyl, $(CH_2)_qSR^{10a}$, $(CH_2)_qOR^{10a}$, $(CH_2)_qNR^{10b}R^{10c}$, $(CH_2)_qCOR^{10d}$, $(CH_2)_qCONR^{10b}R^{10c}$, $(CH_2)_qNR^{10b}COR^{10d}$, $(CH_2)_qCONR^{10b}(OR^{10a})$, $(CH_2)_qCO_2R^{10a}$, $O(CH_2)_qCO_2R^{10a}$, $(CH_2)_qNR^{10b}CO_2R^{10a}$, $(CH)_qSO_2NR^{10b}R^{10c}$, $(CH_2)_qNR^{10b}SO_2R^{10d}$, $(CH_2)_qSOR^{10d}$, $(CH_2)_qSO_2R^{10d}$, oxo, $(CH_2)_qCN$, N_3, $N{=}CH_2$, NO_2, C(O) 3-8 membered heterocyclyl comprising 1-4 heteroatoms selected from S, O and N, aryl, monocyclic or bicyclic heteroaryl comprising 1-4 heteroatoms selected from S, O and N, C_{3-8}cycloalkyl, and 3-8 membered heterocyclyl comprising 1-4 heteroatoms selected from S, O and N, where aryl, cycloalkyl, heteroaryl, and heterocyclyl are each optionally substituted with 1 to 3 R^{11d} and q is 0, 1, 2, 3, 4, 5, or 6;

R^{11a}, R^{11b}, R^{11c}, and R^{11d} are independently selected from the group consisting of halo, C_{1-8}alkyl, haloC_{1-8}alkyl, OH, C_{1-8}alkoxy, haloC_{1-8}alkoxy, $C(O)C_{1-8}$alkyl, CO_2C_{1-8}alkyl, and SO_2C_{1-8}alkyl;

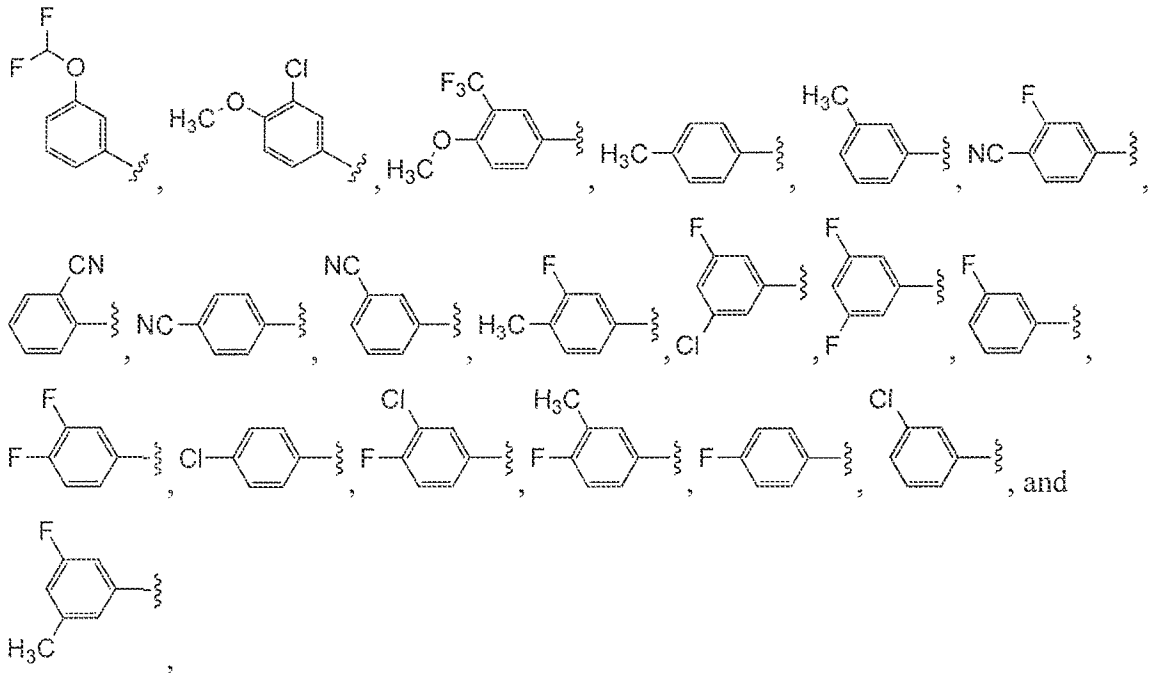
R^{4a}, R^{4b}, R^{4c}, R^{6a}, R^{6b}, R^{8a}, R^{8b}, R^{8c}, R^{10a}, R^{10b}, and R^{10c} are independently selected from the group consisting of H, C_{1-8}alkyl, C_{2-8}alkenyl, and haloC_{1-8}alkyl;

R^{4d} and R^{10d} are independently selected from the group consisting of C_{1-8}alkyl, C_{2-8}alkenyl, and haloC_{1-8}alkyl; and

the wavy line indicates the point of attachment to the rest of the molecule.

[0074] In one group of embodiments, T is phenyl substituted with 1 to 5 R^1.

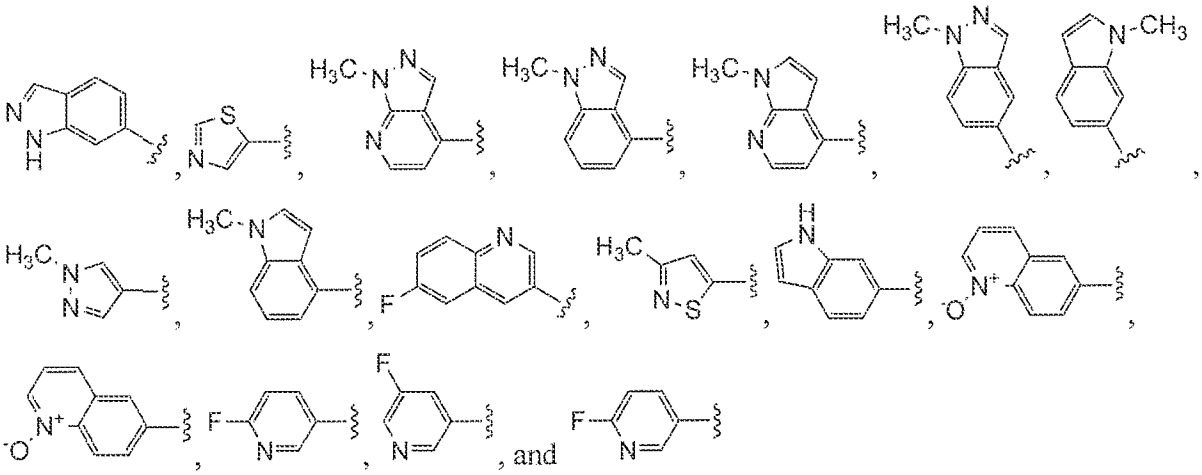
[0075] In one group of embodiments, T is selected from the group consisting of



where the wavy line indicates the point of attachment to the rest of the molecule.

[0076] In one group of embodiments, T is monocyclic or bicyclic heteroaryl comprising 1-4 heteroatoms selected from S, O and N, optionally substituted with 1 to 5 R^1.

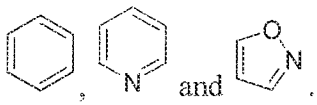
[0077] In one group of embodiments, T is selected from the group consisting of



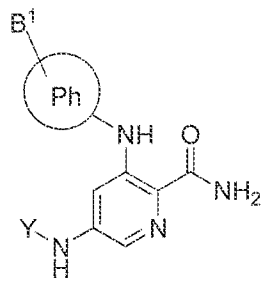
where the wavy line indicates the point of attachment to the rest of the molecule.

[0078] In one group of embodiments, at least one R^1 is –L-W.

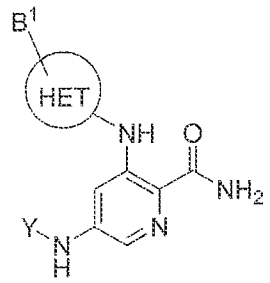
[0079] In one group of embodiments, –L-W is –CO-NR^aR^b where R^a and R^b together form a four to six membered ring optionally substituted with 1 to 3 groups independently selected from halo, C_{1-8}alkyl, and haloC_{1-8}alkyl or L is a bond and W is selected from the group consisting of



[0080] In one group of embodiments, provided is a compound of Formula (Ia) or (Ib) or a tautomer or a pharmaceutically acceptable salt thereof



(Ia)



(Ib)

wherein

Ph is phenyl optionally substituted with 1 to 3 R^1;

HET is monocyclic or bicyclic heteroaryl comprising 1-4 heteroatoms selected from S, O and N, optionally substituted with 1 to 3 R^1; and

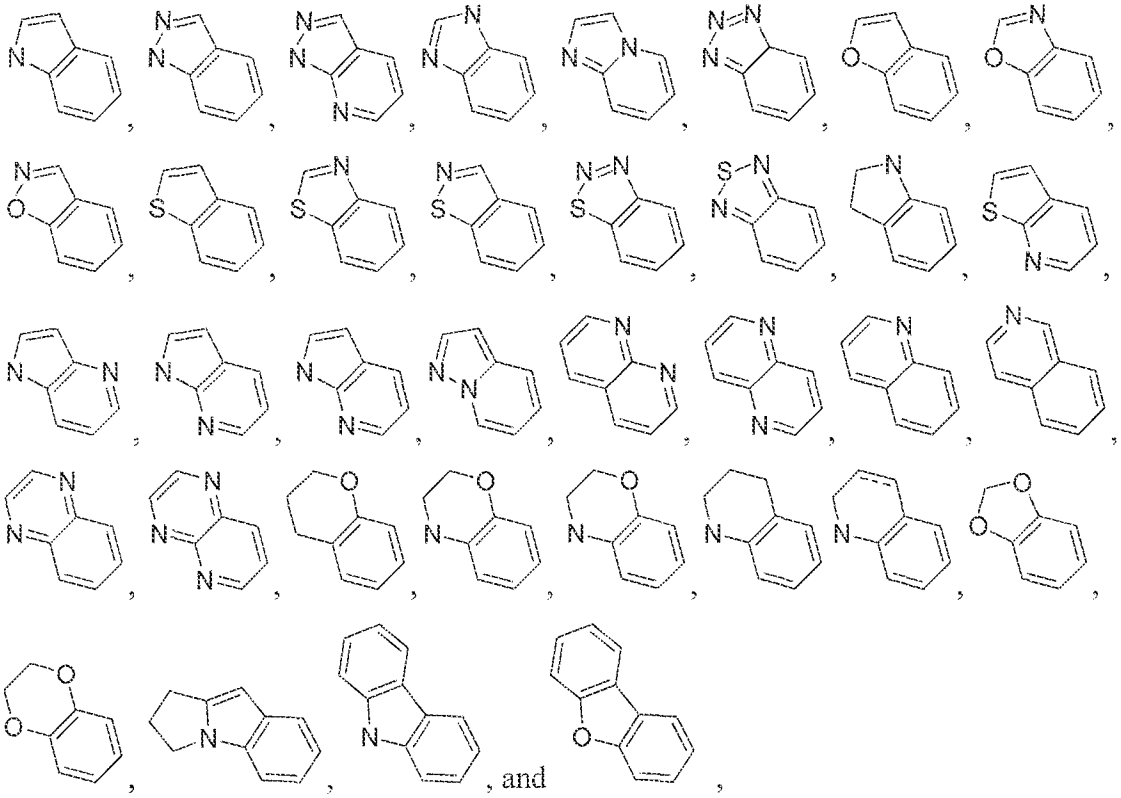
B^1 is selected from the group consisting of CO-NR^aR^b, phenyl, monocyclic or bicyclic heteroaryl comprising 1-4 heteroatoms selected from S, O and N, and 3-8 membered heterocyclyl comprising 1-4 heteroatoms selected from S, O and N, wherein phenyl, heteroaryl, and heterocyclyl are each optionally substituted with 1 to 3 R^2, and R^a and R^b together form a four to six membered heterocyclic ring optionally substituted with one to three groups independently selected from halo, C_{1-8}alkyl, and haloC_{1-8}alkyl.

[0081] In one group of embodiments, B^1 in Formula (Ia) is monocyclic or bicyclic heteroaryl comprising 1-4 heteroatoms selected from S, O and N or 3-8 membered heterocyclyl comprising 1-4 heteroatoms selected from S, O and N, each optionally substituted with 1 to 3 R^2, and B^1 in Formula (Ib) is phenyl or 3-8 membered heterocyclyl comprising 1-4 heteroatoms selected from S, O and N, each optionally substituted with 1 to 3 R^2.

[0082] In one group of embodiments, W or B^1 is substituted with 1 to 3 R^2.

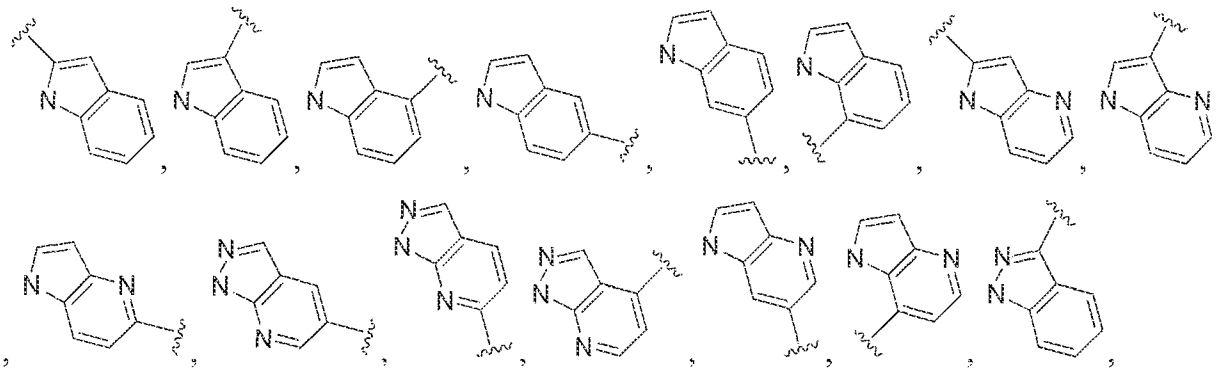
[0083] In one group of embodiments, R^1 and R^2 are independently selected from the group consisting of halo, C_{1-8}alkyl, haloC_{1-8}alkyl, cyano, oxo, OH, O(C_{1-8}alkyl), and O(haloC_{1-8}alkyl).

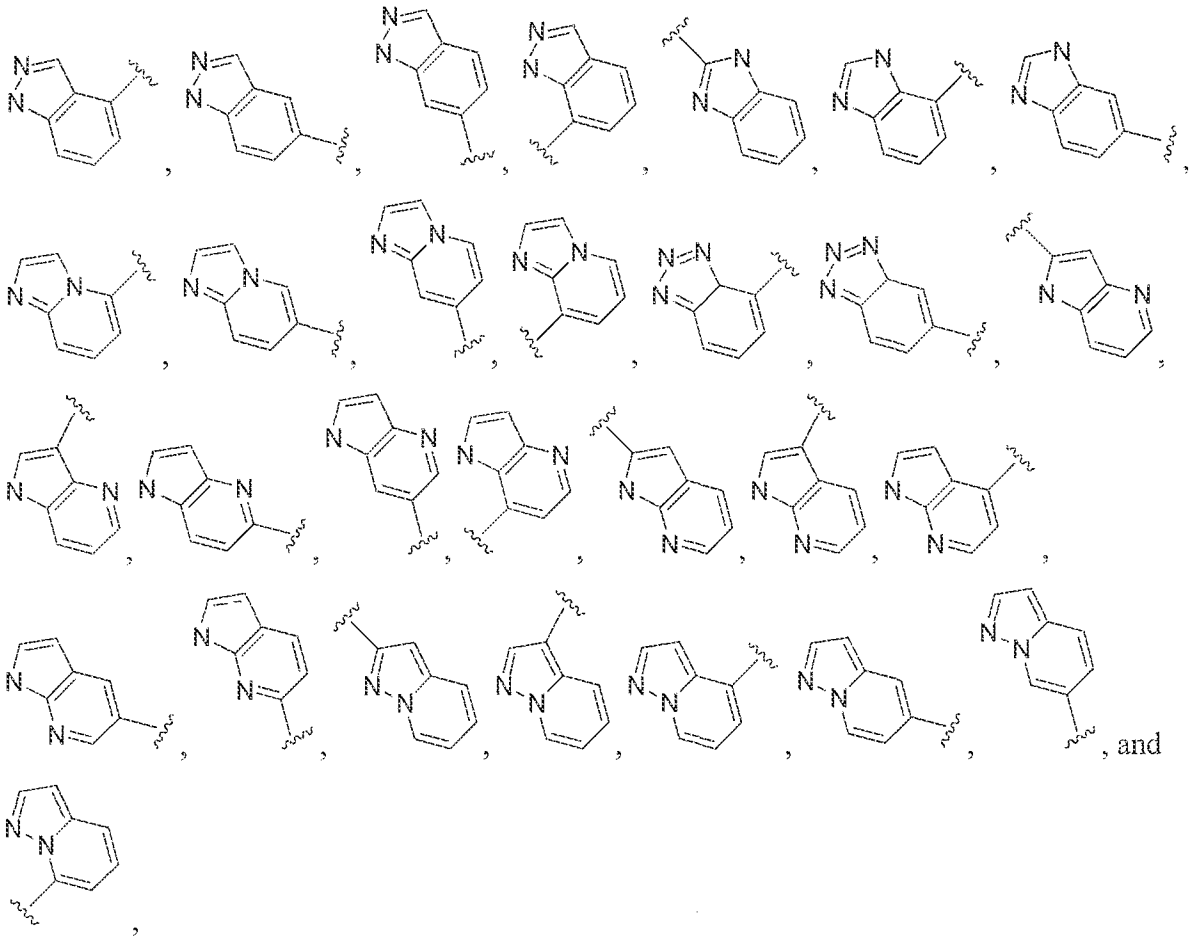
[0084] In one group of embodiments, X^1 or HET is selected from the group consisting of



where the point of attachment to the rest of the molecule is at a carbon ring atom.

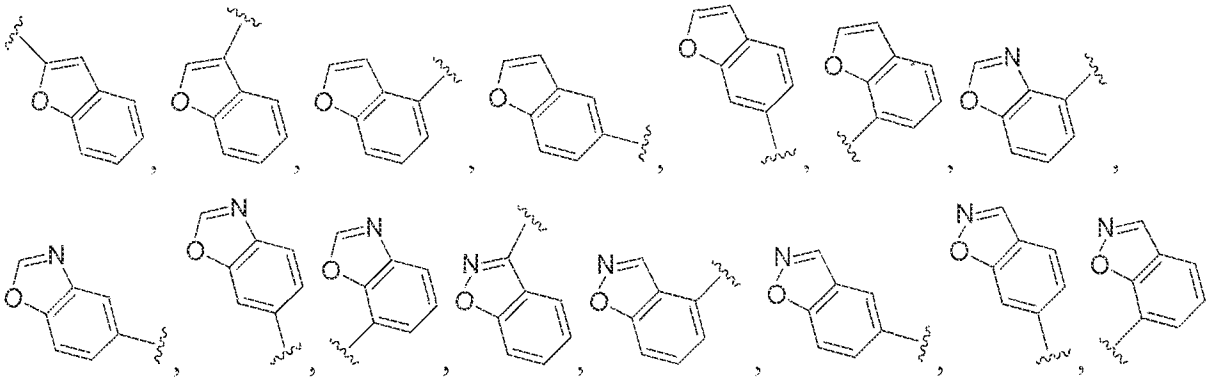
[0085] In one group of embodiments, X^1 or HET is selected from the group consisting of

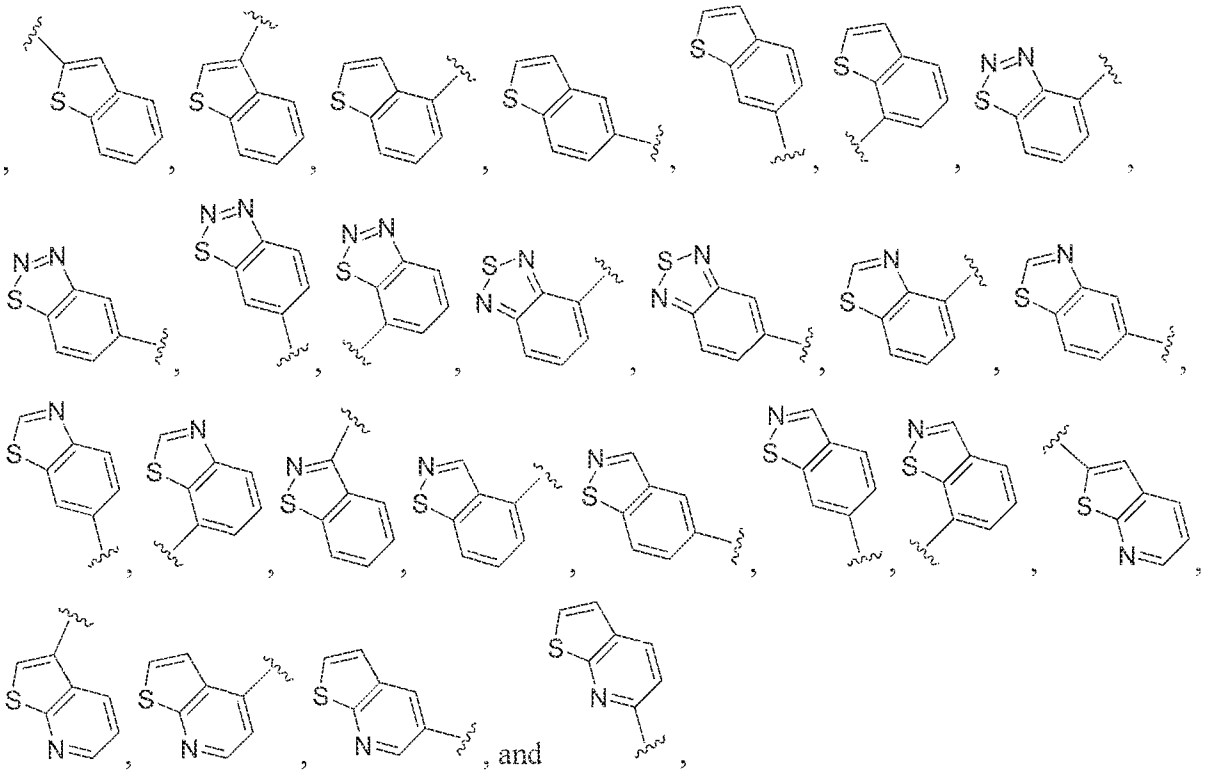




where the wavy line indicates the point of attachment to the rest of the molecule.

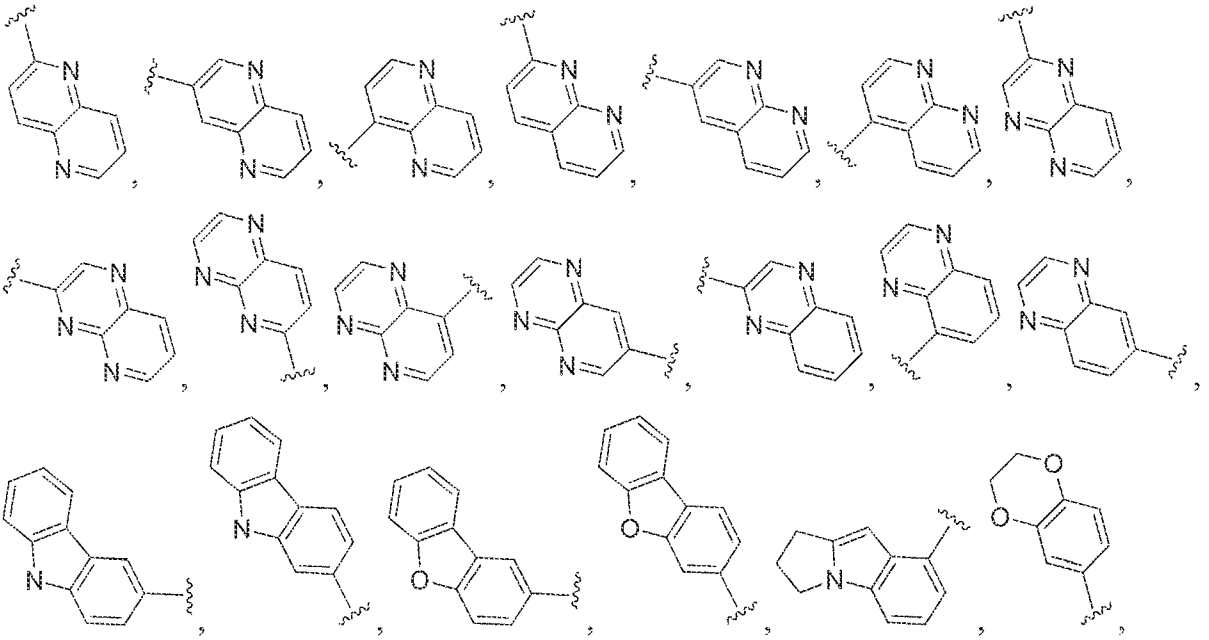
[0086] In one group of embodiments, X^1 or HET is selected from the group consisting of

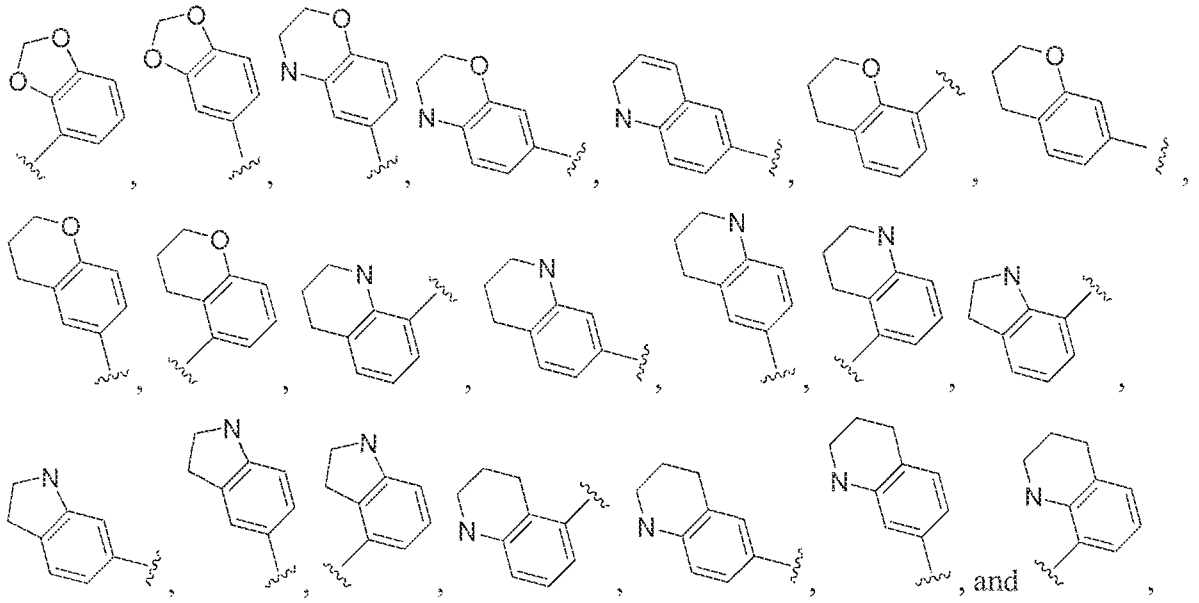




where the wavy line indicates the point of attachment to the rest of the molecule.

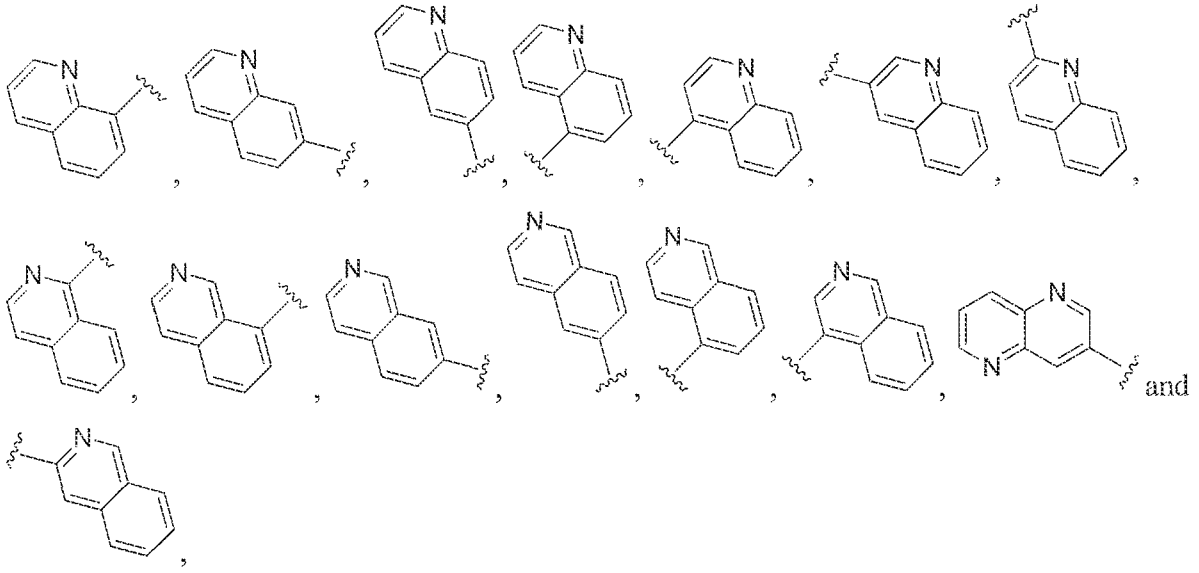
[0087] In one group of embodiments, X^1 or HET is selected from the group consisting of





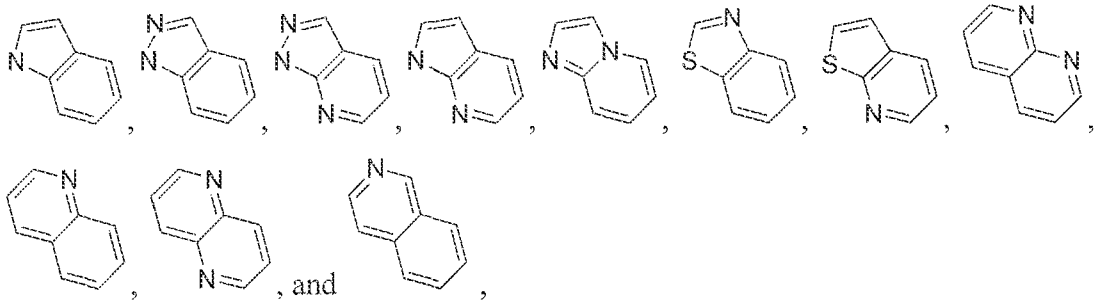
where the wavy line indicates the point of attachment to the rest of the molecule.

[0088] In one group of embodiments, X^1 or HET is selected from the group consisting of



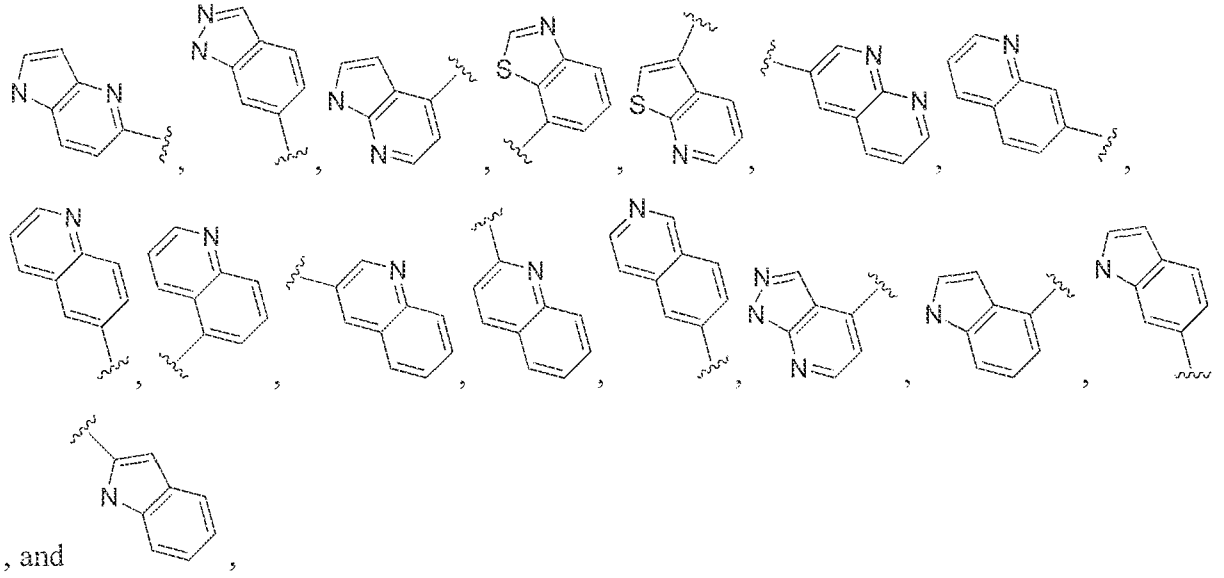
where the wavy line indicates the point of attachment to the rest of the molecule.

[0089] In one group of embodiments, X^1 or HET is selected from the group consisting of



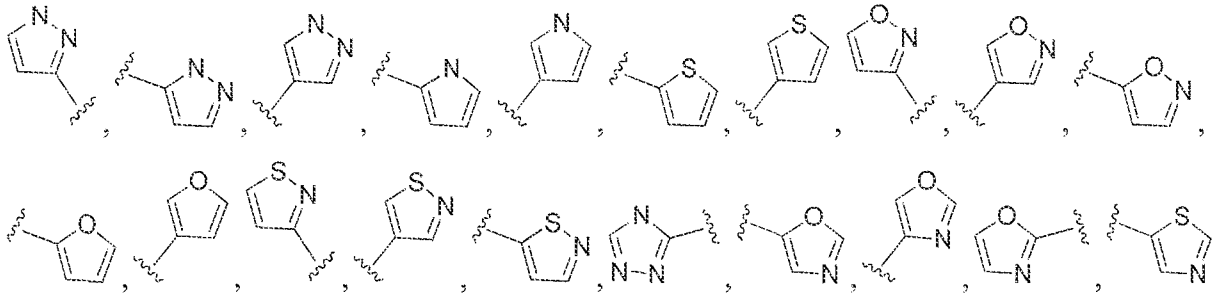
where the point of attachment to the rest of the molecule is at a carbon ring atom.

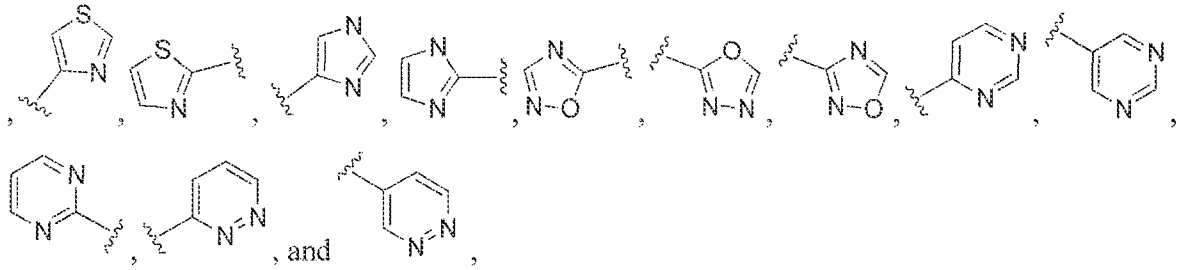
[0090] In one group of embodiments, X^1 or HET is selected from the group consisting of



where the wavy line indicates the point of attachment to the rest of the molecule.

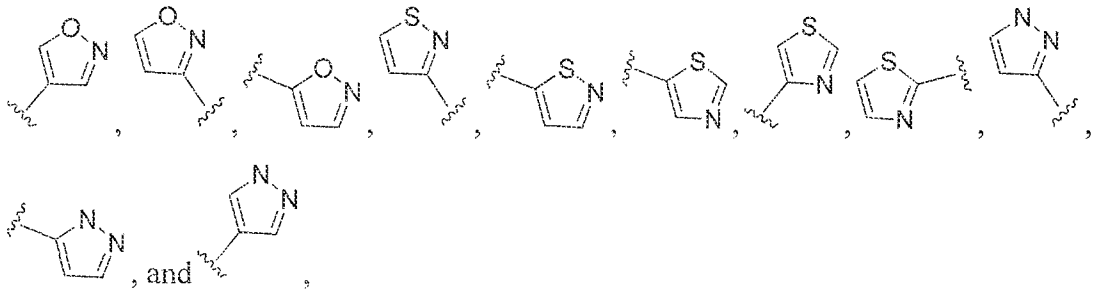
[0091] In one group of embodiments, X^1 or HET is selected from the group consisting of





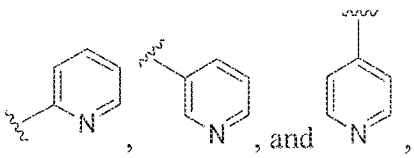
where the wavy line indicates the point of attachment to the rest of the molecule.

[0092] In one group of embodiments, X^1 or HET is selected from the group consisting of



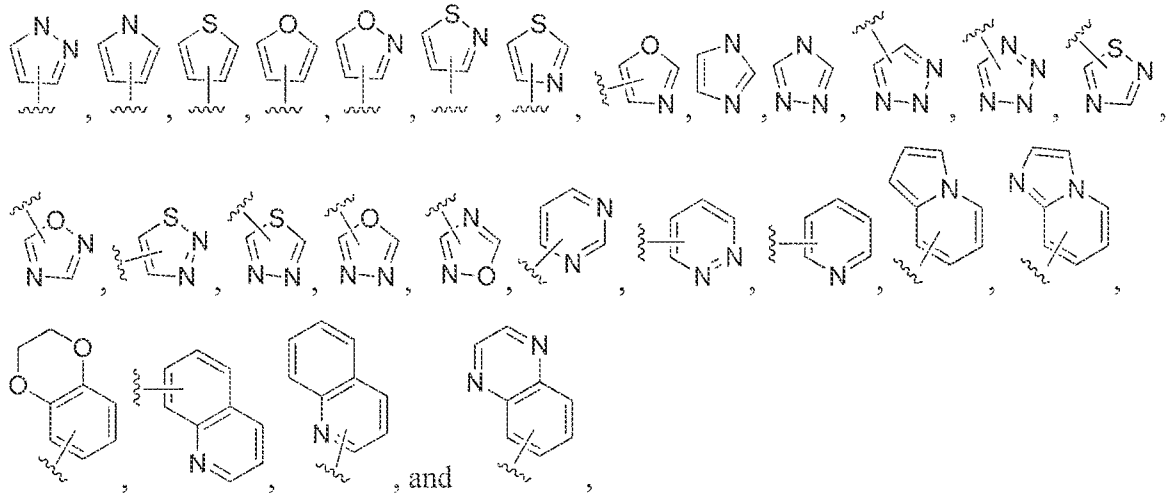
where the wavy line indicates the point of attachment to the rest of the molecule.

[0093] In one group of embodiments, X^1 or HET is selected from the group consisting of



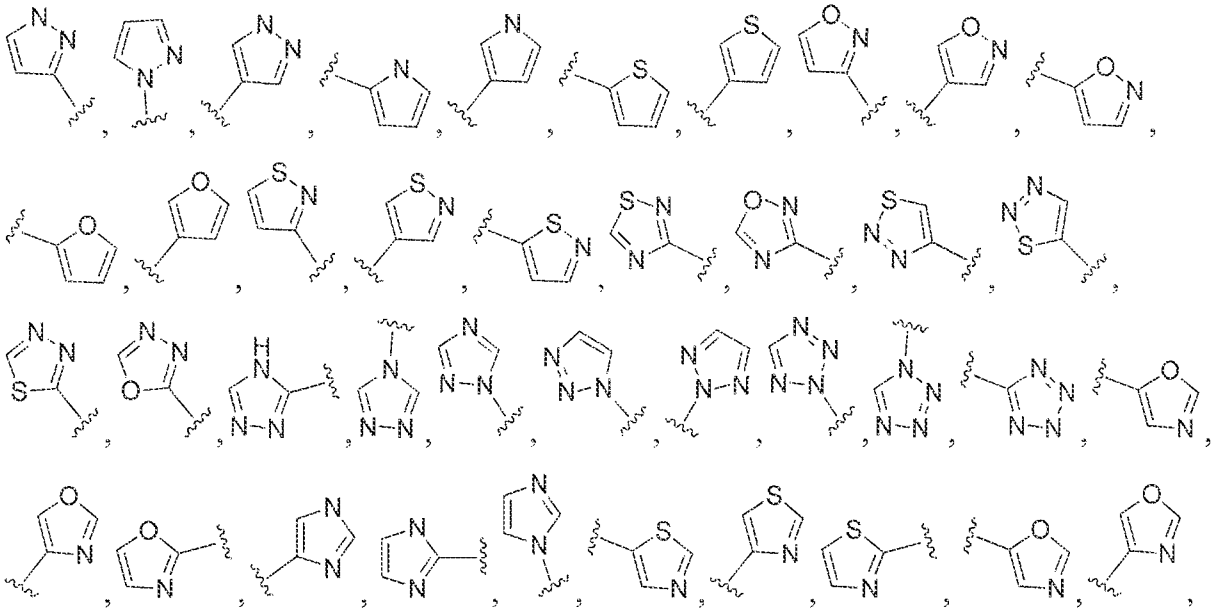
where the wavy line indicates the point of attachment to the rest of the molecule.

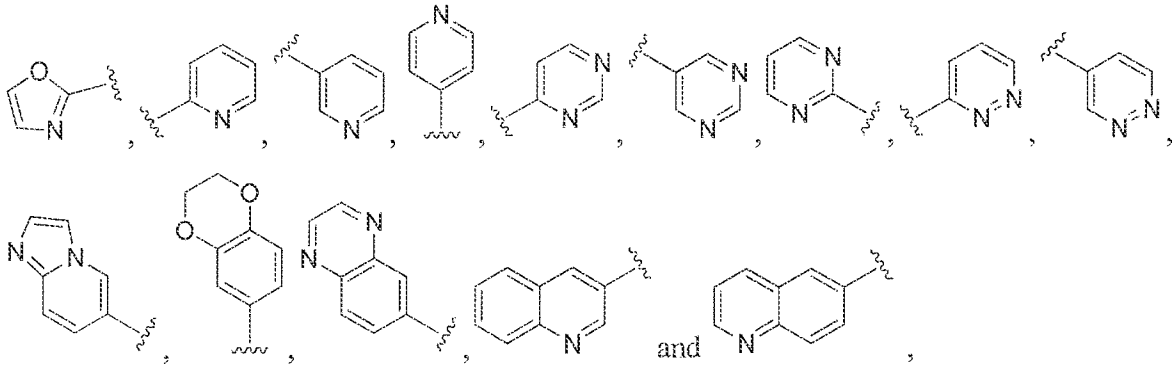
[0094] In one group of embodiments, W or B^1 is selected from the group consisting of



where the wavy line indicates the point of attachment to the rest of the molecule.

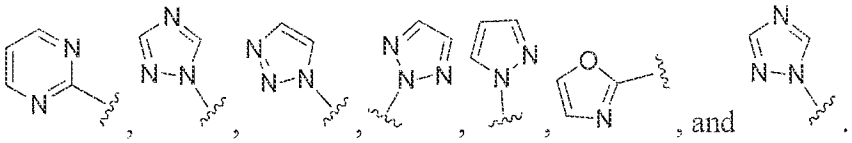
[0095] In one group of embodiments, W or B^1 is selected from the group consisting of



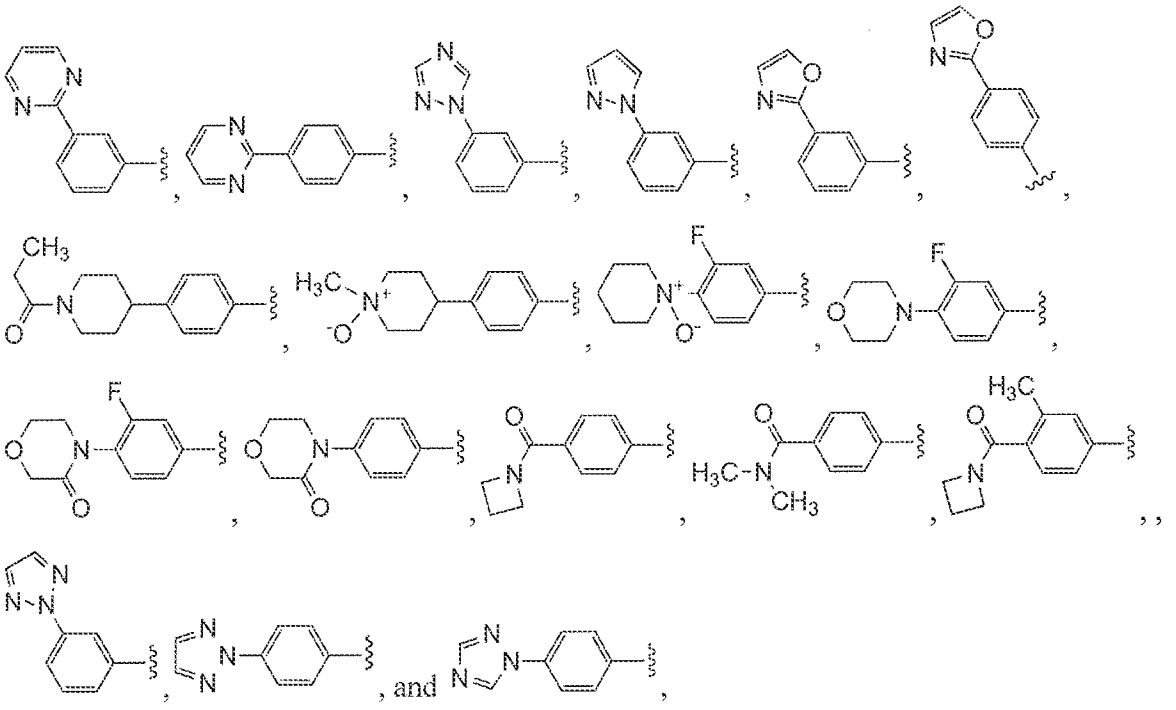


where the wavy line indicates the point of attachment to the rest of the molecule.

[0096] In one group of embodiments, W or B^1 is selected from the group consisting of

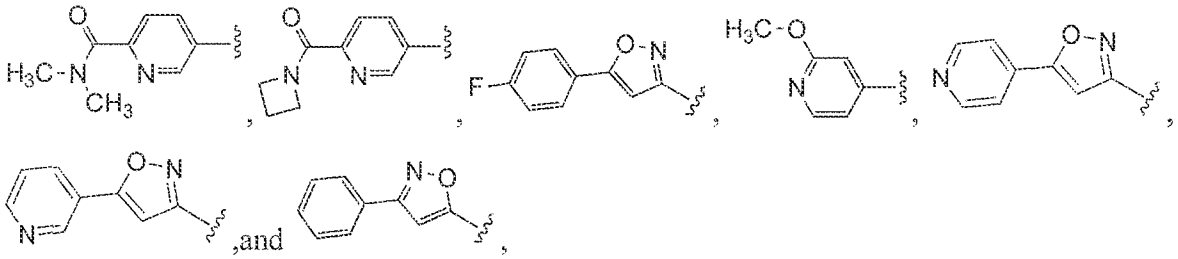


[0097] In one group of embodiments, B^1-Ph- is selected from the group consisting of



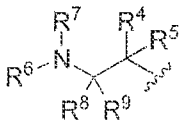
where the wavy line indicates the point of attachment to the rest of the molecule.

[0098] In one group of embodiments, B^1-HET- is selected from the group consisting of



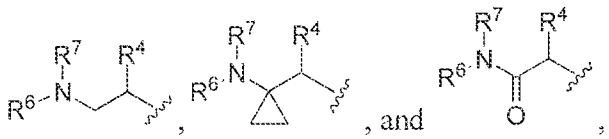
where the wavy line indicates the point of attachment to the rest of the molecule.

[0099] In one group of embodiments, Y is



where the wavy line indicates the point of attachment to the rest of the molecule.

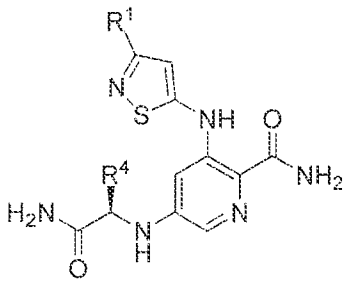
[0100] In one group of embodiments, Y is selected from the group consisting of



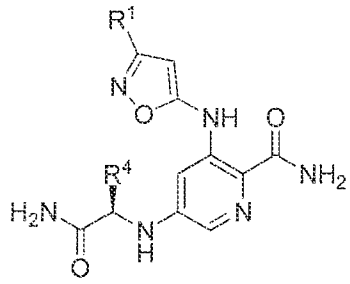
where the wavy line indicates the point of attachment to the rest of the molecule.

[0101] In one group of embodiments, provided is a compound of Formula (II)

or Formula (III) or a tautomer or a pharmaceutically acceptable salt thereof



(II)



(III).

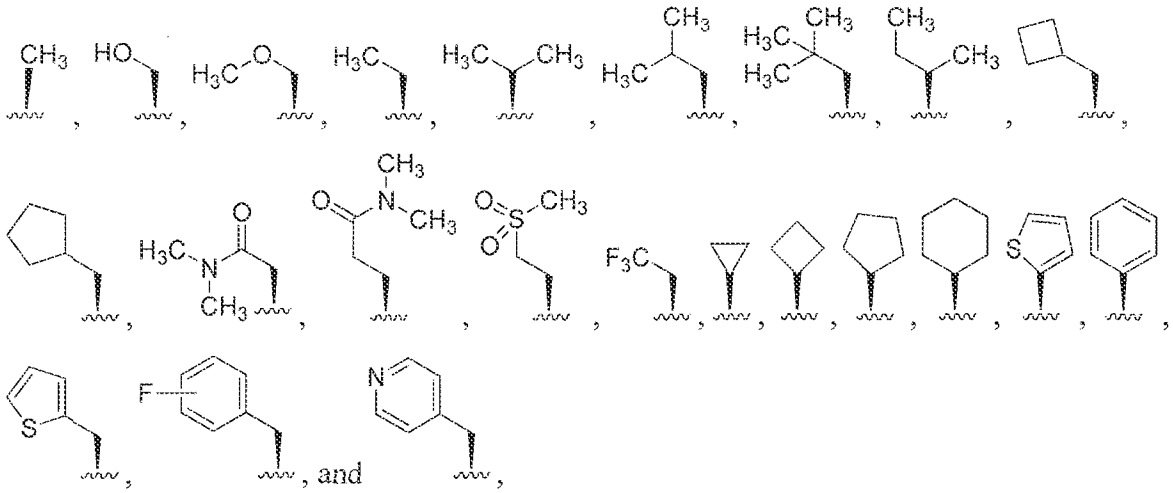
[0102] In one group of embodiments, R^1 is selected from the group consisting of halo, C_{1-8}alkyl, haloC_{1-8}alkyl, cyano, oxo, OH, O(C_{1-8}alkyl), O(haloC_{1-8}alkyl), CO-NR^aR^b, phenyl, heteroaryl, and heterocyclyl, wherein the phenyl, heteroaryl, and heterocyclyl are each optionally substituted with 1 to 3 R^2, and R^a and R^b together form a four to six membered heterocyclic ring optionally substituted with one to three groups independently selected from halo, C_{1-8}alkyl, and

haloC_{1-8}alkyl. In another group of embodiments, R^1 is C_{1-4}alkyl or haloC_{1-4}alkyl. In one group of embodiments, R^1 is C_{1-4}alkyl. In another group of embodiments R^1 is methyl.

[0103] In one group of embodiments, wherein R^6 and R^7 are H and R^4 is selected from the group consisting of H, C_{1-8}alkyl, haloC_{1-8}alkyl, cycloalkyl, (cycloalkyl)C_{1-4}alkyl, (hydroxyl)C_{1-4}alkyl, (C_{1-4}alkoxy)C_{1-4}alkyl, (haloC_{1-4}alkoxy)C_{1-4}alkyl, $(CH_2)_pNR^{4b}R^{4c}$, $(CH)_pSO_2NR^{4b}R^{4c}$, $(CH_2)_pSOR^{4a}$, $(CH_2)_pSO_2R^{4a}$, $(CH_2)_fCONR^{4b}R^{4c}$, $(CH_2)_pNR^{4b}COR^{4d}$, phenyl, heteroaryl, (phenyl)C_{1-8}alkyl, and (heteroaryl)C_{1-8}alkyl wherein the phenyl and heteroaryl are optionally substituted with 1 to 3 groups independently selected from halo, C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxy, and haloC_{1-4}alkoxy.

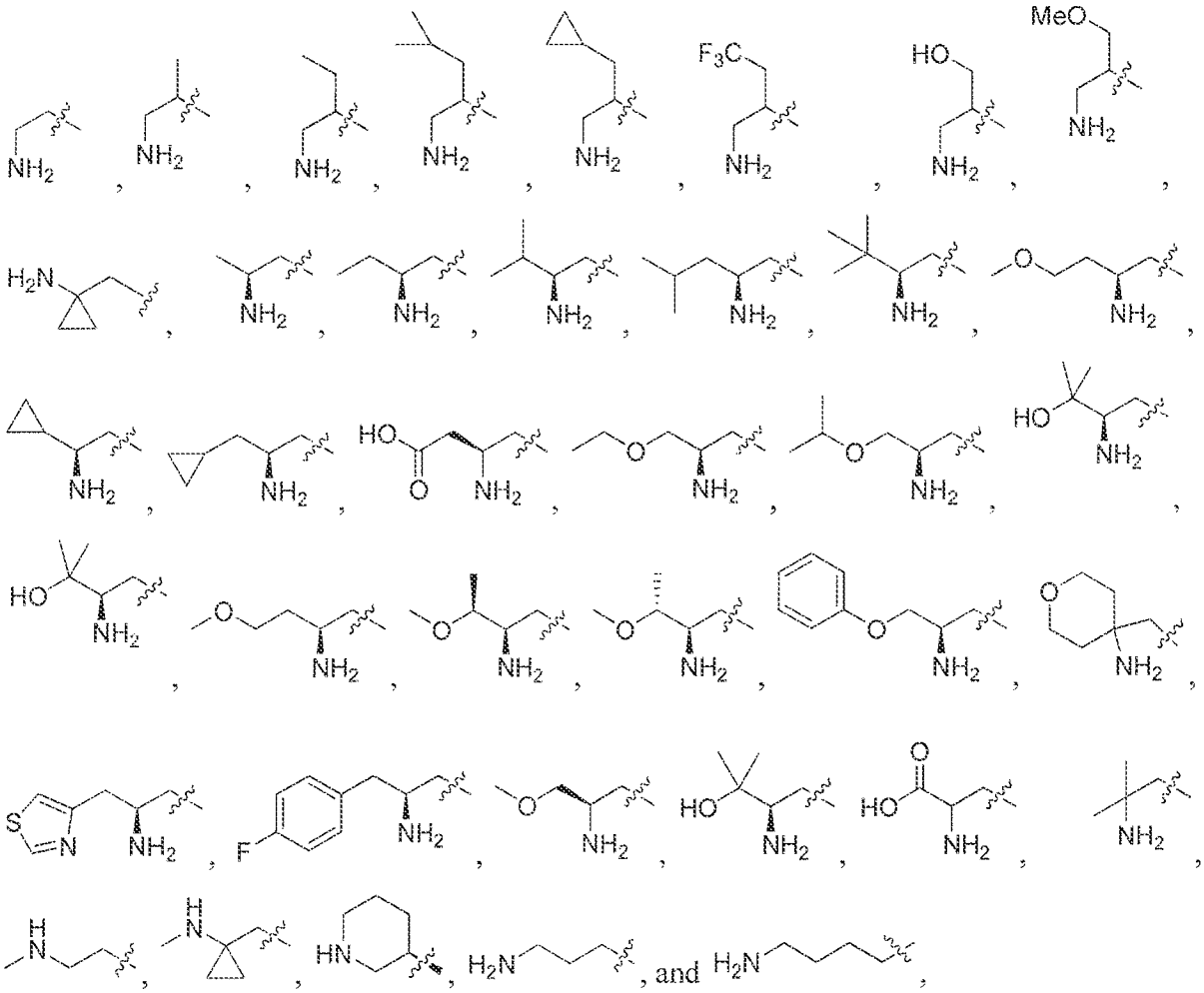
[0104] In one group of embodiments, R^4 is selected from the group consisting of H, methyl, ethyl, propyl, isopropyl, isobutyl, hydroxymethyl, pyridyl, and phenyl, wherein the pyridyl and phenyl are optionally substituted with 1 to 3 groups independently selected from halo, C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxy, and haloC_{1-4}alkoxy.

[0105] In one group of embodiments, R^4 is selected from the group consisting of



where the wavy line indicates the point of attachment to the rest of the molecule.

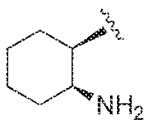
[0106] In one group of embodiments, Y is selected from the group consisting of



where the wavy line indicates the point of attachment to the rest of the molecule.

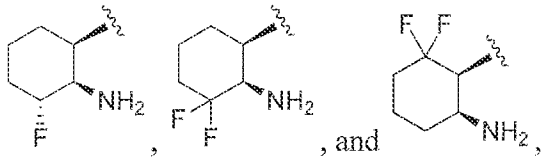
[0107] In one group of embodiments, Y is $(CH_2)_v(X)$ wherein v is 0 and X is cycloalkyl or heterocycloalkyl each optionally substituted with 1 to 3 R^{10}.

[0108] In one group of embodiments, Y is



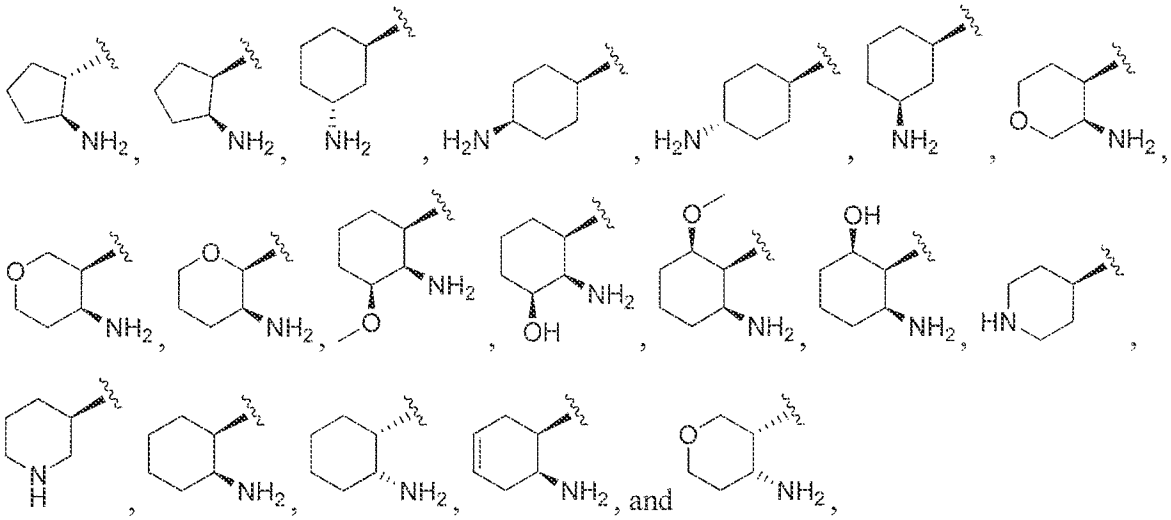
optionally substituted with 1 to 2 halo and where the wavy line indicates the point of attachment to the rest of the molecule.

[0109] In one group of embodiments, Y is selected from the group consisting of



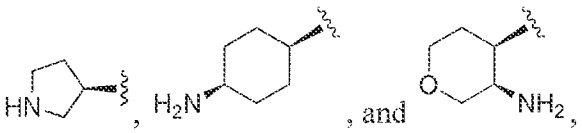
where the wavy line indicates the point of attachment to the rest of the molecule.

[0110] In one group of embodiments, Y is selected from the group consisting of



where the wavy line indicates the point of attachment to the rest of the molecule.

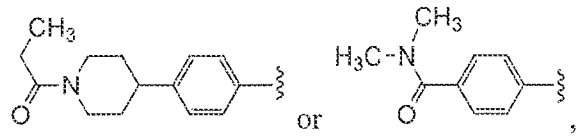
[0111] In one group of embodiments, Y is selected from the group consisting of



where the wavy line indicates the point of attachment to the rest of the molecule.

[0112] In one group of embodiments, Y is $(CH_2)_v(X)$ wherein v is 0 and X is phenyl optionally substituted with 1 to 3 R^{10}.

[0113] In one group of embodiments, Y is



where the wavy line indicates the point of attachment to the rest of the molecule.

[0114] In one group of embodiments, provided is a pharmaceutical composition comprising a compound of any of the above embodiments or a tautomer or pharmaceutically acceptable salt thereof.

[0115] The compounds of the present invention may be prepared by known organic synthesis techniques, including the methods described in more detail in the Examples. In one group of embodiments, provided is a compound of Formula (I) as provided in the Examples. In one group of embodiments, provided is a compound of Formula (Ia) as provided in the Examples. In one group of embodiments, provided is a compound of Formula (Ib) as provided in the Examples. In one group of embodiments, provided is a compound of Formula (II) as provided in the Examples. In one group of embodiments, provided is a compound of Formula (III) as provided in the Examples.

[0116] In one group of embodiments, provided is an intermediate compound used in the preparation of the compounds disclosed herein.

[0117] In one group of embodiments, provided are methods for preparing the compounds disclosed herein.

[0118] In one group of embodiments, certain of the compounds disclosed herein may generally be utilized as the free base. Alternatively, certain of the compounds may be used in the form of acid addition salts.

[0119] It is understood that in another group of embodiments, any of the above embodiments may also be combined with other embodiments listed herein, to form other embodiments of the invention. Similarly, it is understood that in other embodiments, listing of groups includes embodiments wherein one or more of the elements of those groups is not included.

Compositions and Methods of Administration

[0120] Depending on the intended mode of administration, the pharmaceutical compositions may be in the form of solid, semi-solid or liquid dosage forms, preferably in unit dosage form suitable for single administration of a precise dosage. In addition to an effective amount of the active compound(s), the compositions may contain suitable pharmaceutically-acceptable excipients, including adjuvants which facilitate processing of the active compounds into preparations which can be used pharmaceutically. "Pharmaceutically acceptable excipient" refers

to an excipient or mixture of excipients which does not interfere with the effectiveness of the biological activity of the active compound(s) and which is not toxic or otherwise undesirable to the subject to which it is administered.

[0121] For solid compositions, conventional excipients include, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, talc, cellulose, glucose, sucrose, magnesium carbonate, and the like. Liquid pharmacologically administrable compositions can, for example, be prepared by dissolving, dispersing, etc., an active compound as described herein and optional pharmaceutical adjuvants in water or an aqueous excipient, such as, for example, water, saline, aqueous dextrose, and the like, to form a solution or suspension. If desired, the pharmaceutical composition to be administered may also contain minor amounts of nontoxic auxiliary excipients such as wetting or emulsifying agents, pH buffering agents and the like, for example, sodium acetate, sorbitan monolaurate, triethanolamine sodium acetate, triethanolamine oleate, etc.

[0122] The term "administering" refers to administration by any route, including parenteral and transmucosal (*e.g.*, buccal, sublingual, palatal, gingival, nasal, vaginal, rectal, or transdermal).

[0123] For oral administration, the composition will generally take the form of a tablet or capsule, or it may be an aqueous or nonaqueous solution, suspension or syrup. Tablets and capsules are preferred oral administration forms. Tablets and capsules for oral use will generally include one or more commonly used excipients such as lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. When liquid suspensions are used, the active agent may be combined with emulsifying and suspending excipients. If desired, flavoring, coloring and/or sweetening agents may be added as well. Other optional excipients for incorporation into an oral formulation include preservatives, suspending agents, thickening agents, and the like.

[0124] Injectable formulations can be prepared in conventional forms, either as liquid solutions or suspensions, solid forms suitable for solubilization or suspension in liquid prior to injection, or as emulsions or liposomal formulations. The sterile injectable formulation may also be a sterile injectable solution or a suspension in a nontoxic parenterally acceptable diluent or solvent. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution

and isotonic sodium chloride solution. In addition, sterile, fixed oils, fatty esters or polyols are conventionally employed as solvents or suspending media.

[0125] The pharmaceutical compositions of this invention may also be formulated in lyophilized form for parenteral administration. Lyophilized formulations may be reconstituted by addition of water or other aqueous medium and then further diluted with a suitable diluent prior to use. The liquid formulation is generally a buffered, isotonic, aqueous solution. Examples of suitable diluents are isotonic saline solution, 5% dextrose in water, and buffered sodium or ammonium acetate solution. Pharmaceutically acceptable solid or liquid excipients may be added to enhance or stabilize the composition, or to facilitate preparation of the composition.

[0126] Typically, a pharmaceutical composition of the present invention is packaged in a container with a label, or instructions, or both, indicating use of the pharmaceutical composition in the treatment of the indicated disease.

[0127] The pharmaceutical composition may additionally contain one or more other pharmacologically active agents in addition to a compound of this invention.

[0128] Dosage forms containing effective amounts of the modulators are within the bounds of routine experimentation and within the scope of the invention. A therapeutically effective dose may vary depending upon the route of administration and dosage form. The representative compound or compounds of the invention is a formulation that exhibits a high therapeutic index. The therapeutic index is the dose ratio between toxic and therapeutic effects which can be expressed as the ratio between LD_{50} and ED_{50}. The LD_{50} is the dose lethal to 50% of the population and the ED_{50} is the dose therapeutically effective in 50% of the population. The LD_{50} and ED_{50} are determined by standard pharmaceutical procedures in animal cell cultures or experimental animals. It should be understood that a specific dosage and treatment regimen for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health, sex and diet of the patient, and the time of administration, rate of excretion, drug combination, judgment of the treating physician and severity of the particular disease being treated. The amount of active ingredient(s) will also depend upon the particular compound and other therapeutic agent, if present, in the composition.

EXAMPLES

[0129] The following examples are offered to illustrate, but not to limit, the claimed invention.

PREPARATIVE EXAMPLES

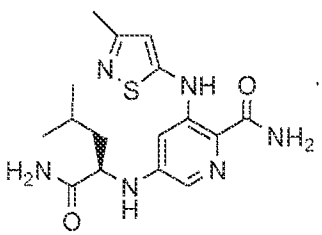
[0130] The starting materials and reagents used in preparing these compounds generally are either available from commercial suppliers, such as Aldrich Chemical Co., or are prepared by methods known to those skilled in the art following procedures set forth in references such as *Fieser and Fieser's Reagents for Organic Synthesis;* Wiley & Sons: New York, 1967-2004, Volumes 1-22; *Rodd's Chemistry of Carbon Compounds,* Elsevier Science Publishers, 1989, Volumes 1-5 and Supplementals; and Organic Reactions, Wiley & Sons: New York, 2005, Volumes 1-65.

[0131] The starting materials and the intermediates of the synthetic reaction schemes can be isolated and purified if desired using conventional techniques, including but not limited to, filtration, distillation, crystallization, chromatography, and the like. Such materials can be characterized using conventional means, including physical constants and spectral data.

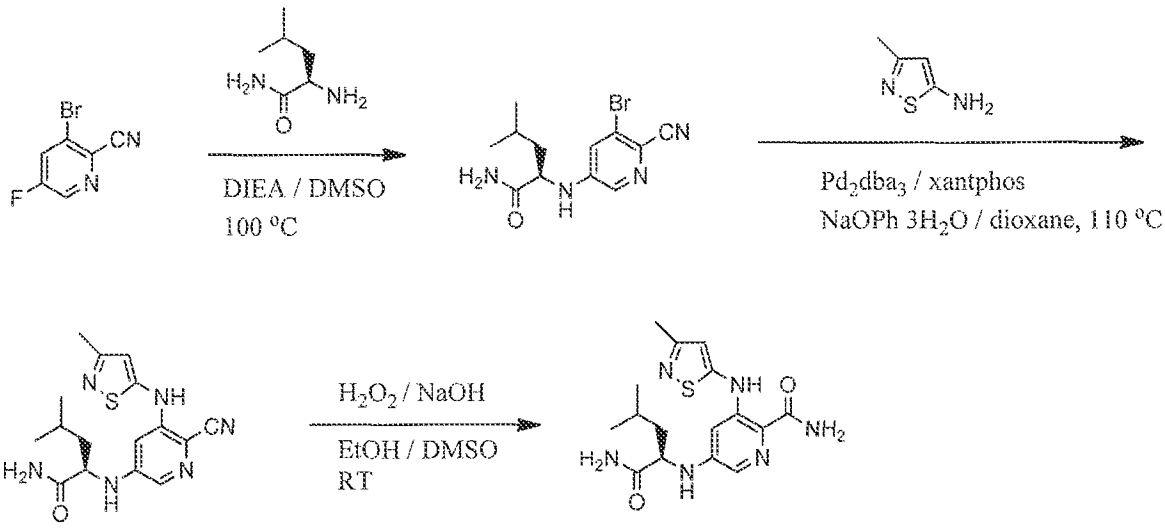
[0132] Unless specified to the contrary, the reactions described herein preferably are conducted under an inert atmosphere at atmospheric pressure at a reaction temperature range of from about -78°C to about 150°C, more preferably from about 0°C to about 125°C, and most preferably and conveniently at about room (or ambient) temperature, e.g., about 20°C to about 75°C.

[0133] Referring to the examples that follow, compounds of the present invention were synthesized using the methods described herein, or other methods known in the art.

Example 1. (R)-5-(1-amino-4-methyl-1-oxopentan-2-ylamino)-3-(3-methylisothiazol-5-ylamino)picolinamide.



Scheme 1

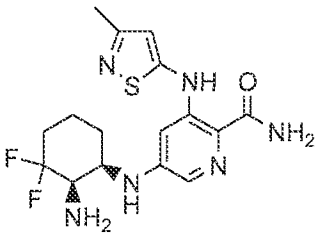


[0134] A solution of 3-bromo-5-fluoropicolinonitrile (363 mg, 1.80 mmol), D-leucinamide hydrochloride (300 mg, 1.80 mmol) and DIEA (0.700 mL, 4.02 mmol) in DMSO (8 mL) was stirred at 100 °C for 1 h. Water and EtOAc were added. Organic phase was separated, washed with H_2O, dried over Na_2SO_4, concentrated in vacuo to give (R)-2-(5-bromo-6-cyanopyridin-3-ylamino)-4-methylpentanamide (538 mg).

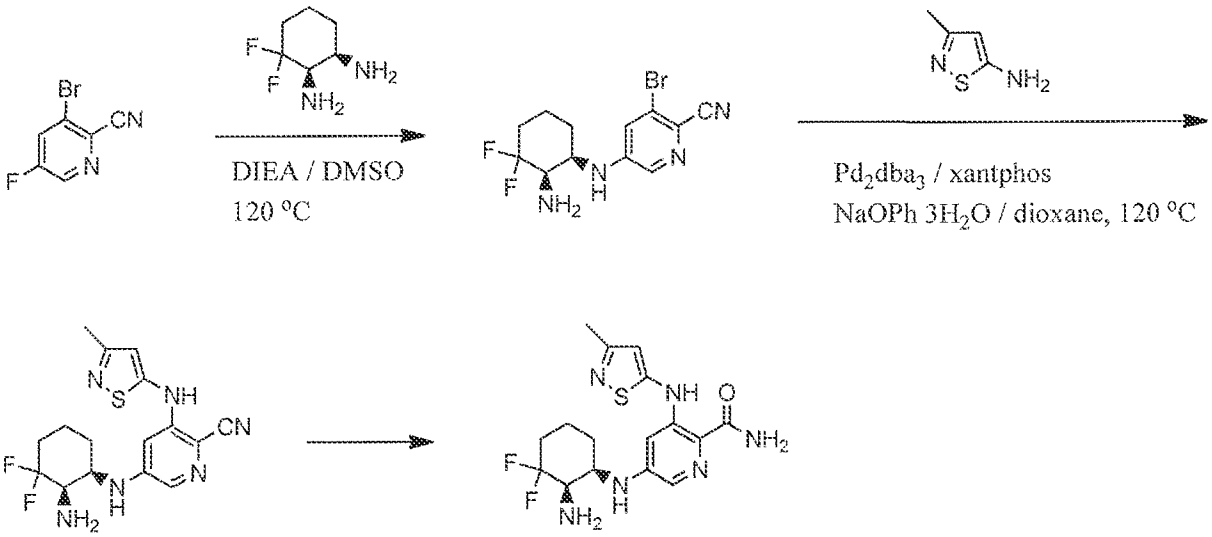
[0135] A mixture of (R)-2-(5-bromo-6-cyanopyridin-3-ylamino)-4-methylpentanamide (538 mg, 1.73 mmol), 3-methylisothiazol-5-amine hydrochloride (275 mg, 1.82 mmol), NaOPh trihydrate (633 mg, 3.72 mmol), xantphos (80 mg, 0.138 mmol) and Pd_2dba_3 (80 mg, 0.087 mmol) in dioxane (10 mL) was degassed with Ar, then was stirred at 110 °C for 20 h. The mixture was concentrated in vacuo. The residue was purified by HPLC to give (R)-2-(6-cyano-5-(3-methylisothiazol-5-ylamino)pyridin-3-ylamino)-4-methylpentanamide (190 mg).

[0136] The compound (R)-2-(6-cyano-5-(3-methylisothiazol-5-ylamino)pyridin-3-ylamino)-4-methylpentanamide (190 mg, 0.552 mmol) was dissolved in EtOH (2 mL) and DMSO (2 mL), aq. 1N NaOH (1.0 mL) and aq. H_2O_2 (30%, 1.0 mL) were added. The mixture was stirred at room temperature for 20 min. HOAc (0.1 mL) was added. The mixture was then concentrated in vacuo. The residue was purified by HPLC to give the titled compound (196 mg). MS 363.2 (M+H); UV: λ = 207.8, 304.6 nm; t 0.586 min.

Example 2. 5-((1R,2R)-2-amino-3,3-difluorocyclohexylamino)-3-(3-methylisothiazol-5-ylamino)picolinamide



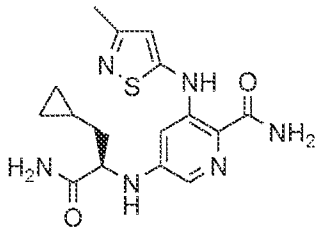
Scheme 2



[0137] A solution of 3-bromo-5-fluoropicolinonitrile (108 mg, 0.537 mmol), (1R,2R)-3,3-difluorocyclohexane-1,2-diamine dihydrochloride (120 mg, 0.538 mmol) and DIEA (0.350 mL, 2.01 mmol) in DMSO (5 mL) was stirred at 120 °C for 2 h. Water and EtOAc were added. Organic phase was separated, washed with water, dried over Na_2SO_4, concentrated in vacuo to give 5-((1R,2R)-2-amino-3,3-difluorocyclohexylamino)-3-bromopicolinonitrile (158 mg).

[0138] A mixture of 5-((1R,2R)-2-amino-3,3-difluorocyclohexylamino)-3-bromopicolinonitrile (79 mg, 0.238 mmol), 3-methylisothiazol-5-amine hydrochloride (50 mg, 0.332 mmol), NaOPh trihydrate (130 mg, 0.764 mmol), xantphos (25 mg, 0.043 mmol) and Pd_2dba_3 (15 mg, 0.016 mmol) in dioxane (2 mL) was degassed with Ar, then was stirred at 120 °C for 5 h. Surprisingly, the expected product was not detected, instead the desired final product was obtained. HOAc (0.1 mL) was added. The mixture was concentrated in vacuo. The residue was purified by HPLC to give the titled compound (18 mg). MS 383.2; UV: λ = 210.2, 302.7 nm; t 0.443 min.

Example 3. (R)-5-(1-amino-3-cyclopropyl-1-oxopropan-2-ylamino)-3-(3-methylisothiazol-5-ylamino)picolinamide

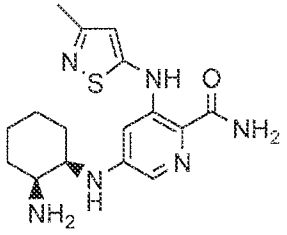


[0139] A solution of 3-bromo-5-fluoropicolinonitrile (185 mg, 0.920 mmol), (R)-2-amino-3-cyclopropylpropanamide hydrochloride (150 mg, 0.912 mmol) and DIEA (0.450 mL, 2.58 mmol) in DMSO (4 mL) was stirred at 100 °C for 20 h. Water and EtOAc were added. Organic phase was separated, washed with water, dried over Na_2SO_4, concentrated in vacuo to give (R)-2-(5-bromo-6-cyanopyridin-3-ylamino)-3-cyclopropylpropanamide (280 mg).

[0140] A mixture of (R)-2-(5-bromo-6-cyanopyridin-3-ylamino)-3-cyclopropylpropanamide (142 mg, 0.460 mmol), 3-methylisothiazol-5-amine hydrochloride (90 mg, 0.597 mmol), K2CO3 (190 mg, 1.37 mmol), xantphos (45 mg, 0.077 mmol) and Pd_2dba_3 (30 mg, 0.032 mmol) in dioxane (3 mL) was degassed with Ar, then was stirred at 120 °C for 20 h. The mixture was concentrated in vacuo. The residue was purified by HPLC to give (R)-2-(6-cyano-5-(3-methylisothiazol-5-ylamino)pyridin-3-ylamino)-3-cyclopropylpropanamide (23 mg).

[0141] The compound (R)-2-(6-cyano-5-(3-methylisothiazol-5-ylamino)pyridin-3-ylamino)-3-cyclopropylpropanamide (23 mg, 0.067 mmol) was dissolved in EtOH (2 mL) and DMSO (1 mL), aq. 1N NaOH (1.0 mL) and aq. H_2O_2 (30%, 1.0 mL) were added. The mixture was stirred at room temperature for 15 min. HOAc (0.1 mL) was added. The mixture was then concentrated in vacuo. The residue was purified by HPLC to give the titled compound (14 mg). MS 361.2 (M+H); UV: λ = 205.4, 304.0 nm; t 0.550 min.

Example 4. 5-((1R,2S)-2-aminocyclohexylamino)-3-(3-methylisothiazol-5-ylamino)picolinamide

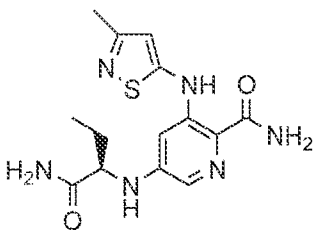


[0142] A solution of 3-bromo-5-fluoropicolinonitrile (177 mg, 0.880 mmol), tert-butyl (1S,2R)-2-aminocyclohexylcarbamate (188 mg, 0.878 mmol) and DIEA (0.300 mL, 1.72 mmol) in DMSO (4 mL) was stirred at 100 °C for 5 h. Water and EtOAc were added. Organic phase was separated, washed with water, dried over Na_2SO_4, concentrated in vacuo to give tert-butyl (1S,2R)-2-(5-bromo-6-cyanopyridin-3-ylamino)cyclohexylcarbamate (345 mg).

[0143] A mixture of tert-butyl (1S,2R)-2-(5-bromo-6-cyanopyridin-3-ylamino)cyclohexylcarbamate (175 mg, 0.443 mmol), 3-methylisothiazol-5-amine hydrochloride (70 mg, 0.464 mmol), NaOPh trihydrate (160 mg, 0.941 mmol), xantphos (40 mg, 0.069 mmol) and Pd_2dba_3 (30 mg, 0.032 mmol) in dioxane (3 mL) was degassed with Ar, then was stirred at 110 °C for 20 h. Water and EtOAc were added. Organic phase was separated, washed with aq. 1N NaOH, dried over Na_2SO_4, concentrated in vacuo to give tert-butyl (1S,2R)-2-(6-cyano-5-(3-methylisothiazol-5-ylamino)pyridin-3-ylamino)cyclohexylcarbamate, which was then dissolved in trifluoroacetic acid (4 mL). The solution was allowed to stand for 1 h. Excess of trifluoroacetic acid was removed in vacuo. The residue was purified by HPLC to give 5-((1R,2S)-2-aminocyclohexylamino)-3-(3-methylisothiazol-5-ylamino)picolinonitrile (130 mg).

[0144] The compound 5-((1R,2S)-2-aminocyclohexylamino)-3-(3-methylisothiazol-5-ylamino)picolinonitrile (130 mg, 0.294 mmol) was dissolved in EtOH (2 mL) and DMSO (1 mL), aq. 1N NaOH (1.0 mL) and aq. H_2O_2 (30%, 1.0 mL) were added. The mixture was stirred at room temperature for 15 min. HOAc (0.1 mL) was added. The mixture was then concentrated in vacuo. The residue was purified by HPLC to give the titled compound (78 mg). MS 347.2 (M+H); UV: λ = 210.8, 301.5 nm; t 0.429 min.

Example 5. (R)-5-(1-amino-1-oxobutan-2-ylamino)-3-(3-methylisothiazol-5-ylamino)picolinamide



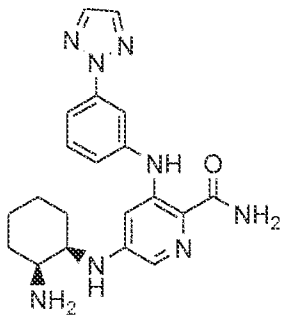
[0145] A solution of 3-bromo-5-fluoropicolinonitrile (142 mg, 0.706 mmol), (R)-2-amino-butanamide hydrochloride (98 mg, 0.707 mmol) and DIEA (0.370 mL, 2.12 mmol) in DMSO (3

mL) was stirred at 100 °C for 2 h. Water and EtOAc were added. Organic phase was separated, washed with water, dried over Na_2SO_4, concentrated in vacuo to give (R)-2-(5-bromo-6-cyanopyridin-3-ylamino)butanamide (185 mg).

[0146] A mixture of (R)-2-(5-bromo-6-cyanopyridin-3-ylamino)butanamide (185 mg, 0.653 mmol), 3-methylisothiazol-5-amine hydrochloride (100 mg, 0.664 mmol), NaOPh trihydrate (240 mg, 1.41 mmol), xantphos (50 mg, 0.086 mmol) and Pd_2dba_3 (40 mg, 0.043 mmol) in dioxane (3 mL) was degassed with Ar, then was stirred at 110 °C for 20 h. The mixture was concentrated in vacuo. The residue was purified by HPLC to give (R)-2-(6-cyano-5-(3-methylisothiazol-5-ylamino)pyridin-3-ylamino)butanamide (42 mg).

[0147] The compound (R)-2-(6-cyano-5-(3-methylisothiazol-5-ylamino)pyridin-3-ylamino)butanamide (42 mg, 0.133 mmol) was dissolved in EtOH (2 mL) and DMSO (1 mL), aq. 1N NaOH (1.0 mL) and aq. H_2O_2 (30%, 1.0 mL) were added. The mixture was stirred at room temperature for 10 min. HOAc (0.1 mL) was added. The mixture was then concentrated in vacuo. The residue was purified by HPLC to give the titled compound (14 mg). MS 335.2 (M+H); UV: λ = 202.3, 304.0 nm; t 0.456 min.

Example 6. 3-(3-(2H-1,2,3-triazol-2-yl)phenylamino)-5-((1R,2S)-2-aminocyclohexylamino)picolinamide

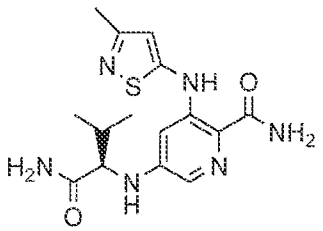


[0148] A mixture of tert-butyl (1S,2R)-2-(5-bromo-6-cyanopyridin-3-ylamino)cyclohexylcarbamate (90 mg, 0.227 mmol), 3-(2H-1,2,3-triazol-2-yl)aniline (40 mg, 0.250 mmol), NaOPh trihydrate (50 mg, 0.294 mmol), xantphos (30 mg, 0.051 mmol) and Pd_2dba_3 (18 mg, 0.019 mmol) in dioxane (3 mL) was degassed with Ar, then was stirred at 110 °C for 20 h. Water and EtOAc were added. Organic phase was separated, washed with aq. 1N NaOH, dried over Na_2SO_4, concentrated in vacuo to give tert-butyl (1S,2R)-2-(5-(3-(2H-1,2,3-

triazol-2-yl)phenylamino)-6-cyanopyridin-3-ylamino)cyclohexylcarbamate, which was then dissolved in trifluoroacetic acid (5 mL). The solution was allowed to stand for 2 h. Excess of trifluoroacetic acid was removed in vacuo. The residue was purified by HPLC to give 3-(3-(2H-1,2,3-triazol-2-yl)phenylamino)-5-((1R,2S)-2-aminocyclohexylamino)picolinonitrile (70 mg).

[0149] The compound 3-(3-(2H-1,2,3-triazol-2-yl)phenylamino)-5-((1R,2S)-2-aminocyclohexylamino)picolinonitrile (70 mg, 0.143 mmol) was dissolved in EtOH (2 mL) and DMSO (1 mL), aq. 1N NaOH (1.0 mL) and aq. H_2O_2 (30%, 1.0 mL) were added. The mixture was stirred at room temperature for 15 min. HOAc (0.1 mL) was added. The mixture was then concentrated in vacuo. The residue was purified by HPLC to give the titled compound (52 mg). MS 393.2 (M+H); UV: λ = 205.4, 272.6 nm; t 0.484 min.

Example 7. (R)-5-(1-amino-3-methyl-1-oxobutan-2-ylamino)-3-(3-methylisothiazol-5-ylamino)picolinamide



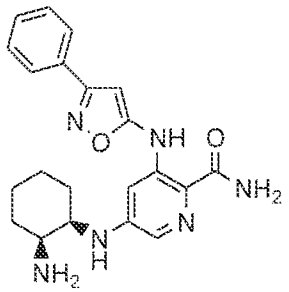
[0150] A solution of 3-bromo-5-fluoropicolinonitrile (300 mg, 1.49 mmol), (R)-2-amino-3-methylbutanamide hydrochloride (228 mg, 1.49 mmol) and DIEA (0.600 mL, 3.45 mmol) in DMSO (6 mL) was stirred at 100 °C for 20 h. Water and EtOAc were added. Organic phase was separated, washed with water, dried over Na_2SO_4, concentrated in vacuo to give (R)-2-(5-bromo-6-cyanopyridin-3-ylamino)-3-methylbutanamide (316 mg).

[0151] A mixture of (R)-2-(5-bromo-6-cyanopyridin-3-ylamino)-3-methylbutanamide (158 mg, 0.531 mmol), 3-methylisothiazol-5-amine hydrochloride (90 mg, 0.597 mmol), NaOPh trihydrate (200 mg, 1.17 mmol), xantphos (40 mg, 0.069 mmol) and Pd_2dba_3 (35 mg, 0.038 mmol) in dioxane (3 mL) was degassed with Ar, then was stirred at 110 °C for 20 h. The mixture was concentrated in vacuo. The residue was purified by HPLC to give (R)-2-(6-cyano-5-(3-methylisothiazol-5-ylamino)pyridin-3-ylamino)-3-methylbutanamide (53 mg).

[0152] The compound (R)-2-(6-cyano-5-(3-methylisothiazol-5-ylamino)pyridin-3-ylamino)-3-methylbutanamide (53 mg, 0.16 mmol) was dissolved in EtOH (2 mL) and DMSO (1 mL), aq.

1N NaOH (1.0 mL) and aq. H_2O_2 (30%, 1.0 mL) were added. The mixture was stirred at room temperature for 10 min. HOAc (0.1 mL) was added. The mixture was then concentrated in vacuo. The residue was purified by HPLC to give the titled compound (30 mg). MS 349.2 (M+H); UV: λ = 205.4, 307.7 nm; t 0.503 min.

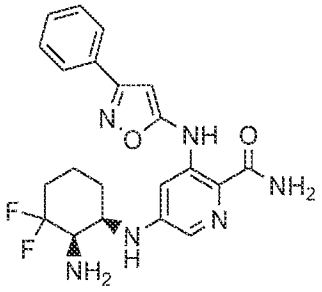
Example 8. 5-((1R,2S)-2-aminocyclohexylamino)-3-(3-phenylisoxazol-5-ylamino)picolinamide



[0153] A mixture of tert-butyl (1S,2R)-2-(5-bromo-6-cyanopyridin-3-ylamino)cyclohexylcarbamate (82 mg, 0.207 mmol), 5-amino-3-phenylisoxazole (40 mg, 0.250 mmol), NaOPh trihydrate (50 mg, 0.294 mmol), xantphos (30 mg, 0.051 mmol) and Pd_2dba_3 (18 mg, 0.019 mmol) in dioxane (2 mL) was degassed with Ar, then was stirred at 110 °C for 4 h. Water and EtOAc were added. Organic phase was separated, washed with aq. 1N NaOH, dried over Na_2SO_4, concentrated in vacuo to give tert-butyl (1S,2R)-2-(6-cyano-5-(3-phenylisoxazol-5-ylamino)pyridin-3-ylamino)cyclohexylcarbamate, which was then dissolved in trifluoroacetic acid (4 mL). The solution was allowed to stand for 30 min. Excess of trifluoroacetic acid was removed in vacuo. The residue was purified by HPLC to give 5-((1R,2S)-2-aminocyclohexylamino)-3-(3-phenylisoxazol-5-ylamino)picolinonitrile (27 mg).

[0154] The compound 5-((1R,2S)-2-aminocyclohexylamino)-3-(3-phenylisoxazol-5-ylamino)picolinonitrile (27 mg) was dissolved in EtOH (1 mL) and DMSO (0.5 mL), aq. 1N NaOH (0.5 mL) and aq. H_2O_2 (30%, 0.5 mL) were added. The mixture was stirred at room temperature for 20 min. HOAc (0.1 mL) was added. The mixture was then concentrated in vacuo. The residue was purified by HPLC to give the titled compound (12 mg). MS 393.2 (M+H); UV: λ = 202.9, 245.0, 295.3 nm; t 0.512 min.

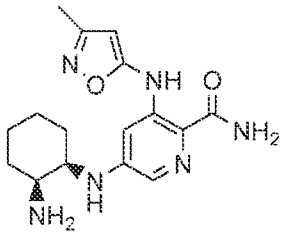
Example 9. 5-((1R,2R)-2-amino-3,3-difluorocyclohexylamino)-3-(3-phenylisoxazol-5-ylamino)picolinamide



[0155] A mixture of 5-((1R,2R)-2-amino-3,3-difluorocyclohexylamino)-3-bromopicolinonitrile (79 mg, 0.238 mmol), 5-amino-3-phenylisoxazole (44 mg, 0.275 mmol), NaOPh trihydrate (55 mg, 0.323 mmol), xantphos (30 mg, 0.051 mmol) and Pd_2dba_3 (18 mg, 0.019 mmol) in dioxane (2 mL) was degassed with Ar, then was stirred at 110 °C for 6 h. The mixture was concentrated in vacuo. The residue was purified by HPLC to give 5-((1R,2R)-2-amino-3,3-difluorocyclohexylamino)-3-(3-phenylisoxazol-5-ylamino)picolinonitrile (26 mg).

[0156] The compound 5-((1R,2R)-2-amino-3,3-difluorocyclohexylamino)-3-(3-phenylisoxazol-5-ylamino)picolinonitrile (26 mg, 0.063 mmol) was dissolved in EtOH (1 mL) and DMSO (1 mL), aq. 1N NaOH (1 mL) and aq. H_2O_2 (30%, 1 mL) were added. The mixture was stirred at room temperature for 20 min. HOAc (0.1 mL) was added. The mixture was concentrated in vacuo. The residue was purified by HPLC to give the titled compound (10 mg). MS 429.5; UV: λ = 300.2 nm; t 0.562 min.

Example 10. 5-((1R,2S)-2-aminocyclohexylamino)-3-(3-methylisoxazol-5-ylamino)picolinamide

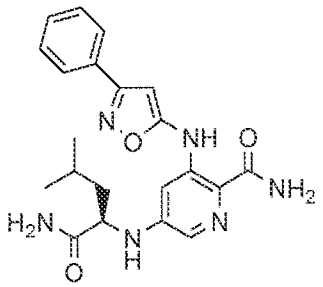


[0157] A mixture of tert-butyl (1S,2R)-2-(5-bromo-6-cyanopyridin-3-ylamino)cyclohexylcarbamate (90 mg, 0.227 mmol), 5-amino-3-methylisoxazole (28 mg, 0.285 mmol), NaOPh trihydrate (55 mg, 0.323 mmol), xantphos (30 mg, 0.051 mmol) and Pd_2dba_3 (18 mg, 0.019 mmol) in dioxane (2 mL) was degassed with Ar, then was stirred at 110 °C for 5 h. Water and EtOAc were added. Organic phase was separated, washed with aq. 1N NaOH, dried over Na_2SO_4, concentrated in vacuo to give tert-butyl (1S,2R)-2-(6-cyano-5-(3-methylisoxazol-

5-ylamino)pyridin-3-ylamino)cyclohexylcarbamate, which was then dissolved in trifluoroacetic acid (5 mL). The solution was allowed to stand for 30 min. Excess of trifluoroacetic acid was removed in vacuo. The residue was purified by HPLC to give 5-((1R,2S)-2-aminocyclohexylamino)-3-(3-methylisoxazol-5-ylamino)picolinonitrile.

[0158] The compound 5-((1R,2S)-2-aminocyclohexylamino)-3-(3-methylisoxazol-5-ylamino)picolinonitrile was dissolved in EtOH (2 mL) and DMSO (1 mL), aq. 1N NaOH (1 mL) and aq. H_2O_2 (30%, 1 mL) were added. The mixture was stirred at room temperature for 20 min. HOAc (0.1 mL) was added. The mixture was then concentrated in vacuo. The residue was purified by HPLC to give the titled compound (10 mg). MS 331.5 (M+H); UV: λ = 204.7, 282.9, 332.3 nm; t 0.413 min.

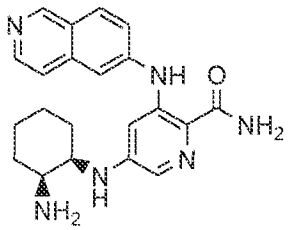
Example 11. (R)-5-(1-amino-4-methyl-1-oxopentan-2-ylamino)-3-(3-phenylisoxazol-5-ylamino)picolinamide



[0159] A mixture of (R)-2-(5-bromo-6-cyanopyridin-3-ylamino)-4-methylpentanamide (80 mg, 0.257 mmol), 5-amino-3-phenylisoxazole (44 mg, 0.275 mmol), NaOPh trihydrate (55 mg, 0.323 mmol), xantphos (30 mg, 0.051 mmol) and Pd_2dba_3 (18 mg, 0.019 mmol) in dioxane (2 mL) was degassed with Ar, then was stirred at 110 °C for 20 h. HOAc (0.1 mL) was added. The mixture was concentrated in vacuo. The residue was purified by HPLC to give (R)-2-(6-cyano-5-(3-phenylisoxazol-5-ylamino)pyridin-3-ylamino)-4-methylpentanamide (15 mg).

[0160] The compound (R)-2-(6-cyano-5-(3-phenylisoxazol-5-ylamino)pyridin-3-ylamino)-4-methylpentanamide (15 mg, 0.038 mmol) was dissolved in EtOH (1 mL) and DMSO (0.5 mL), aq. 1N NaOH (0.5 mL) and aq. H_2O_2 (30%, 0.5 mL) were added. The mixture was stirred at room temperature for 15 min. HOAc (0.1 mL) was added. The mixture was then concentrated in vacuo. The residue was purified by HPLC to give the titled compound (9 mg). MS 409.5 (M+H); UV: λ = 204.7, 295.2 nm; t 0.703 min.

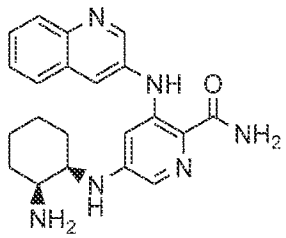
Example 12. 5-((1R,2S)-2-aminocyclohexylamino)-3-(isoquinolin-6-ylamino)picolinamide



[0161] A mixture of tert-butyl (1S,2R)-2-(5-bromo-6-cyanopyridin-3-ylamino)cyclohexylcarbamate (90 mg, 0.227 mmol), 6-aminoisoquinoline (40 mg, 0.277 mmol), NaOPh trihydrate (50 mg, 0.294 mmol), xantphos (30 mg, 0.051 mmol) and Pd_2dba_3 (18 mg, 0.019 mmol) in dioxane (3 mL) was degassed with Ar, then was stirred at 110 °C for 20 h. The mixture was concentrated in vacuo. The residue was then dissolved in trifluoroacetic acid (5 mL). The solution was allowed to stand for 30 min. Excess of trifluoroacetic acid was removed in vacuo. The residue was purified by HPLC to give 5-((1R,2S)-2-aminocyclohexylamino)-3-(isoquinolin-6-ylamino)picolinonitrile (85 mg).

[0162] The compound 5-((1R,2S)-2-aminocyclohexylamino)-3-(isoquinolin-6-ylamino)picolinonitrile (85 mg) was dissolved in EtOH (2 mL) and DMSO (1 mL), aq. 1N NaOH (1.0 mL) and aq. H_2O_2 (30%, 1.0 mL) were added. The mixture was stirred at room temperature for 30 min. HOAc (0.1 mL) was added. The mixture was then concentrated in vacuo. The residue was purified by HPLC to give the titled compound (59 mg). MS 377.2 (M+H); UV: λ = 216.3, 283.6, 316.3 nm; t 0.332 min.

Example 13. 5-((1R,2S)-2-aminocyclohexylamino)-3-(quinolin-3-ylamino)picolinamide

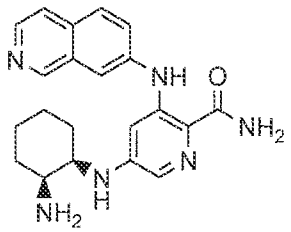


[0163] A mixture of tert-butyl (1S,2R)-2-(5-bromo-6-cyanopyridin-3-ylamino)cyclohexylcarbamate (90 mg, 0.227 mmol), 3-aminoquinoline (40 mg, 0.277 mmol), NaOPh trihydrate (50 mg, 0.294 mmol), xantphos (30 mg, 0.051 mmol) and Pd_2dba_3 (18 mg, 0.019 mmol) in dioxane (3 mL) was degassed with Ar, then was stirred at 110 °C for 20 h. The

mixture was concentrated in vacuo. The residue was then dissolved in trifluoroacetic acid (5 mL). The solution was allowed to stand for 30 min. Excess of trifluoroacetic acid was removed in vacuo. The residue was purified by HPLC to give 5-((1R,2S)-2-aminocyclohexylamino)-3-(quinolin-3-ylamino)picolinonitrile (91 mg).

[0164] The compound 5-((1R,2S)-2-aminocyclohexylamino)-3-(quinolin-3-ylamino)picolinonitrile (91 mg) was dissolved in EtOH (2 mL) and DMSO (1 mL), aq. 1N NaOH (1.0 mL) and aq. H_2O_2 (30%, 1.0 mL) were added. The mixture was stirred at room temperature for 30 min. HOAc (0.1 mL) was added. The mixture was then concentrated in vacuo. The residue was purified by HPLC to give the titled compound (56 mg). MS 377.2 (M+H); UV: λ = 223.6, 285.5 nm; t 0.364 min.

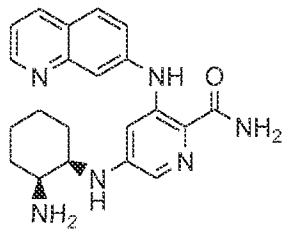
Example 14. 5-((1R,2S)-2-aminocyclohexylamino)-3-(isoquinolin-7-ylamino)picolinamide



[0165] A mixture of tert-butyl (1S,2R)-2-(5-bromo-6-cyanopyridin-3-ylamino)cyclohexylcarbamate (90 mg, 0.227 mmol), 7-aminoisoquinoline (40 mg, 0.277 mmol), NaOPh trihydrate (50 mg, 0.294 mmol), xantphos (30 mg, 0.051 mmol) and Pd_2dba_3 (18 mg, 0.019 mmol) in dioxane (2 mL) was degassed with Ar, then was stirred at 110 °C for 4 h. The mixture was concentrated in vacuo. The residue was then dissolved in trifluoroacetic acid (5 mL). The solution was allowed to stand for 20 h. Excess of trifluoroacetic acid was removed in vacuo. The residue was purified by HPLC to give 5-((1R,2S)-2-aminocyclohexylamino)-3-(isoquinolin-7-ylamino)picolinonitrile.

[0166] The compound 5-((1R,2S)-2-aminocyclohexylamino)-3-(isoquinolin-7-ylamino)picolinonitrile was dissolved in EtOH (2 mL) and DMSO (1 mL), aq. 1N NaOH (1.0 mL) and aq. H_2O_2 (30%, 1.0 mL) were added. The mixture was stirred at room temperature for 15 min. HOAc (0.1 mL) was added. The mixture was then concentrated in vacuo. The residue was purified by HPLC to give the titled compound (62 mg). MS 377.2 (M+H); UV: λ = 200.5, 220.0, 292.3, 325.0 nm; t 0.326 min.

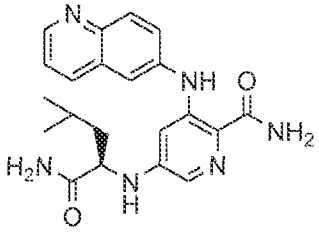
Example 15. 5-((1R,2S)-2-aminocyclohexylamino)-3-(quinolin-7-ylamino)picolinamide



[0167] A mixture of tert-butyl (1S,2R)-2-(5-bromo-6-cyanopyridin-3-ylamino)cyclohexylcarbamate (90 mg, 0.227 mmol), 7-aminoquinoline (40 mg, 0.277 mmol), NaOPh trihydrate (50 mg, 0.294 mmol), xantphos (30 mg, 0.051 mmol) and Pd_2dba_3 (18 mg, 0.019 mmol) in dioxane (2 mL) was degassed with Ar, then was stirred at 110 °C for 4 h. The mixture was concentrated in vacuo. The residue was then dissolved in trifluoroacetic acid (5 mL). The solution was allowed to stand for 20 h. Excess of trifluoroacetic acid was removed in vacuo. The residue was purified by HPLC to give 5-((1R,2S)-2-aminocyclohexylamino)-3-(quinolin-7-ylamino)picolinonitrile.

[0168] The compound 5-((1R,2S)-2-aminocyclohexylamino)-3-(quinolin-7-ylamino)picolinonitrile was dissolved in EtOH (2 mL) and DMSO (1 mL), aq. 1N NaOH (1.0 mL) and aq. H_2O_2 (30%, 1.0 mL) were added. The mixture was stirred at room temperature for 20 min. HOAc (0.1 mL) was added. The mixture was then concentrated in vacuo. The residue was purified by HPLC to give the titled compound (71 mg). MS 377.2 (M+H); UV: λ = 215.1, 291.6 nm; t 0.340 min.

Example 16. (R)-5-(1-amino-4-methyl-1-oxopentan-2-ylamino)-3-(quinolin-6-ylamino)picolinamide

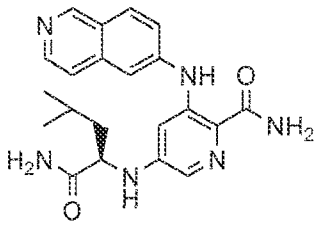


[0169] A mixture of (R)-2-(5-bromo-6-cyanopyridin-3-ylamino)-4-methylpentanamide (80 mg, 0.257 mmol), 6-aminoquinoline (40 mg, 0.277 mmol), NaOPh trihydrate (55 mg, 0.323 mmol), xantphos (30 mg, 0.051 mmol) and Pd_2dba_3 (18 mg, 0.019 mmol) in dioxane (2 mL) was

degassed with Ar, then was stirred at 110 °C for 20 h. The mixture was concentrated in vacuo. The residue was purified by HPLC to give (R)-2-(6-cyano-5-(quinolin-6-ylamino)pyridin-3-ylamino)-4-methylpentanamide.

[0170] The compound (R)-2-(6-cyano-5-(quinolin-6-ylamino)pyridin-3-ylamino)-4-methylpentanamide was dissolved in EtOH (2 mL) and DMSO (1 mL), aq. 1N NaOH (1 mL) and aq. H_2O_2 (30%, 1 mL) were added. The mixture was stirred at room temperature for 1h. HOAc (0.1 mL) was added. The mixture was then concentrated in vacuo. The residue was purified by HPLC to give the titled compound (32 mg). MS 393.2 (M+H); UV: λ = 220.6, 301.5 nm; t 0.415 min.

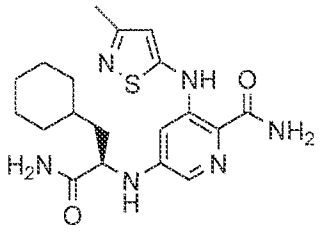
Example 17. (R)-5-(1-amino-4-methyl-1-oxopentan-2-ylamino)-3-(isoquinolin-6-ylamino)picolinamide



[0171] A mixture of (R)-2-(5-bromo-6-cyanopyridin-3-ylamino)-4-methylpentanamide (80 mg, 0.257 mmol), 6-aminoisoquinoline (40 mg, 0.277 mmol), NaOPh trihydrate (55 mg, 0.323 mmol), xantphos (30 mg, 0.051 mmol) and Pd_2dba_3 (18 mg, 0.019 mmol) in dioxane (2 mL) was degassed with Ar, then was stirred at 110 °C for 20 h. The mixture was concentrated in vacuo. The residue was purified by HPLC to give (R)-2-(6-cyano-5-(isoquinolin-6-ylamino)pyridin-3-ylamino)-4-methylpentanamide.

[0172] The compound (R)-2-(6-cyano-5-(isoquinolin-6-ylamino)pyridin-3-ylamino)-4-methylpentanamide was dissolved in EtOH (2 mL) and DMSO (1 mL), aq. 1N NaOH (1 mL) and aq. H_2O_2 (30%, 1 mL) were added. The mixture was stirred at room temperature for 1h. HOAc (0.1 mL) was added. The mixture was then concentrated in vacuo. The residue was purified by HPLC to give the titled compound (33 mg). MS 393.2 (M+H); UV: λ = 219.4, 286.1 nm; t 0.420 min.

Example 18. (R)-5-(1-amino-3-cyclohexyl-1-oxopropan-2-ylamino)-3-(3-methylisothiazol-5-ylamino)picolinamide



[0173] To a solution of N-Boc-β-cyclohexyl-D-alanine (1.00 g, 3.69 mmol) and HOBt hydrate (0.678 g, 4.43 mmol) in DMF (10 mL), EDC (0.850 g, 4.43 mmol) was added. The mixture was stirred for 60 min. Then conc. NH4OH (1.00 mL, ~14.0 mmol) was added. It was stirred for 18 h. Water and EtOAc were added. The organic phase was separated, washed with 5% $NaHCO_3$, dried over Na_2SO_4, concentrated in vacuo to give (R)-tert-butyl 1-amino-3-cyclohexyl-1-oxopropan-2-ylcarbamate as a white solid (0.917 g).

[0174] The white solid (0.917 g, 3.40 mmol) was dissolved in TFA (10 mL). After 2 h of standing, TFA was removed in vacuo. To the residue, nBuOH and aq. 5% $NaHCO_3$ were added. The nBuOH phase was separated, washed with water, concentrated in vacuo to give (R)-2-amino-3-cyclohexylpropanamide (0.519 g).

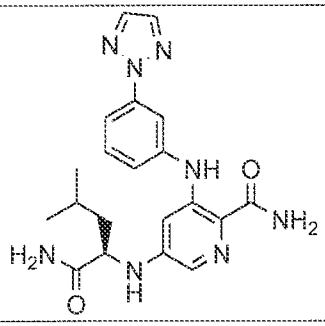
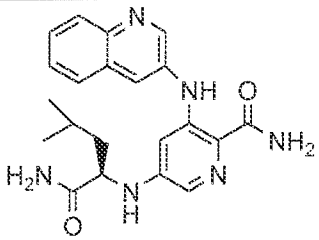
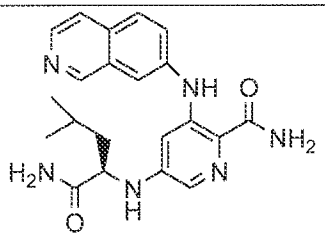
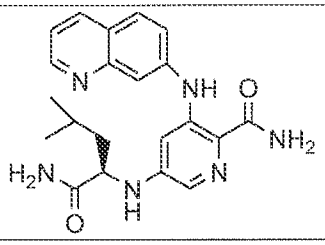
[0175] A solution of 3-bromo-5-fluoropicolinonitrile (83 mg, 0.412 mmol), (R)-2-amino-3-cyclohexylpropanamide (100 mg, 0.588 mmol) and DIEA (0.150 mL, 0.862 mmol) in DMSO (2 mL) was stirred at 110 °C for 20 h. Water and EtOAc were added. Organic phase was separated, washed with water, dried over Na_2SO_4, concentrated in vacuo. The residue was purified by HPLC to give (R)-2-(5-bromo-6-cyanopyridin-3-ylamino)-3-cyclohexylpropanamide (46 mg).

A mixture of (R)-2-(5-bromo-6-cyanopyridin-3-ylamino)-3-cyclohexylpropanamide (46 mg, 0.131 mmol), 3-methylisothiazol-5-amine hydrochloride (28 mg, 0.186 mmol), NaOPh trihydrate (66 mg, 0.388 mmol), xantphos (20 mg, 0.034 mmol) and Pd_2dba_3 (10 mg, 0.011 mmol) in dioxane (2 mL) was degassed with Ar, then was stirred at 110 °C for 20 h. HOAc (0.1 mL) was added. The mixture was concentrated in vacuo. The residue was purified by HPLC to give (R)-2-(6-cyano-5-(3-methylisothiazol-5-ylamino)pyridin-3-ylamino)-3-cyclohexylpropanamide (24 mg).

[0176] The compound (R)-2-(6-cyano-5-(3-methylisothiazol-5-ylamino)pyridin-3-ylamino)-3-cyclohexylpropanamide (24 mg, 0.062 mmol) was dissolved in EtOH (2 mL) and DMSO (1 mL), aq. 1N NaOH (1.0 mL) and aq. H_2O_2 (30%, 1.0 mL) were added. The mixture was stirred

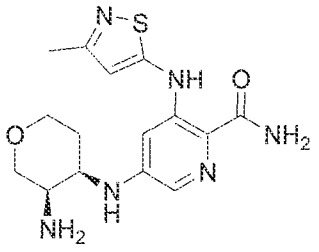
at room temperature for 10 min. HOAc (0.1 mL) was added. The mixture was then concentrated in vacuo. The residue was purified by HPLC to give the titled compound (14 mg). MS 403.2 (M+H); UV: λ = 208.4, 301.5 nm; t 0.643 min.

Table 1

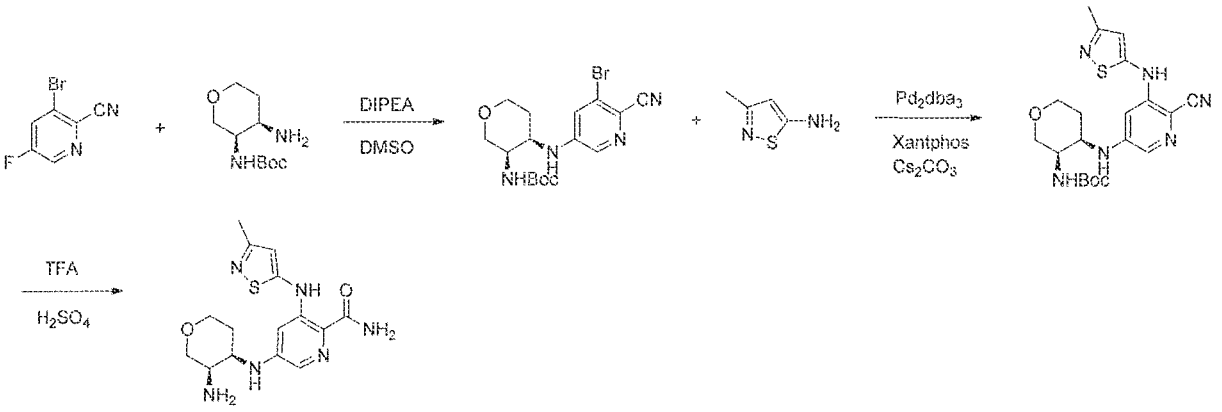
Example 19		(R)-3-(3-(2H-1,2,3-triazol-2-yl)phenylamino)-5-(1-amino-4-methyl-1-oxopentan-2-ylamino)picolinamide
Example 20		(R)-5-(1-amino-4-methyl-1-oxopentan-2-ylamino)-3-(quinolin-3-ylamino)picolinamide
Example 21		(R)-5-(1-amino-4-methyl-1-oxopentan-2-ylamino)-3-(isoquinolin-7-ylamino)picolinamide
Example 22		(R)-5-(1-amino-4-methyl-1-oxopentan-2-ylamino)-3-(quinolin-7-ylamino)picolinamide

[0177] The compounds in Table 1 can be synthesized analogously according to procedures described previously for (R)-5-(1-amino-4-methyl-1-oxopentan-2-ylamino)-3-(3-methylisothiazol-5-ylamino)picolinamide and 5-((1R,2S)-2-aminocyclohexylamino)-3-(3-methylisothiazol-5-ylamino)picolinamide.

Example 23. 5-((3R, 4R)-3-aminotetrahydro-2H-pyran-4-ylamino)-3-(3-methylisothiazol-5-ylamino)picolinamide



Scheme 1



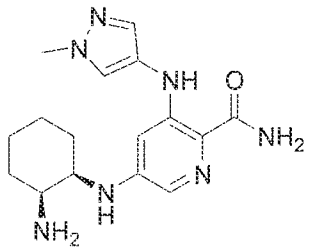
[0178] Step 1: To a solution of 3-bromo-5-fluoropicolinonitrile (120 mg, 0.6 mmol) in DMSO (1.2 ml) was added DIPEA (0.118 ml, 0.66 mmol) and tert-butyl (3R, 4R)-4-aminotetrahydro-2H-pyran-3-ylcarbamate (143 mg, 0.66 mmol). After heated at 100 °C for 3 h, it was cooled and diluted with water, the resulting precipitate was collected by filtration to give tert-butyl (3R, 4R)-4-(5-bromo-6-cyanopyridin-3-ylamino)tetrahydro-2H-pyran-3-ylcarbamate as crude oil.

[0179] Step 2: To a mixture of tert butyl (3R, 4R)-4-(5-bromo-6-cyanopyridin-3-ylamino)tetrahydro-2H-pyran-3-ylcarbamate in Dioxane (3 ml) was added 3-methylisothiazol-5-amine hydrochloride (108 mg, 0.72 mmol), Pd_2dba_3 (55 mg, 0.06 mmol), Xantphos (52 mg, 0.09 mmol) and Cs_2CO_3 (587 mg, 1.8 mmol). After heating at 95 °C for 15 h, the mixture was filtered, the filtrate was concentrated and purified by preparative HPLC to give tert-butyl (3R, 4R)-4-(6-cyano-5-(3-methylisothiazol-5-ylamino)pyridine-3-ylamino)tetrahydro-2H-pyran-3-ylcarbamate (40 mg).

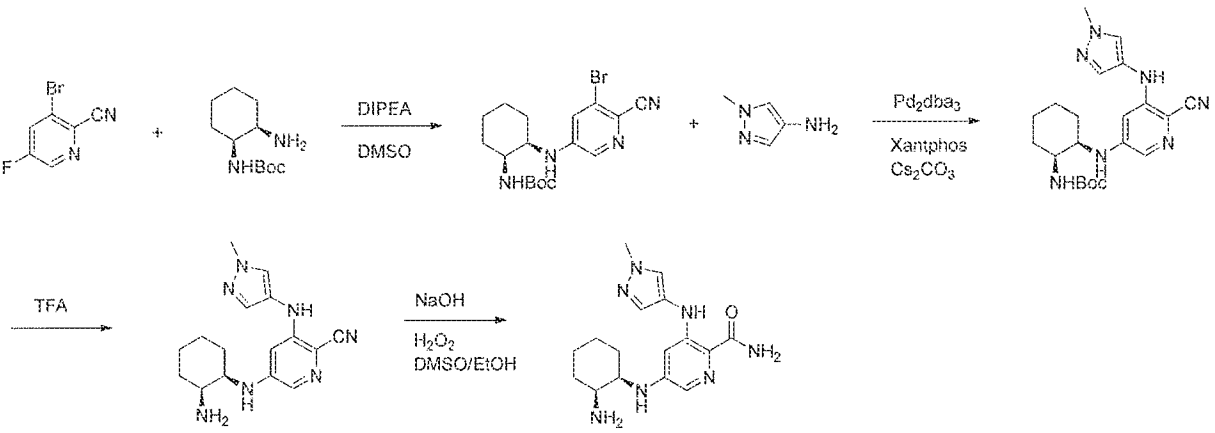
[0180] Step 3: To a solution of tert-butyl (3R, 4R)-4-(6-cyano-5-(3-methylisothiazol-5-ylamino)pyridine-3-ylamino)tetrahydro-2H-pyran-3-ylcarbamate (40 mg) in TFA (2 ml) was added H2SO4 (0.5 ml). After heated at 60 °C for 1 h, it was concentrated and purified by preparative HPLC to give 5-((3R, 4R)-3-aminotetrahydro-2H-pyran-4-ylamino)-3-(3-

methylisothiazol-5-ylamino)picolinamide. MS found for $C_{15}H_{20}N_6O_2S$ as $(M+H)^+$ 349.2, UV: λ = 304.5 nm.

Example 24. 5-((1R,2S)-2-aminocyclohexylamino)-3-(1-methyl-1H-pyrazol-4-ylamino)picolinamide



Scheme 2



[0181] Step 1: To a solution of 3-bromo-5-fluoropicolinonitrile (100 mg, 0.5 mmol) in DMSO (1.0 ml) was added DIPEA (0.098 ml, 0.55 mmol) and tert-butyl (1S,2R)-2-aminocyclohexylcarbamate (118 mg, 0.55 mmol). After heated at 100 °C for 3 h, it was cooled and diluted with water, the resulting precipitate was collected by filtration to give tert-butyl (1S,2R)-2-(5-bromo-6-cyanopyridin-3-ylamino)cyclohexylcarbamate (200 mg).

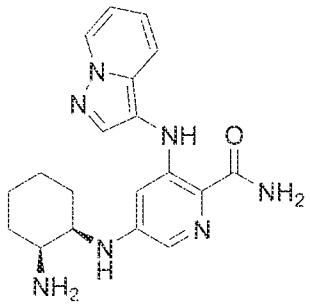
[0182] Step 2: To a mixture of tert-butyl (1S,2R)-2-(5-bromo-6-cyanopyridin-3-ylamino)cyclohexylcarbamate (100 mg, 0.25 mmol) in Dioxane (1.5 ml) was added 1-methyl-1H-pyrazol-4-amine (30 mg, 0.30 mmol), Pd2(dba)3 (23 mg, 0.025 mmol), Xantphos (22 mg, 0.038 mmol) and Cs_2CO_3 (244 mg, 0.75 mmol). After heating at 95 °C for 15 h, the mixture was

filtered, the filtrate was concentrated to give tert-butyl (1S,2R)-2-(6-cyano-5-(1-methyl-1H-pyrazol-4-ylamino)pyridin-3-ylamino)cyclohexylcarbamate as crude product.

[0183] Step 3: To a solution of tert-butyl (1S,2R)-2-(6-cyano-5-(1-methyl-1H-pyrazol-4-ylamino)pyridin-3-ylamino)cyclohexylcarbamate (40 mg) in DCM (1 ml) was added TFA (1.0 ml). After stirring for 1 h, it was concentrated and purified by preparative HPLC to give 5-((1R,2S)-2-aminocyclohexylamino)-3-(1-methyl-1H-pyrazol-4-ylamino)picolinonitrile (50 mg).

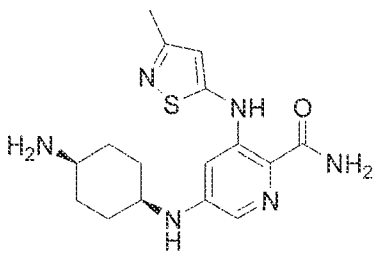
[0184] Step 4: To a solution of 5-((1R,2S)-2-aminocyclohexylamino)-3-(1-methyl-1H-pyrazol-4-ylamino)picolinonitrile (50 mg, 0.16 mmol) in EtOH (1 ml) was added DMSO (0.5 mL), NaOH (1N, 0.5 ml) and H_2O_2 (30%, 0.5 mL), after 15 min, it was concentrated and purified by preparative HPLC to give 5-((1R,2S)-2-aminocyclohexylamino)-3-(1-methyl-1H-pyrazol-4-ylamino)picolinamide (34mg), MS found for $C_{16}H_{23}N_7O$ as $(M+H)^+$ 330.3, UV: λ = 252.3 nm.

Example 25. 5-((1R,2S)-2-aminocyclohexylamino)-3-(pyrazolo[1,5-a]pyridin-3-ylamino)picolinamide



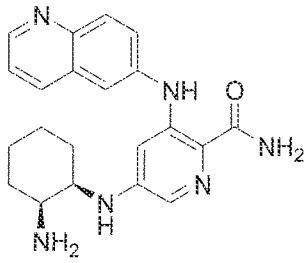
[0185] The title compound was synthesized similar to example 2. MS found for $C_{19}H_{23}N_7O$ as $(M+H)^+$ 366.3, UV: λ = 215.7, 290.2, 336.7.

Example 26. 5-((1S,4S)-4-aminocyclohexylamino)-3-(3-methylisothiazol-5-ylamino)picolinamide



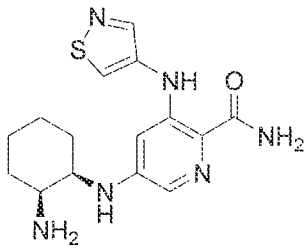
[0186] The title compound was synthesized similar to example 2. MS found for $C_{16}H_{22}N_6OS$ as $(M+H)^+$ 347.2, UV: λ = 305.6 nm.

Example 27. 5-((1R,2S)-2-aminocyclohexylamino)-3-(quinolin-6-ylamino)picolinamide



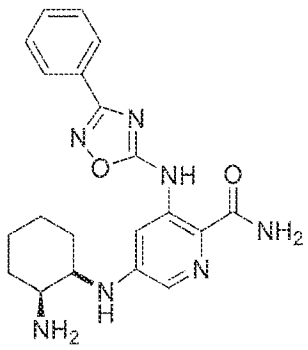
[0187] The title compound was synthesized similar to example 2. MS found for $C_{21}H_{24}N_6O$ as $(M+H)^+$ 377.2, UV: λ = 294.9 nm.

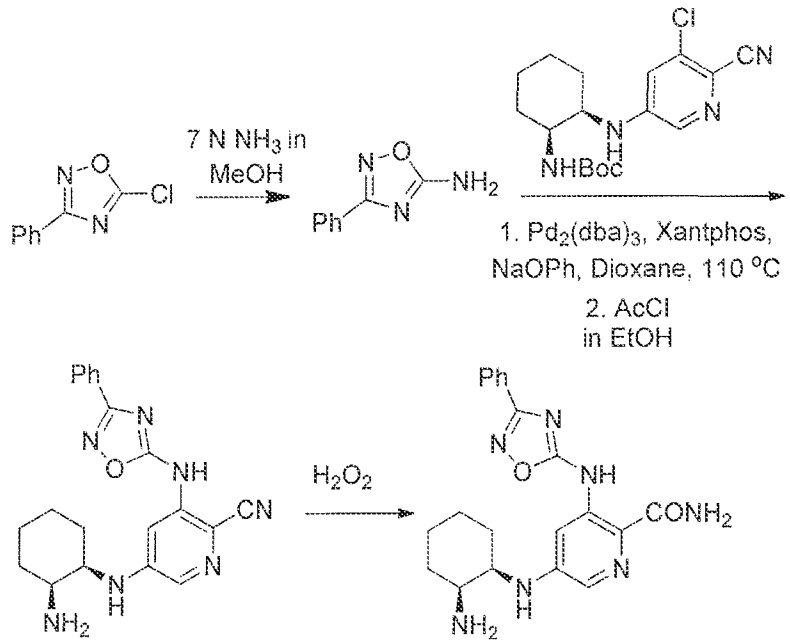
Example 28. 5-((1R,2S)-2-aminocyclohexylamino)-3-(isothiazol-4-ylamino)picolinamide



[0188] The title compound was synthesized similar to example 2. MS found for $C_{15}H_{20}N_6OS$ as $(M+H)^+$ 333.2, UV: λ = 261.7, 294.9 nm.

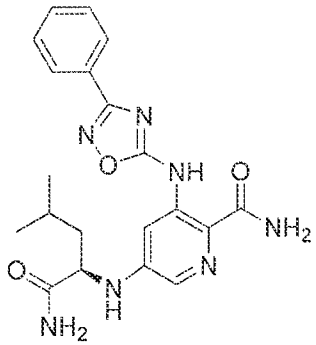
Example 29. Preparation of 5-(((1R,2S)-2-aminocyclohexyl)amino)-3-((3-phenyl-1,2,4-oxadiazol-5-yl)amino)picolinamide





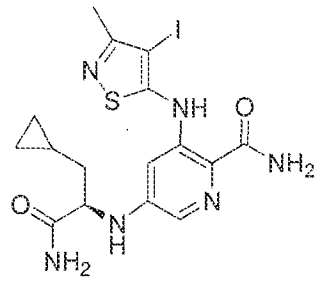
[0189] The title compound was synthesized in a manner similar to that described in Example 1. MS found for $C_{20}H_{23}N_7O_2$ as $(M+H)^+$ 394.2.

Example 30. Preparation of (R)-5-((1-amino-4-methyl-1-oxopentan-2-yl)amino)-3-((3-phenyl-1,2,4-oxadiazol-5-yl)amino)picolinamide



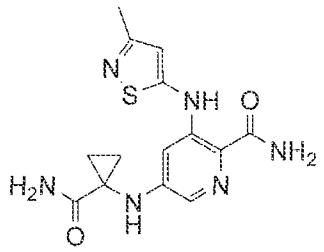
[0190] The title compound was synthesized in a manner similar to that described in Example 1. MS found for $C_{20}H_{23}N_7O_3$ as $(M+H)^+$ 410.4. UV: λ =263, 323 nm.

Example 31. Preparation of (R)-5-((1-amino-3-cyclopropyl-1-oxopropan-2-yl)amino)-3-((4-iodo-3-methylisothiazol-5-yl)amino)picolinamide



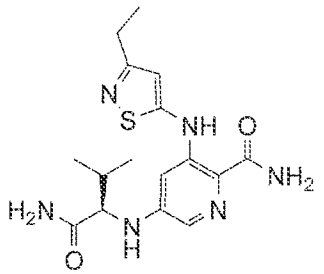
[0191] The title compound was synthesized in a manner similar to that described in Example 1. MS found for $C_{16}H_{19}IN_6O_2S$ as $(M+H)^+$ 487.3. UV: λ =207, 308.

Example 32. 5-(1-carbamoylcyclopropylamino)-3-(3-methylisothiazol-5-ylamino)picolinamide.



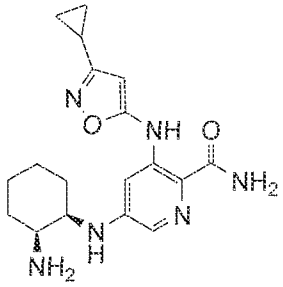
[0192] The title compound was synthesized in a manner similar to that described in Example 1. MS found for $C_{14}H_{16}N_6O_2S$ as (M+H)+ 333.2. UV: λ = 304.5 nm.

Example 33. (R)-5-(1-amino-3-methyl-1-oxobutan-2-ylamino)-3-(3-ethylisothiazol-5-ylamino)picolinamide.



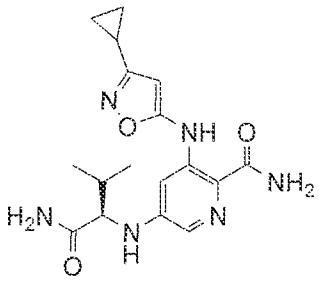
[0193] The title compound was synthesized in a manner similar to that described in Example 1. MS found for $C_{16}H_{22}N_6O_2S$ as $(M+H)^+$ 363.2. UV: λ = 305.6 nm.

Example 34. 5-((1R,2S)-2-aminocyclohexylamino)-3-(3-cyclopropylisoxazol-5-ylamino)picolinamide.



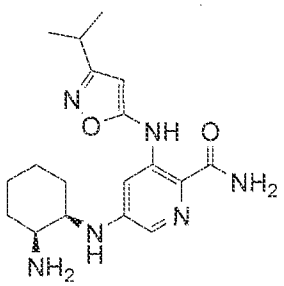
[0194] The title compound was synthesized in a manner similar to that described in Example 2. MS found for $C_{18}H_{24}N_6O_2$ as $(M+H)^+$ 357.3. UV: $\lambda = 286.6$ nm.

Example 35. (R)-5-(1-amino-3-methyl-1-oxobutan-2-ylamino)-3-(3-cyclopropylisoxazol-5-ylamino)picolinamide.



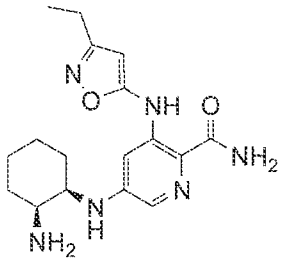
[0195] The title compound was synthesized in a manner similar to that described in Example 1. MS found for $C_{17}H_{22}N_6O_3$ as $(M+H)^+$ 359.3. UV: $\lambda = 287.8$ nm.

Example 36. 5-((1R,2S)-2-aminocyclohexylamino)-3-(3-isopropylisoxazol-5-ylamino)picolinamide.



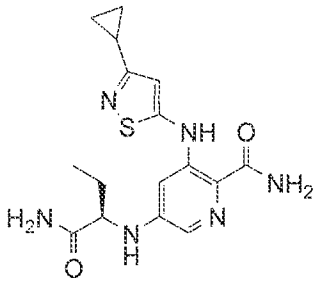
[0196] The title compound was synthesized in a manner similar to that described in Example 2. MS found for $C_{18}H_{26}N_6O_2$ as $(M+H)^+$ 359.3. UV: $\lambda = 287.8$.

Example 37. 5-((1R,2S)-2-aminocyclohexylamino)-3-(3-ethylisoxazol-5-ylamino)picolinamide.



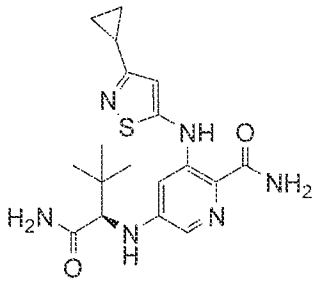
[0197] The title compound was synthesized in a manner similar to that described in Example 2. MS found for $C_{17}H_{24}N_6O_2$ as $(M+H)^+$ 345.3. UV: λ = 285.4 nm.

Example 38. (R)-5-(1-amino-1-oxobutan-2-ylamino)-3-(3-cyclopropylisothiazol-5-ylamino)picolinamide.



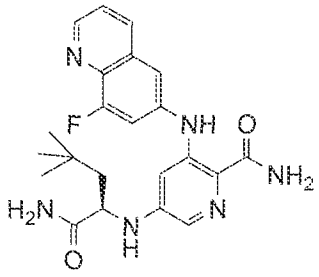
[0198] The title compound was synthesized in a manner similar to that described in Example 1. MS found for $C_{16}H_{20}N_6O_2S$ as $(M+H)^+$ 361.3. UV: λ =304.5 nm.

Example 39. (R)-5-(1-amino-3,3-dimethyl-1-oxobutan-2-ylamino)-3-(3-cyclopropylisothiazol-5-ylamino)picolinamide.



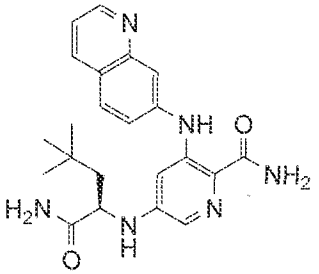
[0199] The title compound was synthesized in a manner similar to that described in Example 1. MS found for $C_{18}H_{24}N_6O_2S$ as $(M+H)^+$ 389.3. UV: λ =305.9 nm.

Example 40. (R)-5-(1-amino-4,4-dimethyl-1-oxopentan-2-ylamino)-3-(8-fluoroquinolin-6-ylamino)picolinamide.



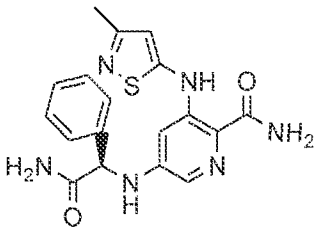
[0200] The title compound was synthesized in a manner similar to that described in Example 1. MS found for $C_{22}H_{25}FN_6O_2$ as $(M+H)^+$ 425.4. UV: λ = 219.4, 299.1 nm.

Example 41. (R)-5-(1-amino-4,4-dimethyl-1-oxopentan-2-ylamino)-3-(quinolin-7-ylamino)picolinamide.



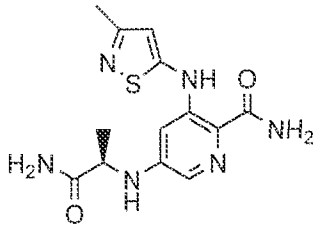
[0201] The title compound was synthesized in a manner similar to that described in Example 1. MS found for C22H26N6O2 as $(M+H)^+$ 407.4. UV: λ = 290.5.

Example 42. (R)-5-(2-amino-2-oxo-1-phenylethylamino)-3-(3-methylisothiazol-5-ylamino)picolinamide



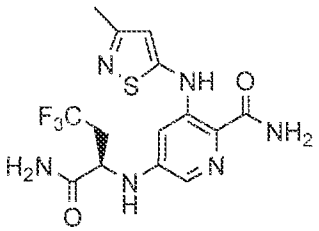
[0202] The title compound was synthesized in a manner similar to that described in Example 1. MS found for $C_{18}H_{18}N_6O_2S$ as $(M+H)^+$ MS 383.2; UV: λ = 201.7, 303.4 nm; t 0.527 min.

Example 43. (R)-5-(1-amino-1-oxopropan-2-ylamino)-3-(3-methylisothiazol-5-ylamino)picolinamide



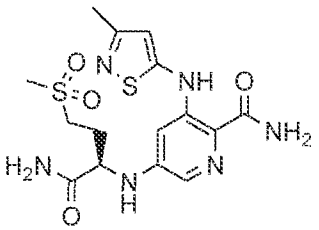
[0203] The title compound was synthesized in a manner similar to that described in Example 1. MS found for $C_{13}H_{16}N_6O_2S$ as $(M+H)^+$ MS 321.1; UV: λ = 200.0, 305.8 nm; t 0.412 min.

Example 44. (R)-5-(1-amino-4,4,4-trifluoro-1-oxobutan-2-ylamino)-3-(3-methylisothiazol-5-ylamino)picolinamide



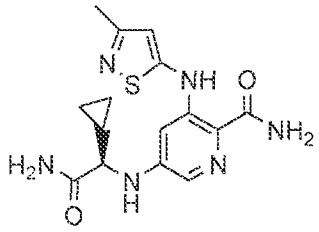
[0204] The title compound was synthesized in a manner similar to that described in Example 1. MS found for $C_{14}H_{15}F_3N_6O_2S$ as $(M+H)^+$ MS 389.2; UV: λ = 208.4, 308.9 nm; t 0.503 min.

Example 45. (R)-5-(1-amino-4-(methylsulfonyl)-1-oxobutan-2-ylamino)-3-(3-methylisothiazol-5-ylamino)picolinamide



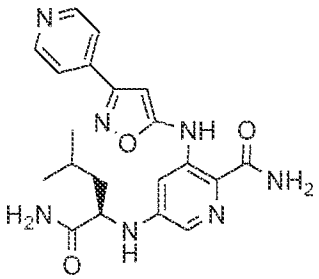
[0205] The title compound was synthesized in a manner similar to that described in Example 1. MS found for $C_{15}H_{20}N_6O_4S_2$ as $(M+H)^+$ MS 413.2; UV: λ = 200.5, 305.2 nm; t 0.388 min.

Example 46. (R)-5-(2-amino-1-cyclopropyl-2-oxoethylamino)-3-(3-methylisothiazol-5-ylamino)picolinamide



[0206] The title compound was synthesized in a manner similar to that described in Example 1. MS found for $C_{15}H_{18}N_6O_2S$ as $(M+H)^+$ MS 347.2. UV: λ =UV 201.1, 307.1 nm.

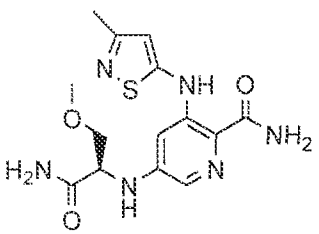
Example 47. (R)-5-(1-amino-4-methyl-1-oxopentan-2-ylamino)-3-(3-(pyridin-4-yl)isoxazol-5-ylamino)picolinamide



[0207] A solution of 3-oxo-3-(pyridin-4-yl)propanenitrile (298 mg, 2.04 mmol) and NH_2OH hydrochloride (146 mg, 2.10 mmol) in 1N NaOH (5 mL, 5.00 mmol) was stirred at 100 °C for 20 h. After cooling, solids precipitated out, which were collected by filtration, dried on vacuum to give 3-(pyridin-4-yl)isoxazol-5-amine (61 mg).

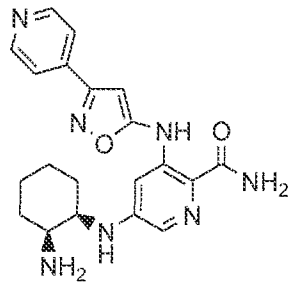
[0208] The title compound was synthesized in a manner similar to that described in Example 1, by using 3-(pyridin-4-yl)isoxazol-5-amine in the place of 3-methylisothiazol-5-amine. MS found for $C_{20}H_{23}N_7O_3$ as $(M+H)^+$ MS 410.3. UV: λ = 200.5, 280.6, 330.5 nm.

Example 48. (R)-5-(1-amino-3-methoxy-1-oxopropan-2-ylamino)-3-(3-methylisothiazol-5-ylamino)picolinamide



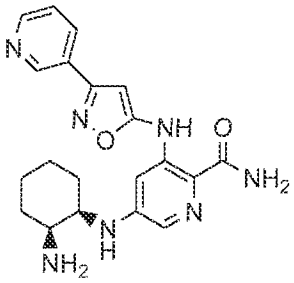
[0209] The title compound was synthesized in a manner similar to that described in Example 1. MS found for $C_{14}H_{18}N_6O_3S$ as $(M+H)^+$ MS 351.2. UV: $\lambda = 202.9, 303.2$ nm.

Example 49. 5-((1R,2S)-2-aminocyclohexylamino)-3-(3-(pyridin-4-yl)isoxazol-5-ylamino)picolinamide



[0210] The title compound was synthesized in a manner similar to that described in Example 4. MS found for $C_{20}H_{23}N_7O_2$ as $(M+H)^+$ MS 394.3. UV: $\lambda = 202.2, 278.0, 329.8$ nm.

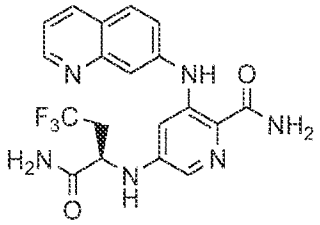
Example 50. 5-((1R,2S)-2-aminocyclohexylamino)-3-(3-(pyridin-3-yl)isoxazol-5-ylamino)picolinamide



[0211] A solution of 3-oxo-3-(pyridin-3-yl)propanenitrile (302 mg, 2.06 mmol) and NH_2OH hydrochloride (145 mg, 2.08 mmol) in 1N NaOH (4 mL, 4.00 mmol) was stirred at 100 °C for 20 h. After cooling, solids precipitated out, which were collected by filtration, dried on vacuum to give 3-(pyridin-3-yl)isoxazol-5-amine (149 mg).

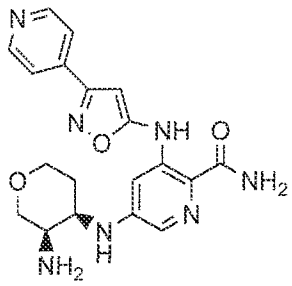
[0212] The title compound was synthesized in a manner similar to that described in Example 4, by using 3-(pyridin-3-yl)isoxazol-5-amine in the place of 3-methylisothiazol-5-amine. MS found for $C_{20}H_{23}N_7O_2$ as $(M+H)^+$ MS 394.4. UV: $\lambda = 204.7, 275.5$ nm.

Example 51. (R)-5-(1-amino-4,4,4-trifluoro-1-oxobutan-2-ylamino)-3-(quinolin-7-ylamino)picolinamide



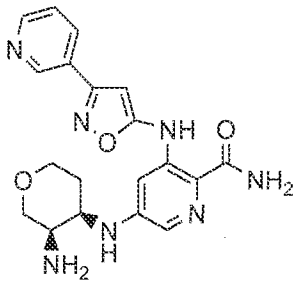
[0213] The title compound was synthesized in a manner similar to that described in Example 1. MS found for $C_{19}H_{17}F_3N_6O_2$ as $(M+H)^+$ MS 419.2. UV: λ = 289.8 nm.

Example 52. 5-((3R,4R)-3-aminotetrahydro-2H-pyran-4-ylamino)-3-(3-(pyridin-4-yl)isoxazol-5-ylamino)picolinamide



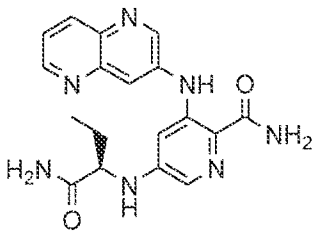
[0214] The title compound was synthesized in a manner similar to that described in Example 23. MS found for $C_{19}H_{21}N_7O_3$ as $(M+H)^+$ MS 396.3. UV: λ = 200.5, 279.3, 329.3 nm.

Example 53. 5-((3R,4R)-3-aminotetrahydro-2H-pyran-4-ylamino)-3-(3-(pyridin-3-yl)isoxazol-5-ylamino)picolinamide



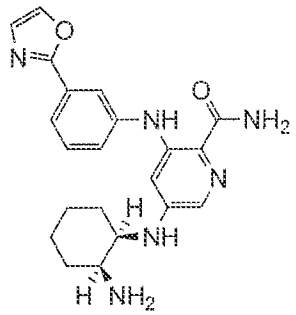
[0215] The title compound was synthesized in a manner similar to that described in Example 23. MS found for $C_{19}H_{21}N_7O_3$ as $(M+H)^+$ MS 396.2. UV: λ = 201.7, 273.2 nm.

Example 54. (R)-3-(1,5-naphthyridin-3-ylamino)-5-(1-amino-1-oxobutan-2-ylamino)picolinamide



[0216] The title compound was synthesized in a manner similar to that described in Example 1. MS found for $C_{18}H_{19}N_7O_2$ as $(M+H)^+$ MS 366.3. UV: λ = 205.6, 300.5 nm.

Example 55. 5-(((1R,2S)-2-aminocyclohexyl)amino)-3-((3-(oxazol-2-yl)phenyl)amino)picolinamide.



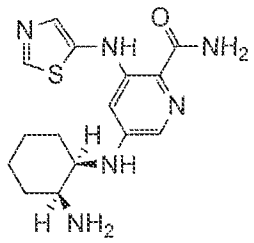
[0217] The mixture of 3-bromo-5-fluoropicolinonitrile (500 mg, 2.5 mmol), tert-butyl (1S,2R)-2-aminocyclohexylcarbamate (1.07 g, 5.0 mmol), DIEA (1.3 mL, 7.5 mmol) in 10 mL NMP are stirred at 100°C for 1 h. The mixture was cooled to RT, diluted with EtOAc, washed with brine three times, dried over $MgSO_4$, concentrated in vacuo, and subjected to flash column with 10-55% EtOAc in hexane to afford tert-butyl (1S,2R)-2-(5-bromo-6-cyanopyridin-3-ylamin o)cyclohexylcarbamate (1.12 g, 100%).

[0218] The mixture of tert-butyl (1S,2R)-2-(5-bromo-6-cyanopyridin-3-ylamino)cyclohexylcarbamate (116 mg, 0.29 mmol), 3-(oxazol-2-yl)aniline (47 mg, 0.29 mmol), XantPhos (35 mg, 0.06 mmol), $Pd_2(dba)_3$ (27 mg, 0.03 mmol), Cs_2CO_3 (200 mg, 0.60 mmol) in 15 mL dioxane was degassed with argon stream, stirred at 110°C in argon atmosphere for overnight and then cooled to RT. The mixture was diluted with EtOAc, filtered through celite, concentrated in vacuo, subjected to flash column with 0-66% EtOAc in hexane.

[0219] The isolated coupling product was treated with TFA at RT for 20 m and concentrated in vacuo to dryness. It was dissolved in 1 mL DMSO/ 10mL MeOH matrix. To it were added KOH

(100 mg) and then 1 mL 30% H_2O_2. The mixture was stirred at RT for 1 h. It was quenched with acetonitrile, acidified with TFA, concentrated in vacuo and subjected to reverse phase preparative HPLC to isolate the title compound (62 mg). MS found for $C_{21}H_{24}N_6O_2$ as $(M+H)^+$ 393.6. UV: $\lambda \approx 278$ nm. ^{1}H NMR: (CD_3OD) δ 8.02 (1H, t, J=0.8Hz), 7.96 (1H, t, J=2.0Hz), 7.75-7.72 (2H, m), 7.52 (1H, t, J=8.0Hz), 7.35-7.33 (2H, m), 7.10 (1H, d, J=2.0Hz), 3.89 (1H, m), 3.52 (1H, m), 1.83-1.51 (8H, m) ppm. UV: $\lambda = 278$ nm.

Example 56. 5-(((1R,2S)-2-aminocyclohexyl)amino)-3-(thiazol-5-ylamino)picolinamide.



[0220] The title compound was synthesized in a manner similar to that described in Example 5-(((1R,2S)-2-aminocyclohexyl)amino)-3-((3-(oxazol-2-yl)phenyl)amino)picolinamide with 5-thiazolamine. MS found for $C_{15}H_{20}N_6OS$ as $(M+H)^+$ 333.3. UV: $\lambda = 244, 292$ nm. ^{1}H NMR: (CD_3OD) δ 9.09 (1H, s), 7.91 (1H, s), 7.88 (1H, s), 6.60 (1H, s), 3.90 (1H, m), 3.38 (1H, m), 1.83-1.41 (8H, m) ppm.

[0221] The *in vitro* and *in vivo* human Syk activities of the inventive compounds can be determined by various procedures known in the art, such as a test for their ability to inhibit the activity of human plasma Syk. The potent affinities for human Syk inhibition exhibited by the inventive compounds can be measured by an IC_{50} value (in nM). The IC_{50} value is the concentration (in nM) of the compound required to provide 50% inhibition of human Syk proteolytic activity. The smaller the IC_{50} value, the more active (potent) is a compound for inhibiting Syk activity.

[0222] An *in vitro* assay for detecting and measuring inhibition activity against Syk is as follows:

Inhibition of Syk tyrosine phosphorylation activity

[0223] SYK tyrosine phosphorylation activity is measured using the LANCE™ Technology developed by Perkin Elmer Life and Analytical Sciences (Boston, MA). LANCE™ refers to

homogeneous time resolved fluorometry applications using techniques such as time-resolved fluorescence resonance energy transfer assay (TR-FRET) (see generally for procedures in Perkin Elmer Application Note- How to Optimize a Tyrosine Kinase Assay Using Time Resolved Fluorescence-Based LANCE Detection, wwww.perkinelmer.com/lifesciences). The assay principle involves detection of a phosphorylated substrate using energy transfer from a phosphospecific europium-labeled antibody to streptavidin-allophycocyanin as an acceptor.

[0224] Molecules are reconstituted in 30 % DMSO and serially diluted 1:3 with the final dilution containing DMSO in the absence of the candidate molecule. The final DMSO concentration in the assay is 3%. Kinase assays are performed as a two part reaction. The first reaction is a kinase reaction and which comprises of a candidate molecule, full length active recombinant SYK enzyme (Millipore, CA) and biotin-labeled SYK-specific substrate biotin-DEEDYESP-OH. The second reaction involves termination of the kinase reaction and the simultaneous addition of the detection reagents- europium-labeled anti-phosphotyrosine reagent (Eu-W1024-PY100, Perkin Elmer, Boston, MA) and Streptavidin-Allophycocyanin detection reagent (SA-APC, Prozyme, CA). The kinase reaction is performed in a black U-bottom 96-well microtitre plate. The final reaction volume is 50 µL and contains a final concentration of 1 nM active SYK enzyme, 550 nM SYK-substrate, and 100 µM ATP diluted in a buffer containing 50 mM Tris pH 7.5, 5 mM $MgCl_2$, and 1mM DTT. The reaction is allowed to proceed for 1 hour at room temperature. The quench buffer contains 100 mM Tris pH 7.5, 300 mM $NaCl_2$, 20 mM EDTA, 0.02% Brij35, and 0.5% BSA. The detection reagents are added to the reaction mixture at the following dilutions- 1:500 for Eu-W1024-PY100 and 1:250 for SA-APC. The kinase reaction is terminated by the addition of 50 µL quench buffer containing the detection reagents. The detection is allowed to proceed for 1 hr at room temperature. Detection of the phosphorlated substrate in the absence and presence of inhibitors is measured in the TR-FRET instrument, Analyst HT (Molecular Probes, Sunnyvale, CA) and the condition for measurements are set up using CriterionHost Release 2.0 (Molecular Probes, Sunnyvale, CA). The settings used are a follows: excitation 360 nm, emission 665 – 7.5 nm, beam splitter 350 nm 50/50, flash 100 pulses, delay 60 us, integration 400 us, *z*-height 2 mm. Inhibition of SYK-tyrosine kinase activity is calculated as the maximum response observed in the presence of inhibitor, compared to that in the absence of inhibitor. IC_{50}s were derived by non-linear regression analysis.

[0225] Intracellular phospho-flow cytometry can be used to test compound inhibition of Syk activity in the non-Hodgkin's lymphoma cell line Ramos. $1x10^6$ cells in log phase growth were aliqoted; Syk kinase is activated by incubating cells for 10 minutes with 3μg/ml antibody specific to the B cell receptor. Directly following, cells are fixed in 1% paraformaldehyde for 5 minutes at room temperature, washed in phosphate buffered saline, and then permeablized by incubation for 2 hours in ice cold methanol. Cells are again washed in phosphate buffered saline, then incubated for 30 minutes with antibody specific for phosphorylated Erk (Y204), which are indicators of Syk kinase activity. All antibodies used are purchased from BD Pharmingen (San Jose, CA). After incubation with antibodies, cells are again washed and subjected to flow cytometry.

[0226] Syk has been implicated experimentally in B cell development, proliferation, and survival. Moreover, Syk is implicated as an oncogene. Expression of constitutively active Syk in adoptively transferred bone marrow cells induces leukemia in mice, and over-activity of Syk is associated with a variety of lymphomas in humans Given the role of Syk in B cell biology, its selective inhibition may be sufficient to provide clinical benefit in B cell proliferative disorders, while reducing toxicities that may arise due to suppression of other off-target kinases.

[0227] The anti-proliferative effects of compounds on non-Hodgkin's lymphoma B cell lines SUDHL-4, SUDHL-6, and Toledo can also assessed. SUDHL-4 and SUDHL-6 require B cell receptor signaling for growth and survival, while the Toledo cell line (serving here as a negative control) does not. Cells are aliquoted into each well of a 96-well plate and incubated with increasing concentrations of compound for 72 hours, after which cell survival and proliferation is determined using the MTT assay (Chemicon International, Inc., Temecula, CA) following protocols supplied by the manufacturer.

[0228] Induction of apoptosis in non-Hodgkin's lymphoma B cell lines SUDHL-4, SUDHL-6, and Toledo is assessed by measuring the apoptotis marker Caspase 3. Cells were incubated with 1, 3, or 10μM compound for 24, 48, and 72 hours. At the conclusion of each time point, cells are processed for flow cytometry analysis using the Monoclonal Rabbit Anti-Active Caspase-3 Antibody Kit and related protocols (BD Pharmingen).

[0229] Syk activity is not only required for B cell signaling, proliferation, and survival, as shown, but is also critical for cellular activation upon cross-linking of the B cell receptor. B cell

activation leads to increased cell surface expression of several proteins involved in cell signaling, antigen presentation, and adhesion. Among these, CD80, CD86, and CD69 are commonly measured to determine B cell activation status. Primary mouse B cells isolated from spleen can be aliquoted and incubated with increasing concentrations of compound (0.05 to 2μM) in the presence of goat anti-mouse IgD (eBiosciences, Inc., San Diego, CA) for 20 hours to cross-link the B cell receptor. Cells are washed and incubated for 30 minutes on ice with antibodies specific for the CD80, CD86, and CD69 B cell activation markers. B cells are identified from the pooled population by staining with the B cell marker CD45RO. All antibodies are purchased from BD Pharmingen.

[0230] In the table below, activity in the Syk assays is provided as follows: +++++ = IC_{50} < 0.0010 μM; ++++ = 0.0010 μM < IC_{50} < 0.010 μM, +++ = 0.010 μM < IC_{50} < 0.10 μM, ++ = 0.10 μM < IC_{50} < 1 μM, + = IC_{50} > 1 μM.

Table 1

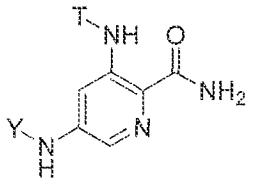
Example No.	Syk IC50
1	++++
2	+++
3	++++
4	++++
5	+++
6	+++
7	+++
8	++++
9	++
10	+++
11	++++
12	+++
13	++
14	+++
15	+++
16	+++
17	+++
18	+++

Example No.	Syk IC50
23	++++
24	++
25	++
26	+++
27	+++
28	++
29	+++
30	+++
31	++
32	++++
33	+++
34	++++
35	+++
36	+++
37	+++
38	++++
39	+++
40	+++
41	++++
42	+++
43	+++
44	+++++
45	+++
47	++++
48	+++
49	++++
50	+++
51	++++
52	+++
53	+++
54	++
55	+++
56	+

[0231] All patents, patent applications, publications and presentations referred to herein are incorporated by reference in their entirety. Any conflict between any reference cited herein and the teaching of this specification is to be resolved in favor of the latter. Similarly, any conflict between an art-recognized definition of a word or phrase and a definition of the word or phrase as provided in this specification is to be resolved in favor of the latter.

WHAT IS CLAIMED IS:

1. A compound of Formula (I):



(I)

or a tautomer or a pharmaceutically acceptable salt thereof, wherein

T is $(CH_2)_d(X^1)$ where X^1 is selected from the group consisting of aryl and monocyclic or bicyclic heteroaryl comprising 1-4 heteroatoms selected from S, O and N, wherein aryl and heteroaryl are optionally substituted with 1 to 5 R^1 and d is 0 or 1;

each R^1 is independently selected from the group consisting of halo, C_{1-8}alkyl, C_{2-8}alkenyl, haloC_{1-8}alkyl, $(CH_2)_nSR^{1a}$, $(CH_2)_nOR^{1a}$, $O(CH_2)_jOR^{1a}$, $(CH_2)_nNR^{1b}R^{1c}$, $(CH_2)_nCOR^{1e}$, $(CH_2)_nCONR^{1b}R^{1c}$, $(CH_2)_nNR^{1b}COR^{1e}$, $(CH_2)_nCONR^{1b}(OR^{1a})$, $(CH_2)_nCO_2R^{1a}$, $O(CH_2)_nCO_2R^{1a}$, $(CH_2)_nNR^{1b}CO_2R^{1a}$, $(CH)_nSO_2NR^{1b}R^{1c}$, $(CH_2)_nNR^{1b}SO_2R^{1e}$, $(CH_2)_nSOR^{1e}$, $(CH_2)_nSO_2R^{1e}$, oxo, $(CH_2)_nCN$, N_3, NO_2, and –L-W, where n is 0, 1, 2, 3, 4, 5, or 6 and j is 1, 2, 3, 4, 5, or 6;

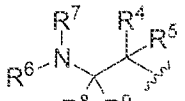
L is selected from the group consisting of $-O(CH_2)_b-$, -SO-, $-SO_2-$, -CO-, $-NR^{1d}-$, $-CONR^{1d}(CH_2)_b-$, $-NR^{1d}CO-$, $-NR^{1d}SO_2-$, $-SO_2NR^{1d}-$, a bond, and $-(CH_2)_z-$ where b is 0, 1, 2, 3, 4, or 5 and z is 1, 2, 3, 4, or 5;

W is selected from the group consisting of aryl, monocyclic or bicyclic heteroaryl comprising 1-4 heteroatoms selected from S, O and N, C_{3-8}cycloalkyl, and 3-8 membered heterocyclyl comprising 1-4 heteroatoms selected from S, O and N, each optionally substituted with 1 to 3 R^2;

each R^2 is independently selected from the group consisting of halo, C_{1-8}alkyl, C_{2-8}alkenyl, haloC_{1-8}alkyl, $(CH_2)_mSR^{2a}$, $(CH_2)_mOR^{2a}$, $O(CH_2)_kOR^{2a}$, $(CH_2)_mNR^{2b}R^{2c}$, $(CH_2)_mCOR^{2e}$, $(CH_2)_mCONR^{2b}R^{2c}$, $(CH_2)_mNR^{2b}COR^{2e}$, $(CH_2)_mCONR^{2b}(OR^{2a})$, $(CH_2)_mCO_2R^{2a}$, $O(CH_2)_mCO_2R^{2a}$, $(CH_2)_mNR^{2b}CO_2R^{2a}$, $(CH)_mSO_2NR^{2b}R^{2c}$, $(CH_2)_mNR^{2b}SO_2R^{2e}$, $(CH_2)_mSOR^{2e}$, $(CH_2)_mSO_2R^{2e}$, oxo, $(CH_2)_mCN$, N_3, and NO_2, where m is 0, 1, 2, 3, 4, 5, or 6 and k is 1, 2, 3, 4, 5, or 6;

R^{1a}, R^{1b}, R^{1c}, R^{1d}, R^{2a}, R^{2b}, and R^{2c} are independently selected from the group consisting of H, C_{1-8}alkyl, C_{2-8}alkenyl, and haloC_{1-8}alkyl;

R^{1e} and R^{2e} are independently selected from the group consisting of C_{1-8}alkyl, C_{2-8}alkenyl, and haloC_{1-8}alkyl;

Y is  or $(CH_2)_v(X^2)$, wherein

v is 0, 1, 2, or 3;

X^2 is selected from the group consisting of CH_2CH_3, $(CH_2)_3NH_2$, C_{3-8}cycloalkyl, 3-8 membered heterocyclyl comprising 1-4 heteroatoms selected from S, O and N, aryl, and monocyclic or bicyclic heteroaryl comprising 1-4 heteroatoms selected from S, O and N, wherein cycloalkyl, heterocyclyl, aryl, and heteroaryl are each optionally substituted with 1 to 3 R^{10};

R^4 is selected from the group consisting of H, halo, C_{1-8}alkyl, C_{2-8}alkenyl, haloC_{1-8}alkyl, $(CH_2)_pSR^{4a}$, $(CH_2)_pSOR^{4a}$, $(CH_2)_pSO_2R^{4a}$, $(CH_2)_pOR^{4a}$, $(CH_2)_pNR^{4b}R^{4c}$, $(CH_2)_fCONR^{4b}R^{4c}$, $(CH_2)_pNR^{4b}COR^{4d}$, $(CH_2)_fCO_2R^{4a}$, $(CH_2)_pNR^{4b}CO_2R^{4a}$, $(CH_2)_f$ C_{3-8}cycloalkyl, $(CH_2)_p(O)$ C_{3-8}cycloalkyl, $(CH_2)_p(S)$ C_{3-8}cycloalkyl, $(CH)_pSO_2NR^{4b}R^{4c}$, $(CH_2)_pNH$ C_{3-8}cycloalkyl, $(CH_2)_fCN$, $(CH_2)_f$(aryl), $(CH_2)_f$(monocyclic or bicyclic heteroaryl comprising 1-4 heteroatoms selected from S, O and N), $(CH_2)_f$(aryl)(monocyclic or bicyclic heteroaryl comprising 1-4 heteroatoms selected from S, O and N), $(CH_2)_f$(3-8 membered heterocyclyl comprising 1-4 heteroatoms selected from S, O and N), $(CH_2)_p(O)(CH_2)_f$(aryl), $(CH_2)_p(O)(CH_2)_f$(monocyclic or bicyclic heteroaryl comprising 1-4 heteroatoms selected from S, O and N), $(CH_2)_p(O)(CH_2)_fC_{3-8}$cycloalkyl, and $(CH_2)_p(O)(CH_2)_f$(3-8 membered heterocyclyl comprising 1-4 heteroatoms selected from S, O and N), where aryl, heteroaryl, cycloalkyl, and heterocyclyl are each optionally substituted with 1 to 3 R^{11a}, f is 0, 1, 2, 3, 4, 5, or 6, and p is 1, 2, 3, 4, 5, or 6; or R^4 and R^5 together form =O or a 3 to 8 membered carbocyclic or heterocyclic ring optionally substituted with 1 to 3 R^{11a};

R^5 is selected from the group consisting of H and C_{1-8}alkyl;

R^6 is selected from the group consisting of H, C_{1-8}alkyl, OH, O(C_{1-8}alkyl), CO_2R^{6a}, $CO(NR^{6a}R^{6b})$, and C_{3-8}cycloalkyl; or R^6 together with R^7 and the atoms to which they are attached to form a heterocyclyl ring optionally substituted with 1 to 3 R^{11b};

R^7 is selected from the group consisting of H, C_{1-8}alkyl, and cycloalkyl;

R^8 is selected from the group consisting of H, C_{1-8}alkyl, $(CH_2)_uNR^{8b}R^{8c}$, $(CH_2)_gCONR^{8b}R^{8c}$, $(CH_2)_gCO(CH_2)_uNR^{8b}R^{8c}$, $(CH_2)_gCO_2R^{8a}$, $(CH_2)_uOR^{8a}$, $CH(C_{1-8}alkyl)OR^{8a}$, $(CH_2)_g$ C_{3-8}cycloalkyl, (CH_2) 3-8 membered heterocyclyl comprising 1-4 heteroatoms selected from S, O and N, $(CH_2)_g$aryl, (CH_2) monocyclic or bicyclic heteroaryl comprising 1-4 heteroatoms selected from S, O and N, and $(CH_2)_u(O)$(aryl), where aryl, cycloalkyl, heteroaryl, and heterocyclyl are each optionally substituted with 1 to 3 R^{11c}, g is 0, 1, 2, 3, 4, 5, or 6 and u is 1, 2, 3, 4, 5, or 6; or R^8 together with R^9 and the atoms to which they are attached to form =O, =S, or a cycloalkyl or heterocyclyl ring optionally substituted with R^{11c};

R^9 is H or alkyl;

R^{10} is independently selected from the group consisting of halo, C_{1-8}alkyl, C_{2-8}alkenyl, haloC_{1-8}alkyl, $(CH_2)_qSR^{10a}$, $(CH_2)_qOR^{10a}$, $(CH_2)_qNR^{10b}R^{10c}$, $(CH_2)_qCOR^{10d}$, $(CH_2)_qCONR^{10b}R^{10c}$, $(CH_2)_qNR^{10b}COR^{10d}$, $(CH_2)_qCONR^{10b}(OR^{10a})$, $(CH_2)_qCO_2R^{10a}$, $O(CH_2)_qCO_2R^{10a}$, $(CH_2)_qNR^{10b}CO_2R^{10a}$, $(CH)_qSO_2NR^{10b}R^{10c}$, $(CH_2)_qNR^{10b}SO_2R^{10d}$, $(CH_2)_qSOR^{10d}$, $(CH_2)_qSO_2R^{10d}$, oxo, $(CH_2)_qCN$, N_3, $N=CH_2$, NO_2, C(O)3-8 membered heterocyclyl comprising 1-4 heteroatoms selected from S, O and N, aryl, monocyclic or bicyclic heteroaryl comprising 1-4 heteroatoms selected from S, O and N, C_{3-8}cycloalkyl, and 3-8 membered heterocyclyl comprising 1-4 heteroatoms selected from S, O and N, where aryl, cycloalkyl, heteroaryl, and heterocyclyl are each optionally substituted with 1 to 3 R^{11d} and q is 0, 1, 2, 3, 4, 5, or 6;

R^{11a}, R^{11b}, R^{11c}, and R^{11d} are independently selected from the group consisting of halo, C_{1-8}alkyl, haloC_{1-8}alkyl, OH, C_{1-8}alkoxy, haloC_{1-8}alkoxy, $C(O)C_{1-8}$alkyl, CO_2C_{1-8}alkyl, and SO_2C_{1-8}alkyl;

R^{4a}, R^{4b}, R^{4c}, R^{6a}, R^{6b}, R^{8a}, R^{8b}, R^{8c}, R^{10a}, R^{10b}, and R^{10c} are independently selected from the group consisting of H, C_{1-8}alkyl, C_{2-8}alkenyl, and haloC_{1-8}alkyl;

R^{4d} and R^{10d} are independently selected from the group consisting of C_{1-8}alkyl, C_{2-8}alkenyl, and haloC_{1-8}alkyl; and

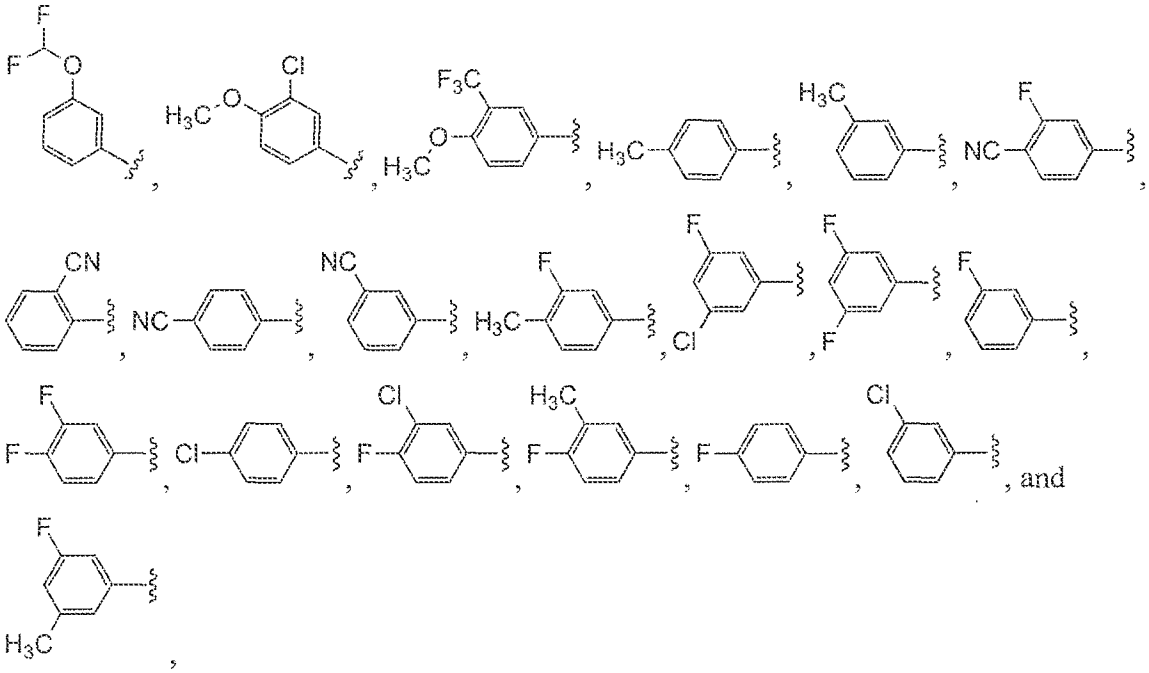
the wavy line indicates the point of attachment to the rest of the molecule;

provided that when Y is 2-aminocyclohexyl or dimethylaminoethyl and T is phenyl or naphthalene then, T is substituted with at least one R^1 selected from the group consisting of C_{2-8}alkenyl, $O(CH_2)_jOR^{1a}$, $(CH_2)_nCONR^{1b}R^{1c}$, $(CH_2)_nNR^{1b}COR^{1e}$, $(CH_2)_nCONR^{1b}(OR^{1a})$,

$(CH_2)_nCO_2R^{1a}$, $O(CH_2)_nCO_2R^{1a}$, $(CH_2)_nNR^{1b}CO_2R^{1a}$, $(CH)_nSO_2NR^{1b}R^{1c}$, $(CH_2)_nNR^{1b}SO_2R^{1c}$, $(CH_2)_nSOR^{1e}$, $(CH_2)_nSO_2R^{1e}$, N_3, and –L-W where L is selected from the group consisting of -SO-, $-SO_2-$, -CO-, $-NR^{1d}-$, $-CONR^{1d}(CH_2)_b-$, $-NR^{1d}CO-$, $-NR^{1d}SO_2-$, $-SO_2NR^{1d}-$, a bond, and $-(CH_2)_z-$.

2. A compound of claim 1 or a tautomer or a pharmaceutically acceptable salt thereof, wherein T is phenyl substituted with 1 to 5 R^1.

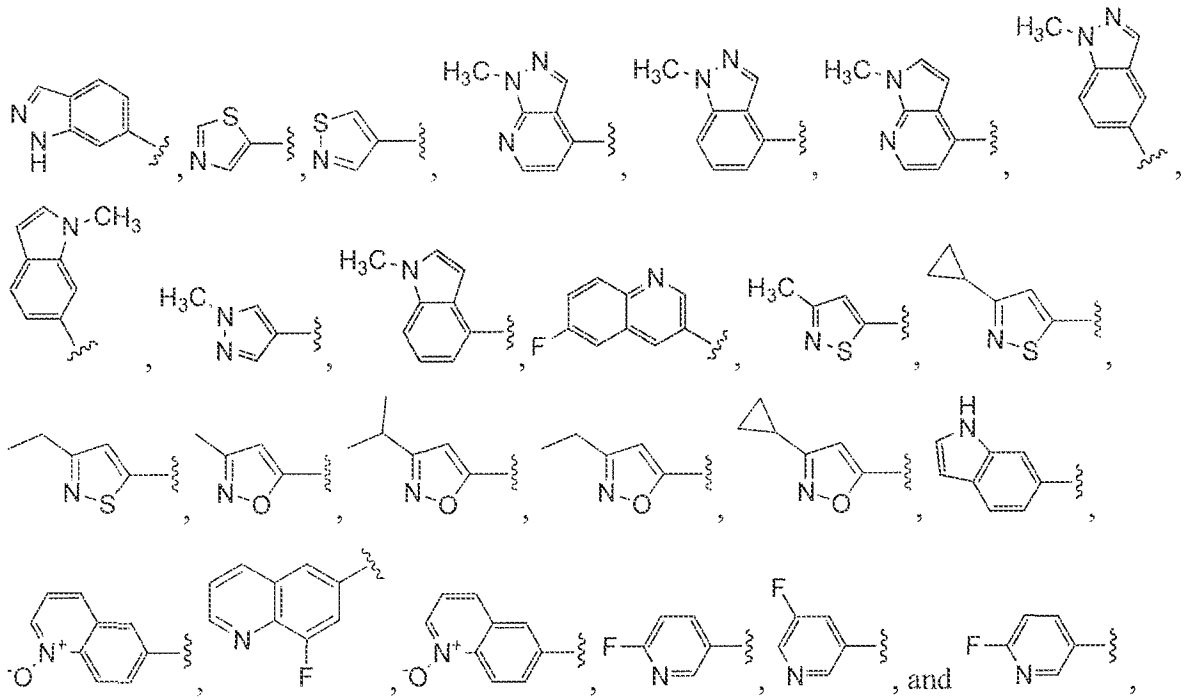
3. A compound of claim 1 or a tautomer or a pharmaceutically acceptable salt thereof, wherein T is selected from the group consisting of



where the wavy line indicates the point of attachment to the rest of the molecule.

4. A compound of claim 1 or a tautomer or a pharmaceutically acceptable salt thereof, wherein T is monocyclic or bicyclic heteroaryl comprising 1-4 heteroatoms selected from S, O and N, optionally substituted with 1 to 5 R^1.

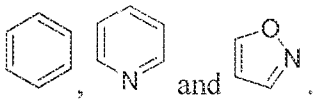
5. A compound of claim 1 or a tautomer or a pharmaceutically acceptable salt thereof, wherein T is selected from the group consisting of



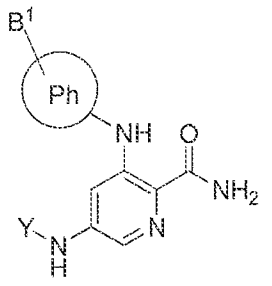
where the wavy line indicates the point of attachment to the rest of the molecule.

6. A compound of any of the preceding claims or a tautomer or a pharmaceutically acceptable salt thereof, wherein at least one R^1 is –L-W.

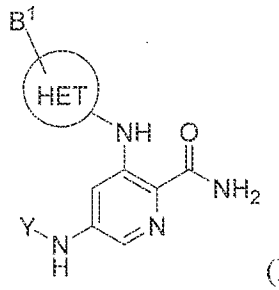
7. A compound of claim 6 or a tautomer or a pharmaceutically acceptable salt thereof, wherein -L-W is –CO-NR^aR^b where R^a and R^b together form a four to six membered ring optionally substituted with 1 to 3 groups independently selected from halo, C_{1-8}alkyl, and haloC_{1-8}alkyl or L is a bond and W is selected from the group consisting of



8. A compound of claim 1 of Formula (Ia) or (Ib) or a tautomer or a pharmaceutically acceptable salt thereof



(Ia)



(Ib)

wherein

Ph is phenyl optionally substituted with 1 to 3 R^1;

HET is monocyclic or bicyclic heteroaryl comprising 1-4 heteroatoms selected from S, O and N, optionally substituted with 1 to 3 R^1; and

B^1 is selected from the group consisting of $CO\text{-}NR^aR^b$, phenyl, monocyclic or bicyclic heteroaryl comprising 1-4 heteroatoms selected from S, O and N, and 3-8 membered heterocyclyl comprising 1-4 heteroatoms selected from S, O and N, wherein phenyl, heteroaryl, and heterocyclyl are each optionally substituted with 1 to 3 R^2, and R^a and R^b together form a four to six membered heterocyclic ring optionally substituted with one to three groups independently selected from halo, $C_{1\text{-}8}$alkyl, and halo$C_{1\text{-}8}$alkyl.

9. A compound of claim 8 or a tautomer or a pharmaceutically acceptable salt thereof wherein

B^1 in Formula (Ia) is monocyclic or bicyclic heteroaryl comprising 1-4 heteroatoms selected from S, O and N or 3-8 membered heterocyclyl comprising 1-4 heteroatoms selected from S, O and N, each optionally substituted with 1 to 3 R^2,

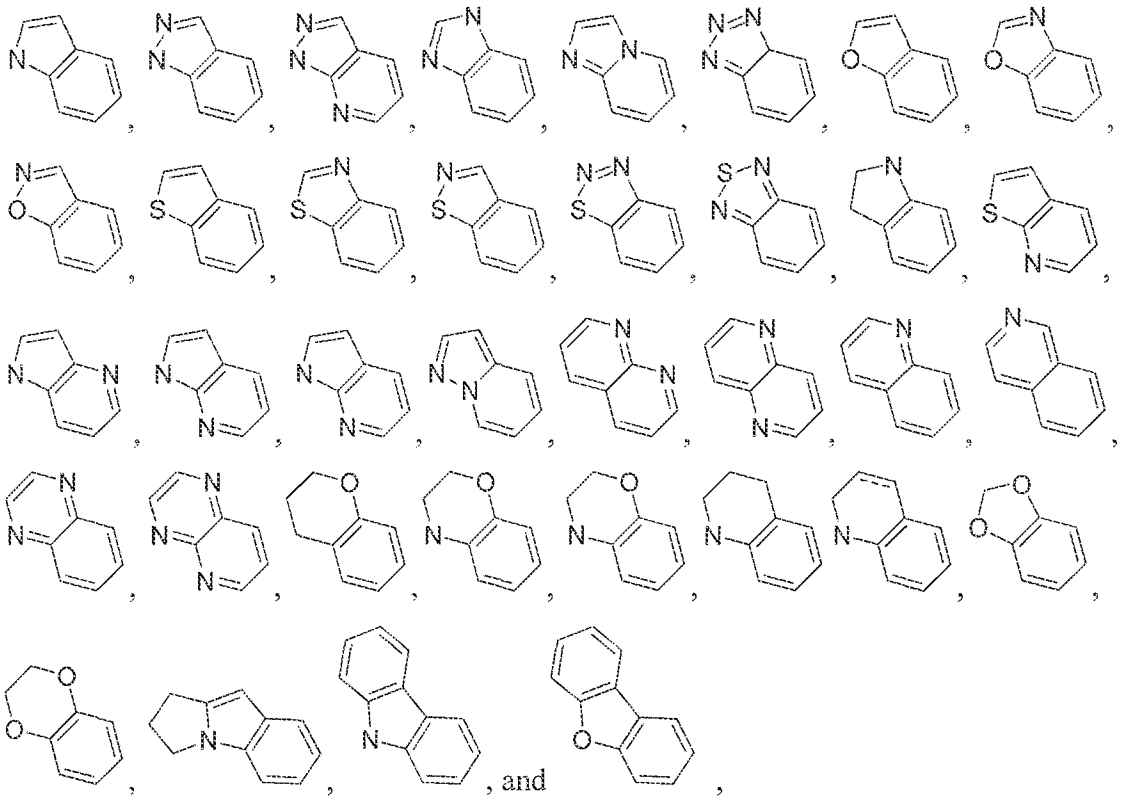
and

B^1 in Formula (Ib) is phenyl or 3-8 membered heterocyclyl comprising 1-4 heteroatoms selected from S, O and N, each optionally substituted with 1 to 3 R^2.

10. A compound of claim 1 or 8 or a tautomer or a pharmaceutically acceptable salt thereof, wherein W or B^1 is substituted with 1 to 3 R^2.

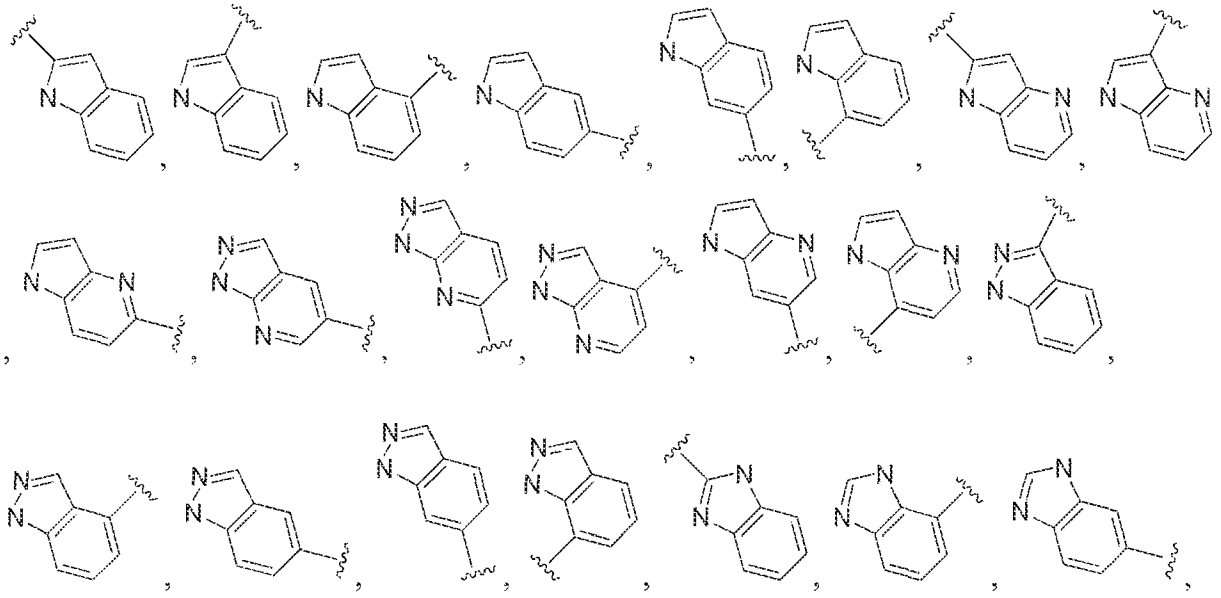
11. A compound of claims 8 to 10 or a tautomer or a pharmaceutically acceptable salt thereof wherein R^1 and R^2 are independently selected from the group consisting of halo, $C_{1\text{-}8}$alkyl, halo$C_{1\text{-}8}$alkyl, cyano, oxo, OH, O($C_{1\text{-}8}$alkyl), and O(halo$C_{1\text{-}8}$alkyl).

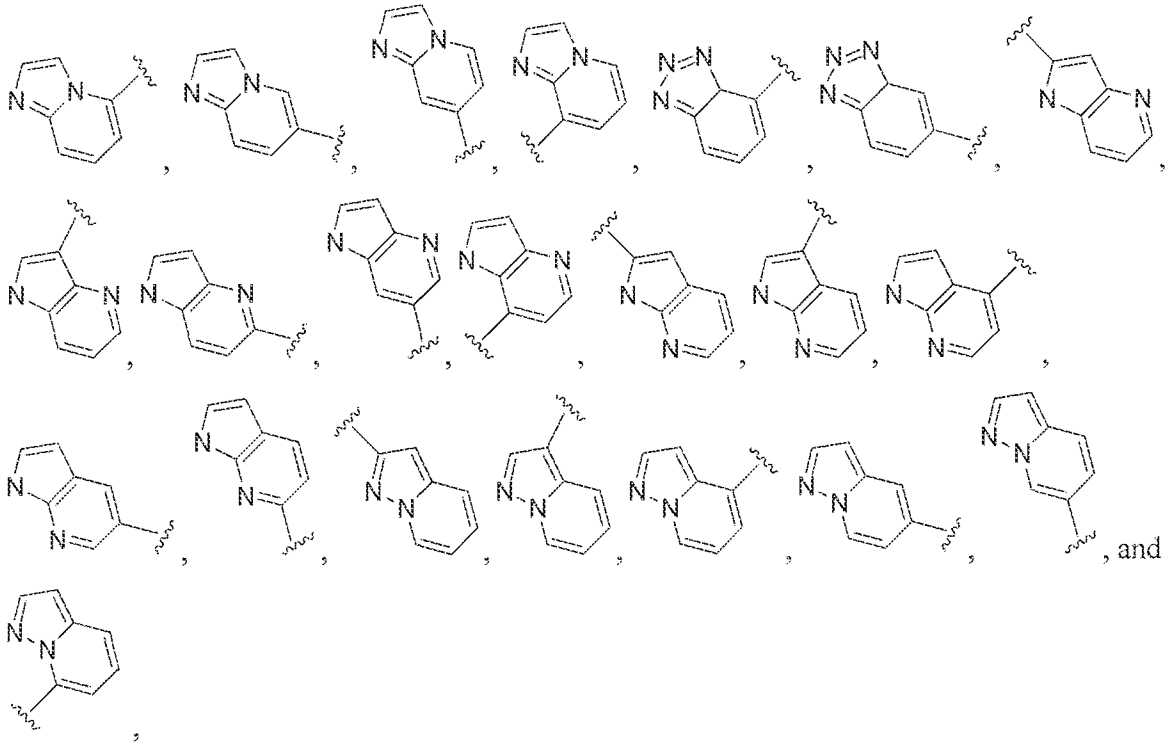
12. A compound of claims 4 to 11 or a tautomer or a pharmaceutically acceptable salt thereof, wherein X^1 or HET is selected from the group consisting of



where the point of attachment to the rest of the molecule is at a carbon ring atom.

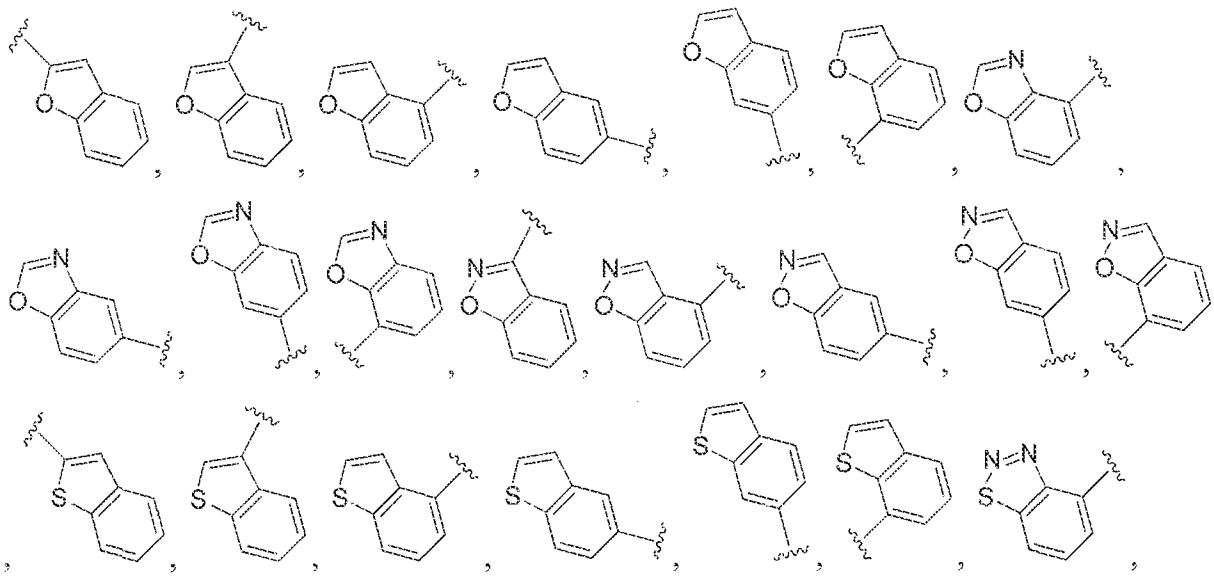
13. A compound of claim 12 wherein X^1 or HET is selected from the group consisting of

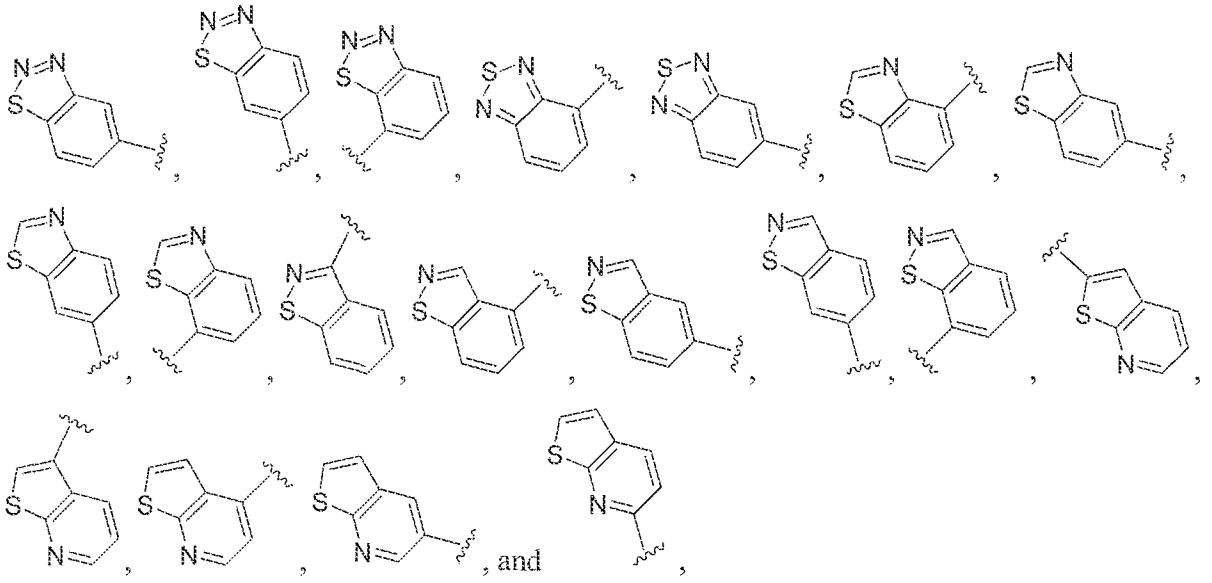




where the wavy line indicates the point of attachment to the rest of the molecule.

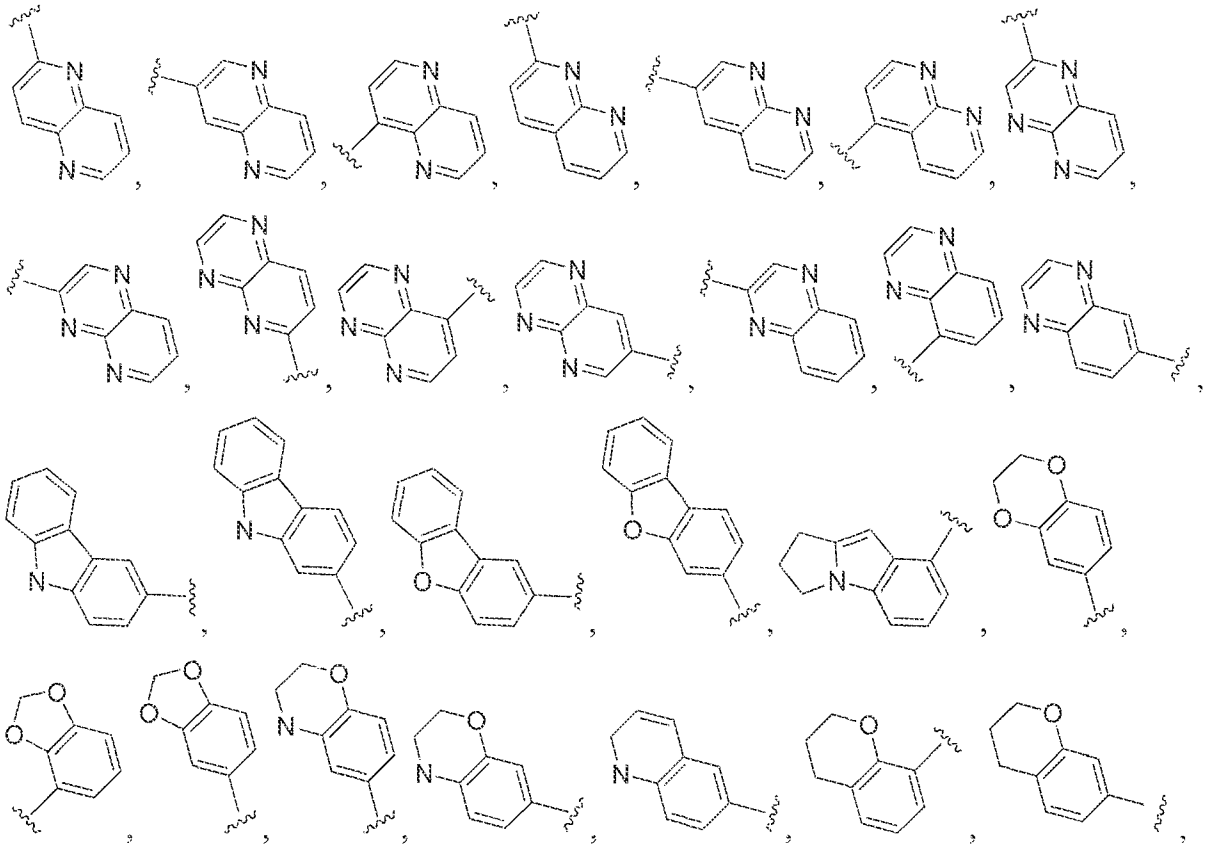
14. A compound of claim 12 wherein X^1 or HET is selected from the group consisting of

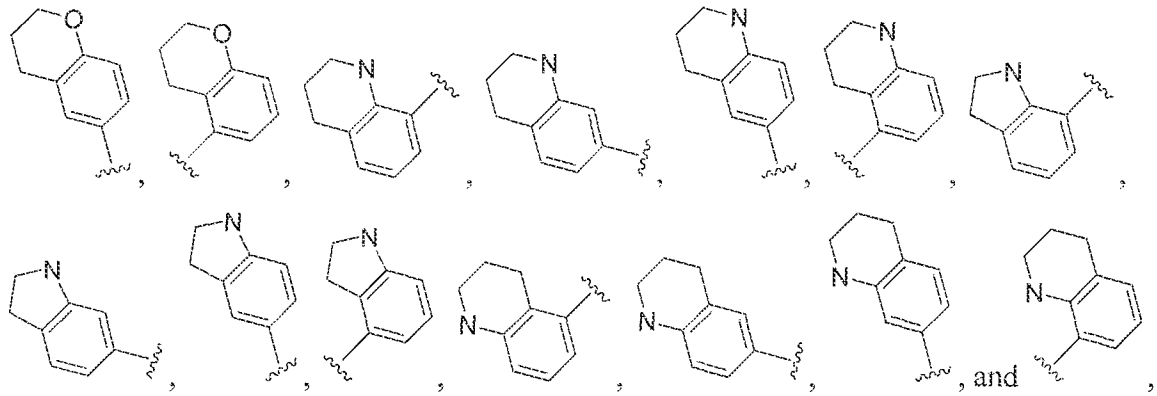




where the wavy line indicates the point of attachment to the rest of the molecule.

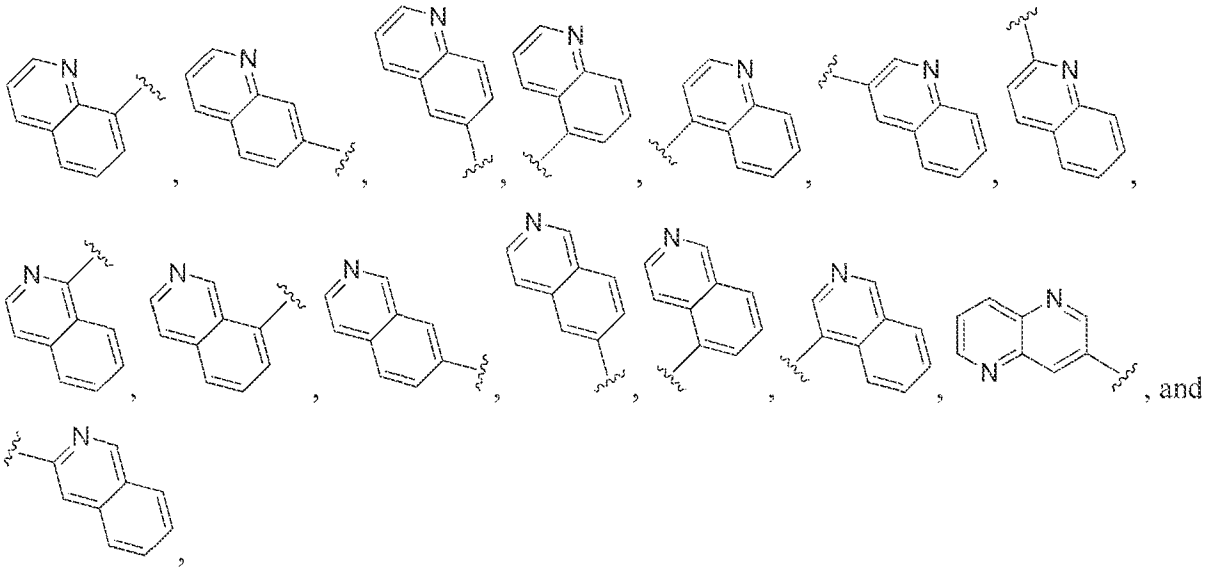
15. A compound of claim 12 wherein X^1 or HET is selected from the group consisting of





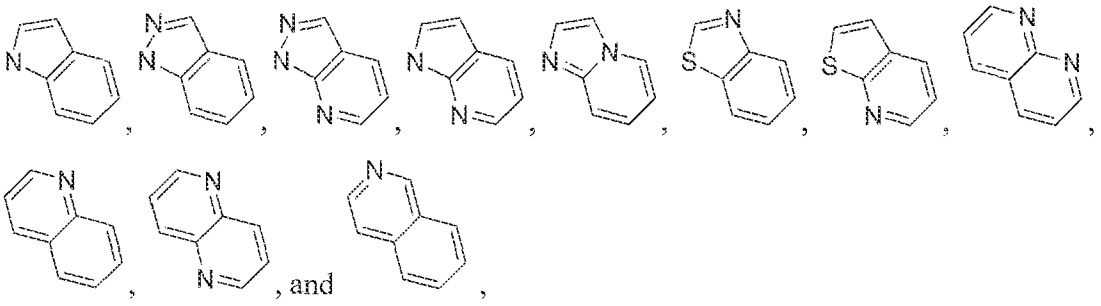
where the wavy line indicates the point of attachment to the rest of the molecule.

16. A compound of claim 12 wherein X^1 or HET is selected from the group consisting of



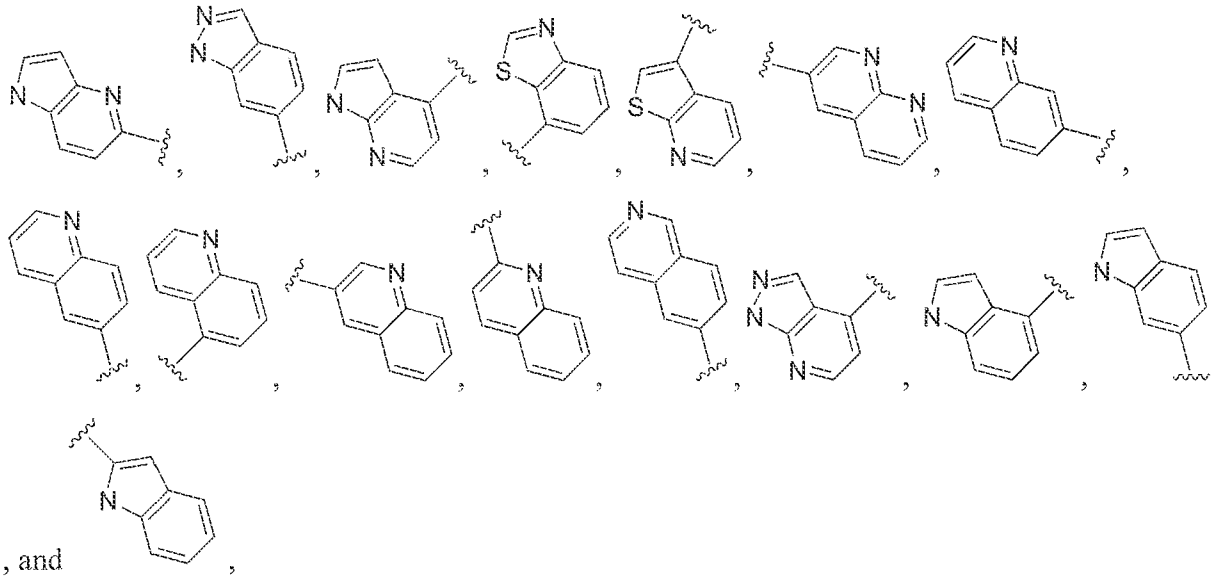
where the wavy line indicates the point of attachment to the rest of the molecule.

17. A compound of claim 12 or a tautomer or a pharmaceutically acceptable salt thereof, wherein X^1 or HET is selected from the group consisting of



where the point of attachment to the rest of the molecule is at a carbon ring atom.

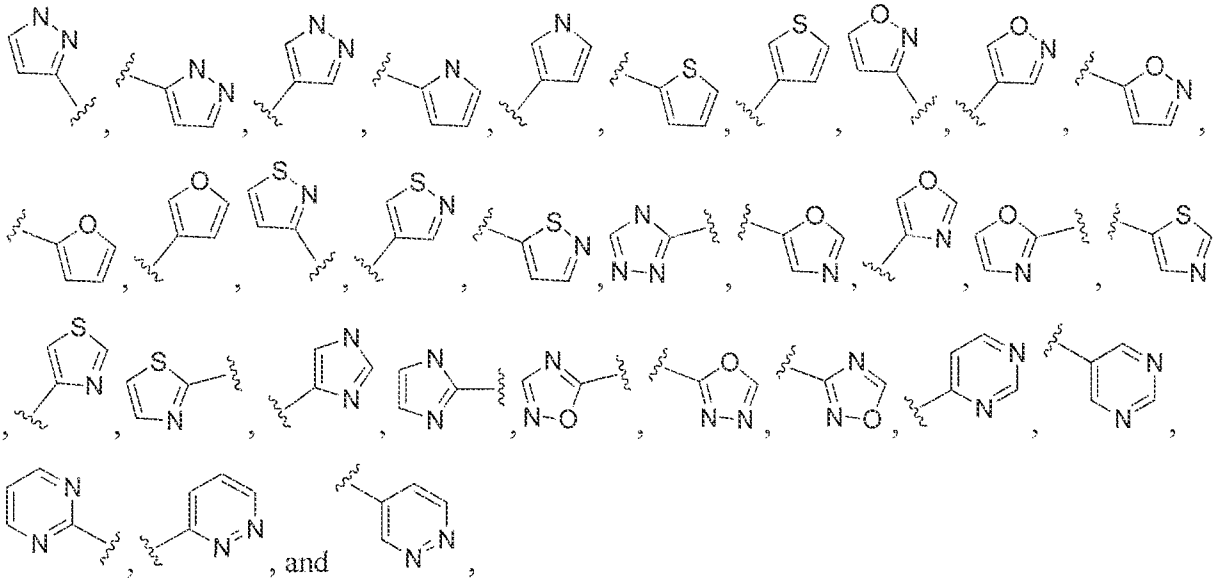
18. A compound of claim 17 wherein X^1 or HET is selected from the group consisting of



, and ,

where the wavy line indicates the point of attachment to the rest of the molecule.

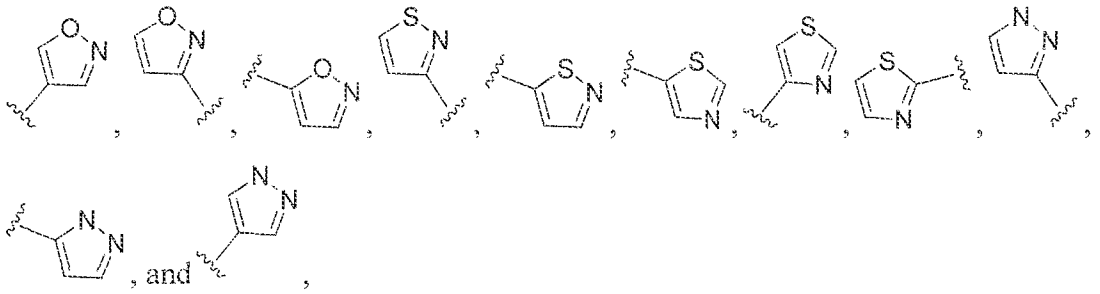
19. A compound of any one of claims 4 to 11 or a tautomer or a pharmaceutically acceptable salt thereof, wherein X^1 or HET is selected from the group consisting of



, and ,

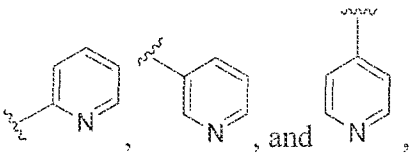
where the wavy line indicates the point of attachment to the rest of the molecule.

20. A compound of claim 19 or a tautomer or a pharmaceutically acceptable salt thereof, wherein X^1 or HET is selected from the group consisting of



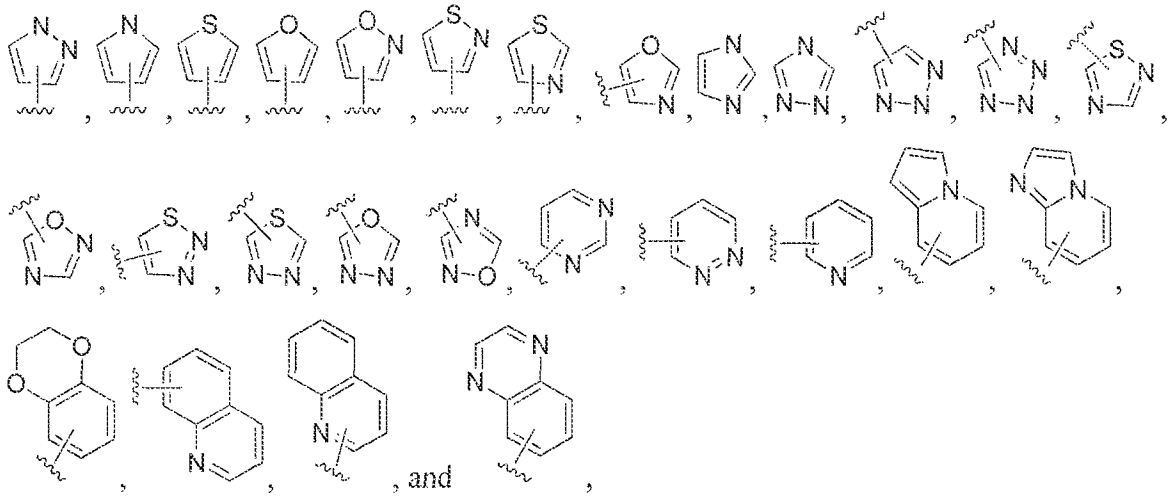
where the wavy line indicates with point of attachment to the rest of the molecule.

21. A compound of any one of claims 4 to 11 or a tautomer or a pharmaceutically acceptable salt thereof, wherein X^1 or HET is selected from the group consisting of



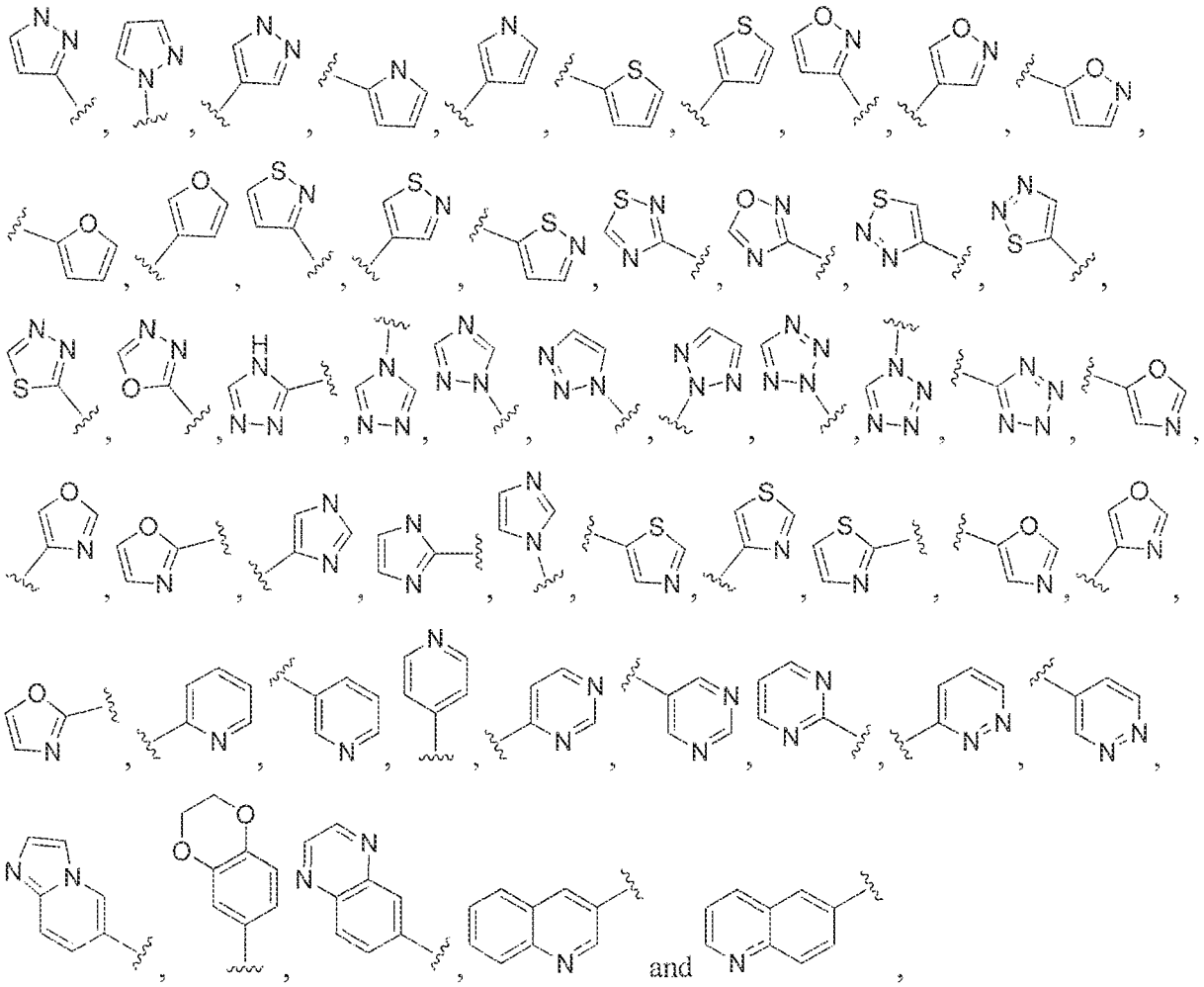
where the wavy line indicates the point of attachment to the rest of the molecule.

22. A compound of any one of the preceding claims one a tautomer or a pharmaceutically acceptable salt thereof, wherein W or B^1 is selected from the group consisting of



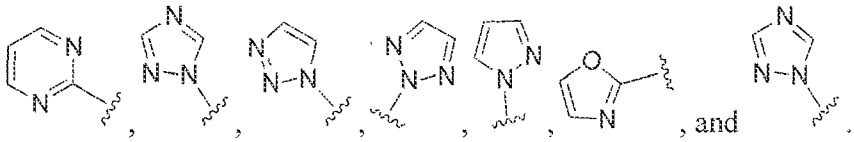
where the wavy line indicates the point of attachment to the rest of the molecule.

23. A compound of claim 22 or a tautomer or a pharmaceutically acceptable salt thereof, wherein W or B^1 is selected from the group consisting of

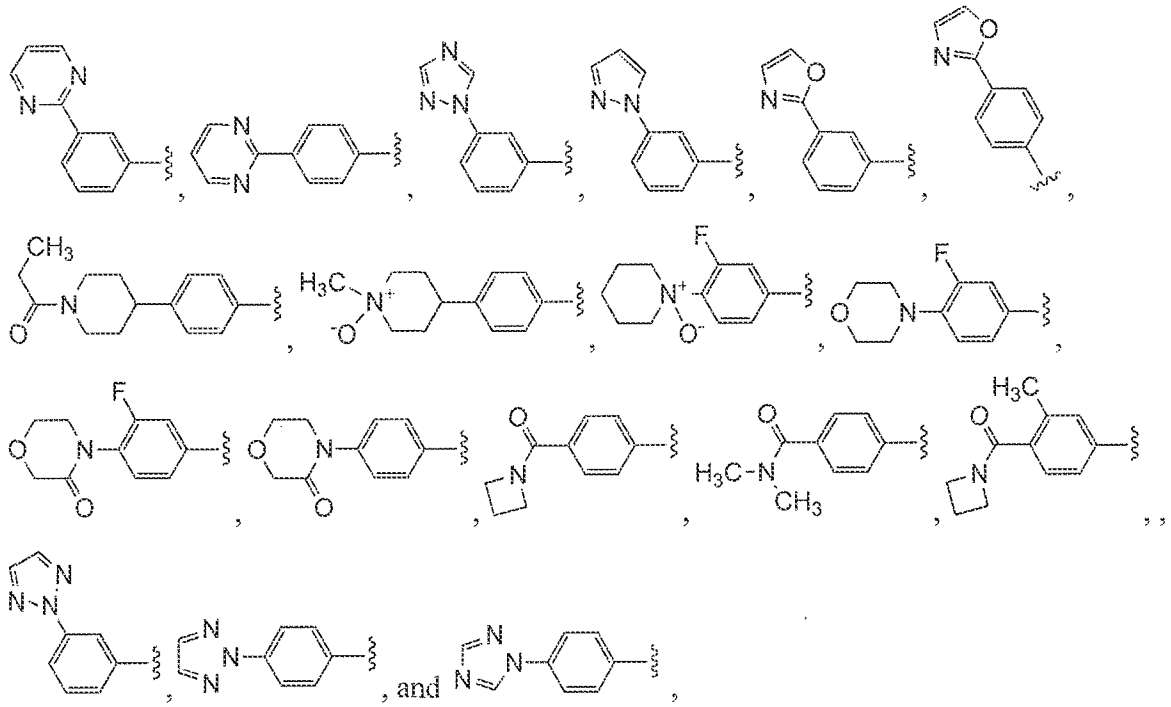


where the wavy line indicates the point of attachment to the rest of the molecule.

24. A compound of claim 23 or a tautomer or a pharmaceutically acceptable salt thereof, wherein W or B^1 is selected from the group consisting of

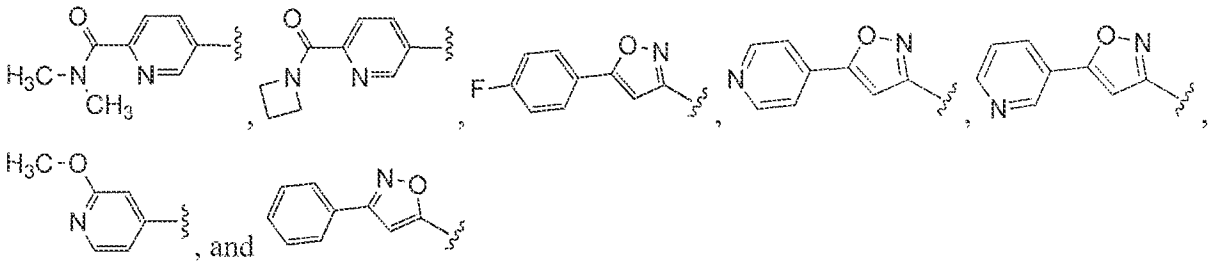


25. A compound of any one of the preceding claims or a tautomer or a pharmaceutically acceptable salt thereof, wherein B^1-Ph- is selected from the group consisting of



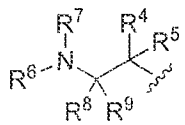
where the wavy line indicates the point of attachment to the rest of the molecule.

26. A compound of any one of the preceding claims or a tautomer or a pharmaceutically acceptable salt thereof, wherein B^1-HET- is selected from the group consisting of



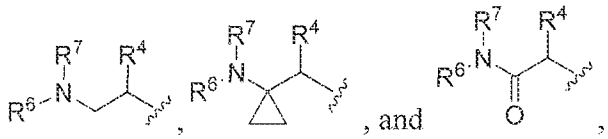
where the wavy line indicates the point of attachment to the rest of the molecule.

27. A compound of any one of the preceding claims or a tautomer or a pharmaceutically acceptable salt thereof, wherein Y is



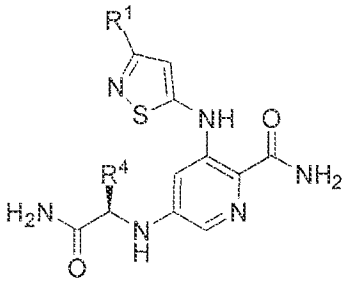
where the wavy line indicates the point of attachment to the rest of the molecule.

28. A compound of any one of the preceding claims or a tautomer or a pharmaceutically acceptable salt thereof, wherein Y is selected from the group consisting of

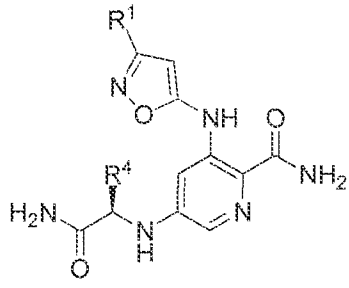


where the wavy line indicates the point of attachment to the rest of the molecule.

29. A compound of claim 28 of Formula (II) or Formula (III) or a tautomer or a pharmaceutically acceptable salt thereof



(II)

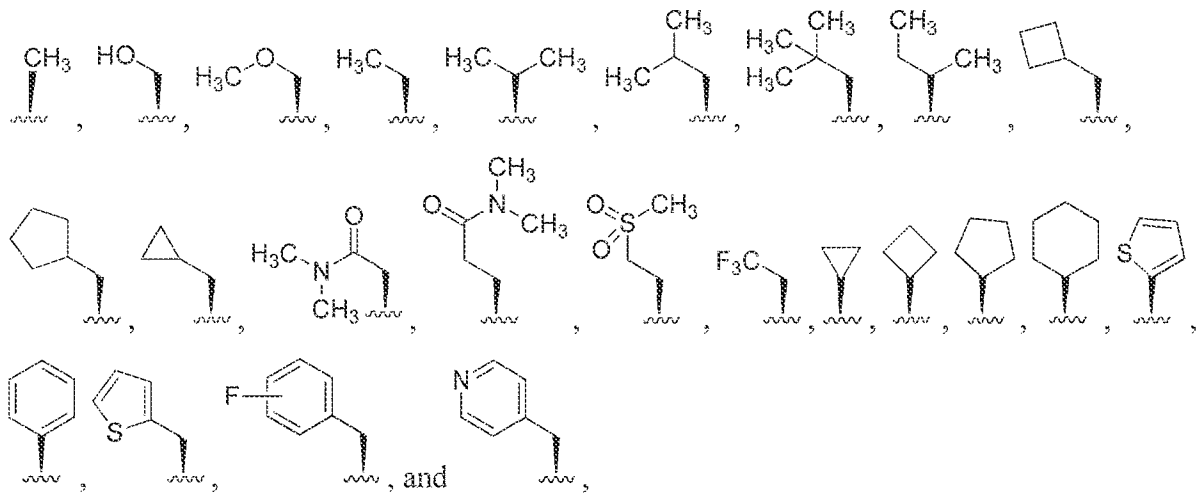


(III).

30. A compound of claim 28 or 29 or a tautomer or a pharmaceutically acceptable salt thereof, wherein R^6 and R^7 are H and R^4 is selected from the group consisting of H, C_{1-8}alkyl, haloC_{1-8}alkyl, cycloalkyl, (cycloalkyl)C_{1-4}alkyl, (hydroxyl)C_{1-4}alkyl, (C_{1-4}alkoxy)C_{1-4}alkyl, (haloC_{1-4}alkoxy)C_{1-4}alkyl, $(CH_2)_pNR^{4b}R^{4c}$, $(CH)_pSO_2NR^{4b}R^{4c}$, $(CH_2)_pSOR^{4a}$, $(CH_2)_pSO_2R^{4a}$, $(CH_2)_fCONR^{4b}R^{4c}$, $(CH_2)_pNR^{4b}COR^{4d}$, phenyl, heteroaryl, (phenyl)C_{1-8}alkyl, and (heteroaryl)C_{1-8}alkyl wherein the phenyl and heteroaryl are optionally substituted with 1 to 3 groups independently selected from halo, C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxy, and haloC_{1-4}alkoxy.

31. A compound of claim 30 or a tautomer or a pharmaceutically acceptable salt thereof, wherein R^4 is selected from the group consisting of H, methyl, ethyl, propyl, isopropyl, isobutyl, hydroxymethyl, pyridyl, and phenyl, wherein the pyridyl and phenyl are optionally substituted with 1 to 3 groups independently selected from halo, C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxy, and haloC_{1-4}alkoxy.

32. A compound of claim 28 or 29 or a tautomer or a pharmaceutically acceptable salt thereof, wherein R^4 is selected from the group consisting of

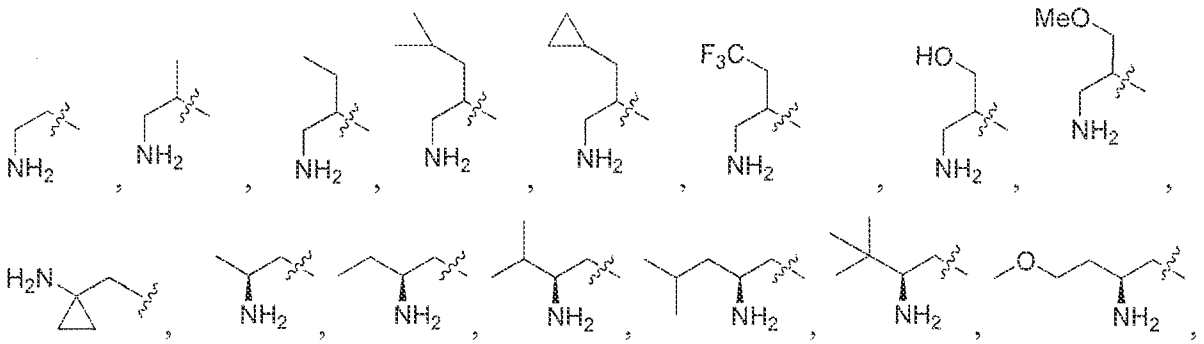


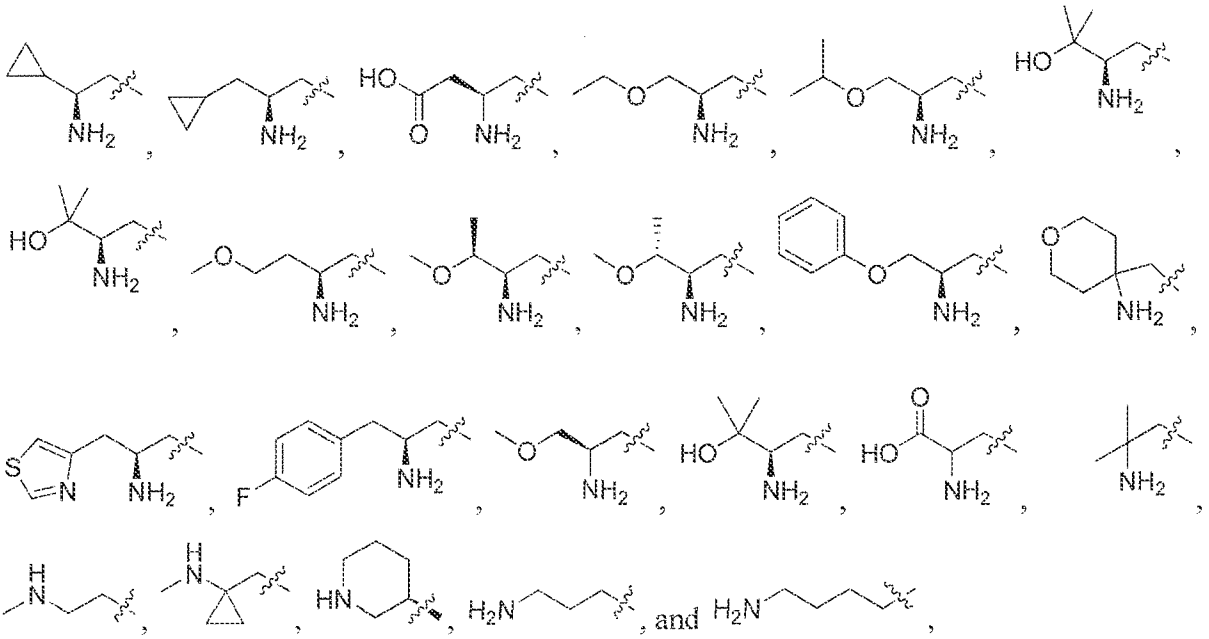
where the wavy line indicates the point of attachment to the rest of the molecule.

33. A compound of any one of claims 29 to 32 or a tautomer or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from the group consisting of halo, C_{1-8}alkyl, haloC_{1-8}alkyl, cyano, oxo, OH, O(C_{1-8}alkyl), O(haloC_{1-8}alkyl), CO-NR^aR^b, phenyl, heteroaryl, and heterocyclyl, wherein the phenyl, heteroaryl, and heterocyclyl are each optionally substituted with 1 to 3 R^2, and R^a and R^b together form a four to six membered heterocyclic ring optionally substituted with one to three groups independently selected from halo, C_{1-8}alkyl, and haloC_{1-8}alkyl.

34. A compound of claim 33 or a tautomer or a pharmaceutically acceptable salt thereof, wherein R^1 is methyl.

35. A compound of claim 27 or a tautomer or a pharmaceutically acceptable salt thereof, wherein Y is selected from the group consisting of

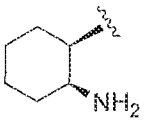




where the wavy line indicates the point of attachment to the rest of the molecule.

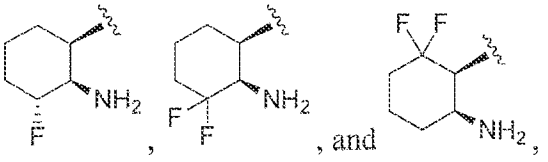
36. A compound of any one claims 1 to 26 or a tautomer or a pharmaceutically acceptable salt thereof, wherein Y is $(CH_2)_v(X)$ wherein v is 0 and X is cycloalkyl or heterocycloalkyl each optionally substituted with 1 to 3 R^{10}.

37. A compound of claim 36 or a tautomer or a pharmaceutically acceptable salt thereof, wherein Y is



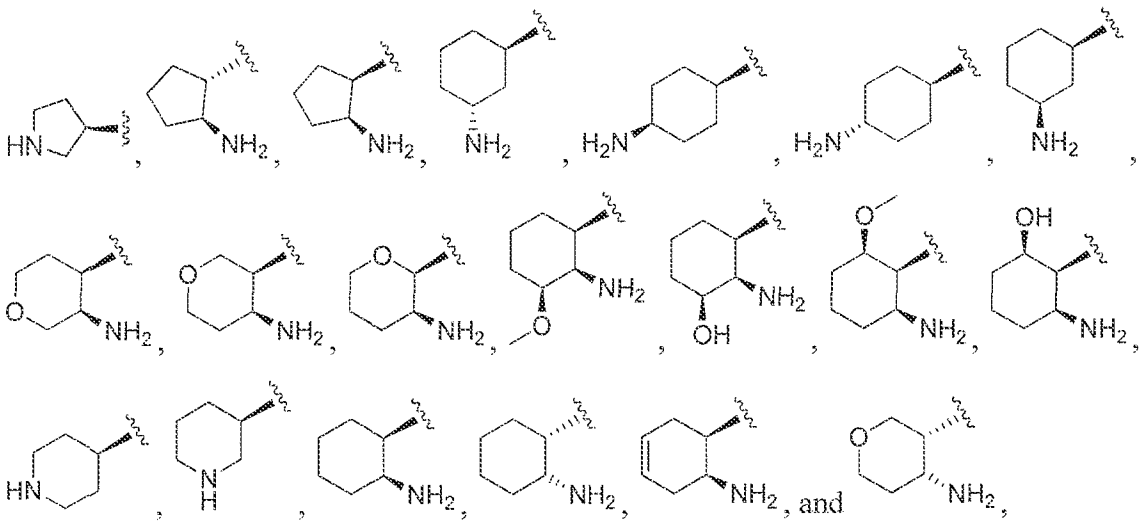
optionally substituted with 1 to 2 halo and where the wavy line indicates the point of attachment to the rest of the molecule.

38. A compound of claim 37 wherein Y is selected from the group consisting of



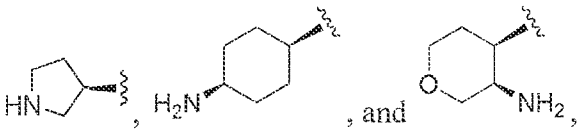
where the wavy line indicates the point of attachment to the rest of the molecule.

39. A compound of claim 36 wherein Y is selected from the group consisting of



where the wavy line indicates the point of attachment to the rest of the molecule.

40. A compound of claim 39 wherein Y is selected from the group consisting of



where the wavy line indicates the point of attachment to the rest of the molecule.

41. A compound or a tautomer or a pharmaceutically acceptable salt thereof having a structure selected from:

(R)-5-(1-amino-4-methyl-1-oxopentan-2-ylamino)-3-(3-methylisothiazol-5-ylamino)picolinamide;

5-((1R,2R)-2-amino-3,3-difluorocyclohexylamino)-3-(3-methylisothiazol-5-ylamino)picolinamid;

(R)-5-(1-amino-3-cyclopropyl-1-oxopropan-2-ylamino)-3-(3-methylisothiazol-5-ylamino)picolinamide;

5-((1R,2S)-2-aminocyclohexylamino)-3-(3-methylisothiazol-5-ylamino)picolinamide;

(R)-5-(1-amino-1-oxobutan-2-ylamino)-3-(3-methylisothiazol-5-ylamino)picolinamide;

3-(3-(2H-1,2,3-triazol-2-yl)phenylamino)-5-((1R,2S)-2-aminocyclohexylamino)picolinamide;

(R)-5-(1-amino-3-methyl-1-oxobutan-2-ylamino)-3-(3-methylisothiazol-5-ylamino)picolinamide;

5-((1R,2S)-2-aminocyclohexylamino)-3-(3-phenylisoxazol-5-ylamino)picolinamide;

5-((1R,2R)-2-amino-3,3-difluorocyclohexylamino)-3-(3-phenylisoxazol-5-ylamino)picolinamide;

5-((1R,2S)-2-aminocyclohexylamino)-3-(3-methylisoxazol-5-ylamino)picolinamide;

(R)-5-(1-amino-4-methyl-1-oxopentan-2-ylamino)-3-(3-phenylisoxazol-5-ylamino)picolinamide;

5-((1R,2S)-2-aminocyclohexylamino)-3-(isoquinolin-6-ylamino)picolinamide;

5-((1R,2S)-2-aminocyclohexylamino)-3-(quinolin-3-ylamino)picolinamide;

5-((1R,2S)-2-aminocyclohexylamino)-3-(isoquinolin-7-ylamino)picolinamide;

5-((1R,2S)-2-aminocyclohexylamino)-3-(quinolin-7-ylamino)picolinamide;

(R)-5-(1-amino-4-methyl-1-oxopentan-2-ylamino)-3-(quinolin-6-ylamino)picolinamide;

(R)-5-(1-amino-4-methyl-1-oxopentan-2-ylamino)-3-(isoquinolin-6-ylamino)picolinamide;

(R)-5-(1-amino-3-cyclohexyl-1-oxopropan-2-ylamino)-3-(3-methylisothiazol-5-ylamino)picolinamide;

(R)-3-(3-(2H-1,2,3-triazol-2-yl)phenylamino)-5-(1-amino-4-methyl-1-oxopentan-2-ylamino)picolinamide;

(R)-5-(1-amino-4-methyl-1-oxopentan-2-ylamino)-3-(quinolin-3-ylamino)picolinamide;

(R)-5-(1-amino-4-methyl-1-oxopentan-2-ylamino)-3-(isoquinolin-7-ylamino)picolinamide;

(R)-5-(1-amino-4-methyl-1-oxopentan-2-ylamino)-3-(quinolin-7-ylamino)picolinamide;

5-((3R, 4R)-3-aminotetrahydro-2H-pyran-4-ylamino)-3-(3-methylisothiazol-5-ylamino)picolinamide;

5-((1R,2S)-2-aminocyclohexylamino)-3-(1-methyl-1H-pyrazol-4-ylamino)picolinamide;

5-((1R,2S)-2-aminocyclohexylamino)-3-(pyrazolo[1,5-a]pyridin-3-ylamino)picolinamide;

5-((1S,4S)-4-aminocyclohexylamino)-3-(3-methylisothiazol-5-ylamino)picolinamide;

5-((1R,2S)-2-aminocyclohexylamino)-3-(isothiazol-4-ylamino)picolinamide;

5-(1-carbamoylcyclopropylamino)-3-(3-methylisothiazol-5-ylamino)picolinamide;

(R)-5-(1-amino-3-methyl-1-oxobutan-2-ylamino)-3-(3-ethylisothiazol-5-ylamino)picolinamide;

5-((1R,2S)-2-aminocyclohexylamino)-3-(3-cyclopropylisoxazol-5-ylamino)picolinamide;

(R)-5-(1-amino-3-methyl-1-oxobutan-2-ylamino)-3-(3-cyclopropylisoxazol-5-ylamino)picolinamide;

5-((1R,2S)-2-aminocyclohexylamino)-3-(3-isopropylisoxazol-5-ylamino)picolinamide;

5-((1R,2S)-2-aminocyclohexylamino)-3-(3-ethylisoxazol-5-ylamino)picolinamide;

(R)-5-(1-amino-1-oxobutan-2-ylamino)-3-(3-cyclopropylisothiazol-5-ylamino)picolinamide;

(R)-5-(1-amino-3,3-dimethyl-1-oxobutan-2-ylamino)-3-(3-cyclopropylisothiazol-5-ylamino)picolinamide;

(R)-5-(1-amino-4,4-dimethyl-1-oxopentan-2-ylamino)-3-(8-fluoroquinolin-6-ylamino)picolinamide;

(R)-5-(1-amino-4,4-dimethyl-1-oxopentan-2-ylamino)-3-(quinolin-7-ylamino)picolinamide;

(R)-5-(2-amino-2-oxo-1-phenylethylamino)-3-(3-methylisothiazol-5-ylamino)picolinamide;

(R)-5-(1-amino-1-oxopropan-2-ylamino)-3-(3-methylisothiazol-5-ylamino)picolinamide;

(R)-5-(1-amino-4,4,4-trifluoro-1-oxobutan-2-ylamino)-3-(3-methylisothiazol-5-ylamino)picolinamide;

(R)-5-(1-amino-4-(methylsulfonyl)-1-oxobutan-2-ylamino)-3-(3-methylisothiazol-5-ylamino)picolinamide;

(R)-5-(2-amino-1-cyclopropyl-2-oxoethylamino)-3-(3-methylisothiazol-5-ylamino)picolinamide;

(R)-5-(1-amino-4-methyl-1-oxopentan-2-ylamino)-3-(3-(pyridin-4-yl)isoxazol-5-ylamino)picolinamide;

(R)-5-(1-amino-3-methoxy-1-oxopropan-2-ylamino)-3-(3-methylisothiazol-5-ylamino)picolinamide;

5-((1R,2S)-2-aminocyclohexylamino)-3-(3-(pyridin-4-yl)isoxazol-5-ylamino)picolinamide;

5-((1R,2S)-2-aminocyclohexylamino)-3-(3-(pyridin-3-yl)isoxazol-5-ylamino)picolinamide;

(R)-5-(1-amino-4,4,4-trifluoro-1-oxobutan-2-ylamino)-3-(quinolin-7-ylamino)picolinamide;

5-((3R,4R)-3-aminotetrahydro-2H-pyran-4-ylamino)-3-(3-(pyridin-4-yl)isoxazol-5-ylamino)picolinamide;

5-((3R,4R)-3-aminotetrahydro-2H-pyran-4-ylamino)-3-(3-(pyridin-3-yl)isoxazol-5-ylamino)picolinamide;

(R)-3-(1,5-naphthyridin-3-ylamino)-5-(1-amino-1-oxobutan-2-ylamino)picolinamide; and

5-(((1R,2S)-2-aminocyclohexyl)amino)-3-((3-(oxazol-2-yl)phenyl)amino)picolinamide.

42. A compound of Formula (Ia) or Formula (Ib) or a tautomer or a pharmaceutically acceptable salt thereof having a structure found claim 41.

43. A compound of Formula (II) or Formula (III) or a tautomer or a pharmaceutically acceptable salt thereof having a structure found in claim 41.

44. A composition comprising a compound of any of the preceding claims or a tautomer or a pharmaceutically acceptable salt thereof in combination with a pharmaceutically acceptable carrier or diluent.

45. A method for inhibiting syk or JAK kinase or a signal transduction pathway mediated at least in part by syk kinase activity comprising contacting a cell with a compound of any one of claims 1 to 43.

46. A method for treating a condition or disorder mediated at least in part by syk kinase activity comprising administering to a subject in need of such treatment a therapeutically effective amount of a composition of claim 42.

47. The method of claim 46 wherein the condition or disorder is selected from the group consisting of cardiovascular disease, inflammatory disease, autoimmune disease, and cell proliferative disorder.

48. The method of claim 47, wherein

said cardiovascular disease is selected from the group consisting of restenosis, thrombosis, immune thrombocytopenic purpura, heparin induced thrombocytopenia, dilated cardiomyopathy, sickle cell disease, atherosclerosis, myocardial infarction, vascular inflammation, unstable angina, and acute coronary syndromes;

said inflammatory disease is selected from the group consisting of allergy, asthma, rheumatoid arthritis, B Cell mediated diseases, Non-Hodgkin's Lymphoma, anti-phospholipid syndrome, lupus, psoriasis, multiple sclerosis, and end stage renal disease;

said autoimmune disease is selected from the group consisting of hemolytic anemia, immune thrombocytopenic purpura, multiple sclerosis, Sjogren's syndrome, diabetes, rheumatoid arthritis, lupus, and psoriasis; and

said cell proliferative disorder is leukemia, a lymphoma, myeloproliferative disorders, hematological malignancies, and chronic idiopathic myelofibrosis.