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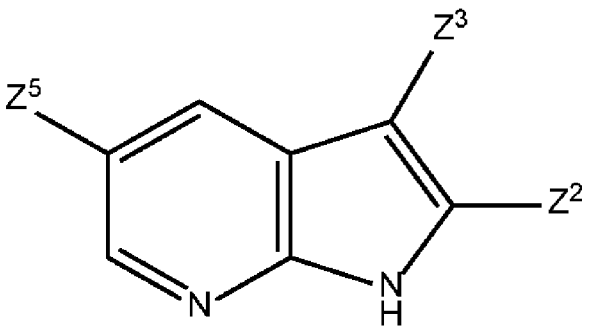
(54) **Title**: COMPOUNDS AND METHODS FOR KINASE MODULATION, AND INDICATIONS THEREFOR



(I)

(57) **Abstract**: Disclosed are compounds of Formula I or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer or a deuterated analog thereof, wherein Z^2, Z^3, and Z^5 are as described herein, compositions thereof, and uses thereof.

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COMPOUNDS AND METHODS FOR KINASE MODULATION, AND INDICATIONS THEREFOR

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit under 35 U.S.C. §119(e) to U.S. Provisional Application Serial No. 62/264,180, filed on December 7, 2015, which is hereby incorporated by reference in its entirety.

FIELD

[0002] The present disclosure relates to protein kinases and compounds which selectively modulate kinases, and uses therefor. Particular embodiments contemplate disease indications which are amenable to treatment by modulation of kinase activity by the compounds of the present disclosure.

BACKGROUND

[0003] FMS-like tyrosine kinase 3 (FLT3) is mutated in about one third of acute myeloid leukemia cases. The most frequent FLT3 mutations in acute myeloid leukemia are internal tandem duplication (ITD) mutations in the juxtamembrane domain (23%) and point mutations in the tyrosine kinase domain (10%). The most frequent kinase domain mutation is the substitution of aspartic acid at position 838 (equivalent to the human aspartic acid residue at position 835) with a tyrosine (FLT3/D835Y), converting aspartic acid to tyrosine. Even though both of these mutations constitutively activate FLT3, patients with an ITD mutation have a much poorer prognosis. It has been previously demonstrated that the FLT3/D835Y knock-in mice survive significantly longer than FLT3/ITD knock-in mice. The majority of these mice develop myeloproliferative neoplasms with a less-aggressive phenotype.

[0004] Secondary mutations in the tyrosine kinase domain (KD) is one of the most common causes of acquired clinical resistance to small molecule tyrosine kinase inhibitors (TKIs) in human cancer. Recent pharmaceutical efforts have focused on the development of "type II" kinase inhibitors, which bind to a relatively non-conserved inactive kinase conformation and exploit an allosteric site adjacent to the ATP-binding pocket as a potential means to increase kinase selectivity. Mutations in FLT3 are the common genetic alteration in patients with acute myeloid leukemia (AML) (TCGA, *N Engl J Med.* 2013, 368: 2059-74) and are primarily comprised of constitutively activating internal tandem duplication (ITD) mutations (of 1-100 amino acids) in the juxtamembrane domain, and to a lesser extent, point mutations, typically within the kinase activation loop. Secondary KD mutations in FLT3-ITD that can cause

resistance to the highly potent type II FLT3 inhibitors, such as, quizartinib, which achieved a composite complete remission (CRc) rate of about 50% in relapsed or chemotherapy-refractory FLT3-ITD+ AML patients treated in large phase II monotherapy studies (Tallman et al., *Blood*, 2013;122:494). An *in vitro* saturation mutagenesis screen of FLT3-ITD identified five quizartinib-resistant KD mutations at three residues: the "gatekeeper" F691 residue, and two amino acid positions within the kinase activation loop (D835 and Y842), a surprisingly limited spectrum of mutations for a type II inhibitor. Mutations at two of these residues (F691L and D835V/Y/F) were subsequently identified in each of eight samples analyzed at the time of acquired clinical resistance to quizartinib (Smith et al., *Nature*, 2012;485:260-3). This finding validated FLT3 as a therapeutic target in AML. The type II multikinase inhibitor sorafenib, which also has some clinical activity in FLT3-ITD+ AML, is ineffective against all identified quizartinib resistance-causing mutants, in addition to other mutant isoforms (Smith et al.). The type I inhibitor crenolanib has been identified a type I inhibitor of quizartinib-resistant D835 mutants (Zimmerman et al. *Blood*, 2013; 122:3607-15); however, no FLT3 inhibitor has demonstrated equipotent inhibition of the F691L mutant, including the ABL/FLT3 inhibitor ponatinib, which was designed to retain activity against the problematic gatekeeper T315I mutant in BCR-ABL (Smith et al., *Blood*, 2013; 121:3165-71).

[0005] 2,5-Azaindole compounds have been described as being active against specific targets. U.S. 2013/0158049 describes 2,5 substituted azaindole compounds that specifically modulate calcium release-activated calcium (CRAC) channels. In another example, U.S. Patent No. 6,770,643 describes 2,5 substituted azaindole compounds that selectively inhibit Syk kinase. In a further example U.S. Patent No. 8,785,89 describes 2,5 substituted azaindole compounds that inhibit MMP-13 metalloprotease.

[0006] There remains a long felt need for new FLT3 inhibitors that can overcome the drawbacks of the FLT3 inhibitors known in the art. There is a further need for new FLT3 inhibitors that are selective for FLT3 over other kinase targets to overcome the drawbacks of the FLT3 inhibitors known in the art.

SUMMARY

[0007] The present disclosure relates to compounds which selectively modulate FLT3 kinases, compositions thereof, and uses therefor. Particular embodiments contemplate disease indications which are amenable to treatment by modulation of kinase activity by the compounds of the present disclosure.

[0008] One embodiment of the disclosure relates to novel 2,5 substituted azaindole compounds, as described herein, or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer or a deuterated analog thereof, wherein these novel compounds can modulate FLT3. In another embodiment, the novel 2,5 substituted azaindole compounds described herein can modulate FLT3 having an ITD mutation and optionally an F691L mutation and/or D835Y mutation. In another embodiment, the compounds described herein are selective for FLT3 kinase over c-kit kinase. In another embodiment, the compounds described herein modulate (TGF-β) receptor type 2 (TGFBR2).

[0009] Another embodiment of the disclosure relates to a pharmaceutical composition comprising a compound having any of the Formulae described in this disclosure, including any one of the compounds listed in Table I or Table II, or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer or a deuterated analog of any of these compounds, and a pharmaceutically acceptable carrier or excipient.

[0010] Another embodiment of the disclosure relates to a pharmaceutical composition comprising a compound having any of the Formulae described in this disclosure, including any one of the compounds listed in Table I or Table II, or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer or a deuterated analog of any of these compounds, another therapeutic agent, and a pharmaceutically acceptable carrier or excipient.

[0011] Another embodiment of the disclosure relates to a method for treating a subject in need thereof with a disease or condition mediated by a FLT3 or c-KIT protein kinase, said method comprising administering to the subject an effective amount a compound having any of the Formulae described in this disclosure, including any one of the compounds listed in Table I or Table II, or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer or a deuterated analog of any of these compounds, wherein the disease or condition is selected from acute myeloid leukemia, stem cell ablation and myelopreparation for stem cell transplant, primary progressive multiple sclerosis, complex regional pain syndrome, reflex sympathetic dystrophy, muscular dystrophy, duchenne muscular dystrophy, causalgia, neuro-inflammation, neuroinflammatory disorders, benign forgetfulness, HIV, binswager type dementia, dementia with lewy bodie, prosencephaly, microencepahy, cerebral palsy, congenital hydrocephalus, abdominal dropsy, progressive supranuclear palsy, glaucoma, addiction disorders, dependencies, alcoholism, tremors, Wilson's disease, vascular dementias, multi infarct dementia, fronto temporal dementia, pseudo-dementia, bladder cancer, basal cell carcinoma, cholangiocarcinoma, colon cancer, endometrial cancer, esophageal cancer, Ewing's sarcoma, gastric cancer, glioma, hepatocellular carcinoma, Hodgkin lymphoma, laryngeal carcinoma, leukemia, liver cancer,

lung cancer, melanoma, mesothelioma, pancreatic cancer, rectal cancer, renal cancer, squamous cell carcinoma, t cell lymphoma, thyroid cancer, monocytic leukemia, pheochromocytoma, malignant peripheral nerve cell tumors, malignant peripheral nerve sheath tumors (MPNST), cutaneous and plexiform neurofibromas, leiomyoadenomatoid tumor, fibroids, uterine fibroids, leiomyosarcoma, papillary thyroid cancer, anaplastic thyroid cancer, medullary thyroid cancer, follicular thyroid cancer, hurthle cell carcinoma, thyroid cancer, ascites, malignant ascites, mesothelioma, salivary gland tumors, mucoepidermoid carcinoma of the salivary gland, acinic cell carcinoma of the salivary gland, gastrointestinal stromal tumors (GIST), tumors that cause effusions in potential spaces of the body, pleural effusions, pericardial effusions, peritoneal effusions aka ascites, giant cell tumors (GCT), GCT of bone other sarcomas, tumor angiogenesis, or paracrine tumor growth.

[0012] Another embodiment of the disclosure relates to a method for treating a subject in need thereof with a disease or condition mediated by a (TGF-β) type 2 receptor.

[0013] Another emobdiment of the disclosure relates to a method for treating a subject suffering from a disease or condition as described herein, said method comprising administering to the subject a pharmaceutical composition comprising a compound having any of the Formulae described in this disclosure, including any one of the compounds listed in Table I or Table II, or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer or a deuterated analog of any of these compounds, and another therapeutic agent, wherein the other therapeutic agent is selected from: i) an alkylating agent selected from adozelesin, altretamine, bizelesin, busulfan, carboplatin, carboquone, carmustine, chlorambucil, cisplatin, cyclophosphamide, dacarbazine, estramustine, fotemustine, hepsulfam, ifosfamide, improsulfan, irofulven, lomustine, mechlorethamine, melphalan, oxaliplatin, piposulfan, semustine, streptozocin, temozolomide, thiotepa, and treosulfan; ii) an antibiotic selected from bleomycin, dactinomycin, daunorubicin, doxorubicin, epirubicin, idarubicin, menogaril, mitomycin, mitoxantrone, neocarzinostatin, pentostatin, and plicamycin; an antimetabolite, including, but not limited to, azacitidine, capecitabine, cladribine, clofarabine, cytarabine, decitabine, floxuridine, fludarabine, 5-fluorouracil, ftorafur, gemcitabine, hydroxyurea, mercaptopurine, methotrexate, nelarabine, pemetrexed, raltitrexed, thioguanine, and trimetrexate; iii) an immunotherapy selected from an IDO inihibitor (non-limiting examples of an IDO inhibitor include indoximod and NLG 919), or an antibody therapy agent selected from alemtuzumab, bevacizumab, cetuximab, galiximab, gemtuzumab, panitumumab, pertuzumab, rituximab, tositumomab, trastuzumab, and 90 Y ibritumomab tiuxetan; a hormone or hormone antagonist, including, but not limited to, anastrozole, androgens, buserelin, diethylstilbestrol, exemestane, flutamide, fulvestrant,

goserelin, idoxifene, letrozole, leuprolide, magestrol, raloxifene, tamoxifen, and toremifene; iv) a taxane selected from DJ-927, docetaxel, TPI 287, paclitaxel and DHA-paclitaxel; v) a retinoid selected from alitretinoin, bexarotene, fenretinide, isotretinoin, and tretinoin; vi) an alkaloid selected from etoposide, homoharringtonine, teniposide, vinblastine, vincristine, vindesine, and vinorelbine; vii) an antiangiogenic agent selected from AE-941 (GW786034, Neovastat), ABT-510, 2-methoxyestradiol, lenalidomide, and thalidomide; viii) a topoisomerase inhibitor selected from amsacrine, edotecarin, exatecan, irinotecan (also active metabolite SN-38 (7-ethyl-10-hydroxy-camptothecin)), rubitecan, topotecan, and 9-aminocamptothecin; ix) a kinase inhibitor selected from erlotinib, gefitinib, flavopiridol, imatinib mesylate, lapatinib, sorafenib, sunitinib malate, AEE-788, AG-013736, AMG 706, AMN107, BMS-354825, BMS-599626, UCN-01 (7-hydroxystaurosporine), vemurafenib, dabrafenib, trametinib, cobimetinib selumetinib and vatalanib; x) a targeted signal transduction inhibitor selected from bortezomib, geldanamycin, and rapamycin; xi) a biological response modifier selected from imiquimod, interferon-.alpha., and interleukin-2; and xii) a chemotherapeutic agent selected from 3-AP (3-amino-2-carboxyaldehyde thiosemicarbazone), altrasentan, aminoglutethimide, anagrelide, asparaginase, bryostatin-1, cilengitide, elesclomol, eribulin mesylate (E7389), ixabepilone, lonidamine, masoprocol, mitoguanazone, oblimersen, sulindac, testolactone, tiazofurin, mTOR inhibitors (e.g. sirolimus, temsirolimus, everolimus, deforolimus), PI3K inhibitors (e.g. BEZ235, GDC-0941, XL147, XL765), Cdk4 inhibitors (e.g. PD-332991), Akt inhibitors, Hsp90 inhibitors (e.g. geldanamycin, radicicol, tanespimycin), farnesyltransferase inhibitors (e.g. tipifarnib) and Aromatase inhibitors (anastrozole letrozole exemestane); xiii) a Mek inhibitor; xiv) a tyrosine kinase inhibitor as described herein; or xv) an EGFR inhibitor.

[0014] Another embodiment of the disclosure relates to a method of (1) identifying the presence of a tumor in a patient; and (2) treating the patient, identified as needing the treatment, by administering a therapeutically effective amount of a compound having any of the Formulae described in this disclosure, including any one of the compounds listed in Table I or Table II, or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer or a deuterated analog of any of these compounds, wherein the step of identifying the patient includes identifying a patient having an oncogenic FLT3 mutant that is encoded by a FLT3 gene having an ITD mutation and optionally an F691L mutation and/or D835Y mutation.

DETAILED DESCRIPTION

I. Definitions

[0015] As used herein the following definitions apply unless clearly indicated otherwise:

[0016] It is noted here that as used herein and the appended claims, the singular forms "a," "an," and "the" include plural reference unless the context clearly dictates otherwise.

[0017] Unless a point of attachment indicates otherwise, the chemical moieties listed in the definitions of the variables of Formula I of this disclosure, and all the embodiments thereof, are to be read from left to right, wherein the right hand side is directly attached to the parent strucuture as defined. However, if a point of attachment is shown on the left hand side of the chemical moiety (e.g., -alkyloxy-(C_1-C_{25})alkyl), then the left hand side of this chemical moiety is attached directly to the parent moiety as defined. It is assumed that when considering generic descriptions of compounds of the described herein for the purpose of constructing a compound, such construction results in the creation of a stable structure. That is, one of ordinary skill in the art would recognize that theoretically some constructs which would not normally be considered as stable compounds (that is, sterically practical and/or synthetically feasible).

[0018] "Halogen" or "halo" refers to all halogens, that is, chloro (Cl), fluoro (F), bromo (Br), or iodo (I).

[0019] "Hydroxyl" or "hydroxy" refers to the group -OH. The term "oxo" refers to C(O) or $-O^-$.

[0020] "Heteroatom" is meant to include oxygen (O), nitrogen (N), and sulfur (S).

[0021] "Alkyl", by itself, or as part of another substituent, means, unless otherwise stated, a straight or branched chain hydrocarbon, having the number of carbon atoms designated (*i.e.* C_{1-6} means one to six carbons). 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. Examples of alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. For each of the definitions herein (e.g., alkyl, alkoxy, arylalkyl, cycloalkylalkyl, heterocycloalkylalkyl, heteroarylalkyl, etc.), when a prefix is not included to indicate the number of carbon atoms in an alkyl portion, the alkyl moiety or portion thereof will have 12 or fewer main chain carbon atoms or 8 or fewer main chain carbon atoms or 6 or fewer main chain carbon atoms. For example, C_{1-6} alkyl refers to a straight or branched hydrocarbon having 1, 2, 3, 4, 5 or 6 carbon atoms and includes, but is not limited to, C_{1-2} alkyl, C_{1-4} alkyl, C_{2-6} alkyl, C_{2-4} alkyl, C_{1-6} alkyl, C_{2-8} alkyl, C_{1-7} alkyl, C_{2-7} alkyl and C_{3-6} alkyl. The term "deuteroalkyl" refers to a deuterated analog of an alkyl group. The term "haloalkyl" refers to an alkyl substituted by one to seven halogen atoms. Haloalkyl includes monohaloalkyl or polyhaloalkyl. For example, the term "C_{1-6}haloalkyl" is

mean to include trifluoromethyl, difluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropoyl, and the like. While it is understood that substitutions are attached at any available atom to produce a stable compound, when optionally substituted alkyl is an R group of a moiety such as -OR (e.g. alkoxy), -SR (e.g. thioalkyl), -NHR (e.g. alkylamino), -C(O)NHR, and the like, substitution of the alkyl R group is such that substitution of the alkyl carbon bound to any O, S, or N of the moiety (except where N is a heteroaryl ring atom) excludes substituents that would result in any O, S, or N of the substituent (except where N is a heteroaryl ring atom) being bound to the alkyl carbon bound to any O, S, or N of the moiety. The term alkyl is meant to encompass alkenyl and alkynyl as defined herein.

[0022] "Alkylene" by itself or as part of another substituent means a linear or branched saturated divalent hydrocarbon moiety derived from an alkane having the number of carbon atoms indicated in the prefix. For example, (*i.e.*, C_{1-6} means one to six carbons; C_{1-6} alkylene is meant to include methylene, ethylene, propylene, 2-methylpropylene, pentylene, hexylene and the like). C_{1-4} alkylene includes methylene -CH_2-, ethylene -CH_2CH_2-, propylene -$CH_2CH_2CH_2$-, and isopropylene -$CH(CH_3)CH_2$- , -$CH_2CH(CH_3)$-, -CH_2-$(CH_2)_2CH_2$-, -CH_2-$CH(CH_3)CH_2$-, -CH_2-$C(CH_3)_2$--CH_2-$CH_2CH(CH_3)$- . Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer, 8 or fewer, or 6 or fewer carbon atoms. When a prefix is not included to indicate the number of carbon atoms in an alkylene portion, the alkylene moiety or portion thereof will have 12 or fewer main chain carbon atoms or 8 or fewer main chain carbon atoms, 6 or fewer main chain carbon atoms, or 4 or fewer main chain carbon atoms, or 3 or fewer main chain carbon atoms, or 2 or fewer main chain carbon atoms, or 1 carbon atom.

[0023] "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. For example, (C_2-C_6)alkenyl is meant to include ethenyl, propenyl, and the like. The term "alkynyl" refers to a monoradical of an unsaturated hydrocarbon, in some embodiments, having from 2 to 20 carbon atoms (in some embodiments, from 2 to 10 carbon atoms, e.g. 2 to 6 carbon atoms) and having from 1 to 6 carbon-carbon triple bonds e.g. 1, 2 or 3 carbon-carbon triple bonds. In some embodiments, alkynyl groups include ethynyl (-C≡CH), propargyl (or propynyl, i.e. -C≡CCH_3), and the like. When a prefix is not included to indicate the number of carbon atoms in an alkenyl or alkynyl portion, the alkenyl or alkynyl moiety or portion thereof will have 12 or fewer main chain carbon atoms or 8 or fewer main chain carbon atoms, 6 or fewer main chain carbon atoms or 4 or fewer main chain carbon atoms. The term "alkenylene" refers to a linear monovalent hydrocarbon radical or a branched monovalent

hydrocarbon radical containing at least one double bond and having the number of carbon atoms indicated in the prefix. The term "alkynylene" refers to 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. Examples of such unsaturated alkyl groups include vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), ethynyl, 1- and 3-propynyl, 3-butynyl, and the higher homologs and isomers.

[0024] "Cycloalkyl" or "Carbocycle" by itself , or as part of another substituent, unless otherwise stated, refers to saturated or unsaturated, non-aromatic monocyclic, bicyclic or tricyclic carbon ring systems having the number of carbon atoms indicated in the prefix or if unspecified having 3-10, also 3-8, and also 3-6, ring members per ring, such as cyclopropyl, cyclopentyl, cyclohexyl, 1-cyclohexenyl, adamantyl, and the like, where one or two ring carbon atoms may optionally be replaced by a carbonyl. Cycloalkyl refers to hydrocarbon rings having the indicated number of ring atoms (*e.g.*, C_{3-8} cycloalkyl means three to eight ring carbon atoms). "Cycloalkyl" or "carbocycle" may form a bridged ring or a spiro ring. The cycloalkyl group may have one or more double or triple bond(s), in which case they would be termed cycloalkenyl and cycloalkynyl respectively. The term "cycloalkylcarbonyl" refers to a –cycloalkyl-C(O)- group, wherein cycloalkyl is as defined herein. The term "alkylcarbonyl" refers to –alkyl-C(O)-, wherein alkyl is as defined herein.

[0025] "Cycloalkylalkyl" refers to an -(alkylene)-cycloalkyl group where alkylene as defined herein has the indicated number of carbon atoms or if unspecified having six or fewer, or four or fewer main chain carbon atoms; and cycloalkyl is as defined herein has the indicated number of carbon atoms or if unspecified having 3-10, also 3-8, and also 3-6, ring members per ring. C_{3-8}cycloalkyl-C_{1-2}alkyl is meant to have 3 to 8 ring carbon atoms and 1 to 2 alkylene chain carbon atoms. Exemplary cycloalkylalkyl includes, e.g., cyclopropylmethylene, cyclobutylethylene, cyclobutylmethylene, and the like.

[0026] "Cycloalkenyl" by itself ,or as part of another substituent, unless otherwise stated, refers to a non-aromatic monocyclic, bicyclic or tricyclic carbon ring system having the number of carbon atoms indicated in the prefix or if unspecified having 3-10, also 3-8, and also 3-6, ring members per ring, which contains at least one carbon-carbon double bond. Exemplary cycloalkenyl includes, e.g., 1-cyclohexenyl, 4-cyclohexenyl, 1-cyclopentenyl, 2-cyclopentenyl and the like.

[0027] "Alkoxy" or "alkoxyl"refers to a –O-alkyl group, where alkyl is as defined herein. The term "alkoxyalkyl" refers to an alkyl group substituted with one or more, such as one to three alkoxy groups. "Cycloalkoxy" refers to a –O-cycloalkyl group, where cycloalkyl is as defined

herein. While it is understood that substitutions on alkoxy are attached at any available atom to produce a stable compound, substitution of alkoxy is such that O, S, or N (except where N is a heteroaryl ring atom), are not bound to the alkyl carbon bound to the alkoxy O. Further, where alkoxy is described as a substituent of another moiety, the alkoxy oxygen is not bound to a carbon atom that is bound to an O, S, or N of the other moiety (except where N is a heteroaryl ring atom), or to an alkene or alkyne carbon of the other moiety. The term "hydroxyalkyl" or "hydroxyalkylene" refers to an alkyl or alkylene as defined herein substituted by at least one hydroxy group as defined herein. The term "carboxylalkyl" refers to –C(O)-alkyl group, wherein alkyl is as defined herein. The term "alkoxycarbonyl" refers to a –C(O)-alkoxy group, wherein alkoxy is as defined herein. The term "cyanoalkyl" or "cyanoalkylene" refers to an alkyl or alkylene as defined herein substituted by at least one cyano group as defined herein. The term "cyanocycloalkyl" refers to a cycloalkyl group as defined herein substituted by at least one cyano group, and the term "cyanocycloalkylalkyl" refers to a cycloalkylalkyl group as defined herein substituted by at least one cyano group.

[0028] "Amino" or "amine" denotes the group -NH_2. The term "cyano" refers to the group –CN.

[0029] "Alkylamino" refers to a –NH-alkyl group, where alkyl is as defined herein. Exemplary alkylamino groups include CH_3NH-, ethylamino, and the like.

[0030] "Alkylsufonyl" refers to a –SO_2-alkyl group, where alkyl is as defined herein. Exemplary alkylsulfonyl groups include CH_3 SO_2-, ethyl SO_2-, and the like.

[0031] "Alkylsufonylalkyl" refers to an -alkyl–SO_2-alkyl group, where alkyl is as defined herein. Exemplary alkylsulfonylalkyl groups include CH_3 SO_2-CH_2-, ethyl SO_2-CH_2-, and the like.

[0032] "Dialkylamino" refers to a –N(alkyl)(alkyl) group, where each alkyl is independently as defined herein. Exemplary dialkylamino groups include dimethylamino, diethylamino, ethylmethylamino, and the like. "Cycloalkylamino" denotes the group -$NR^{dd}R^{ee}$, where R^{dd} and R^{ee} combine with the nitrogen to form a 5-7 membered heterocycloalkyl ring, where the heterocycloalkyl may contain an additional heteroatom within the ring, such as O, N, or S, and may also be further substituted with alkyl. Alternatively, "cycloalkylamino" refers to a –NH-cycloalkyl group, where cycloalkyl is as defined herein. The term "cycloalkylaminocarbonyl" refers to a cycloalkylamino-C(O) group, where cycloalkylamino is as defined herein.

[0033] "Aryl" by itself, or as part of another substituent, unless otherwise stated, refers to a monocyclic, bicyclic or polycyclic polyunsaturated aromatic hydrocarbon radical containing 6 to

14 ring carbon atoms, which can be a single ring or multiple rings (up to three rings) which are fused together or linked covalently. Non-limiting examples of unsubstituted aryl groups include phenyl, 1-naphthyl and 2-naphthyl. The term "arylene" refers to a divalent aryl, wherein the aryl is as defined herein.

[0034] "Arylalkyl" or "aralkyl" refers to -(alkylene)-aryl, where the alkylene group is as defined herein and has the indicated number of carbon atoms, or if unspecified having six or fewer main chain carbon atoms or four or fewer main chain carbon atoms; and aryl is as defined herein. Examples of arylalkyl include benzyl, phenethyl, 1-methylbenzyl, and the like.

[0035] "Heteroaryl" by itself, or as part of another substituent, refers to a monocyclic aromatic ring radical containing 5 or 6 ring atoms, or a bicyclic aromatic radical having 8 to 10 atoms, containing one or more, 1-4, 1-3, or 1-2, heteroatoms independently selected from the group consisting of O, S, and N. Heteroaryl is also intended to include oxidized S or N, such as sulfinyl, sulfonyl and N-oxide of a tertiary ring nitrogen. A carbon or nitrogen atom is the point of attachment of the heteroaryl ring structure such that a stable compound is produced. Examples of heteroaryl groups include, but are not limited to, pyridyl, pyridazinyl, pyrazinyl, indolizinyl, benzo[b]thienyl, quinazolinyl, purinyl, indolyl, quinolinyl, pyrimidinyl, pyrrolyl, pyrazolyl, oxazolyl, thiazolyl, thienyl, isoxazolyl, oxathiadiazolyl, isothiazolyl, tetrazolyl, imidazolyl, triazolyl, furanyl, benzofuryl, indolyl, triazinyl, quinoxalinyl, cinnolinyl, phthalaziniyl, benzotriazinyl, benzimidazolyl, benzopyrazolyl, benzotriazolyl, benzisoxazolyl, isobenzofuryl, isoindolyl, indolizinyl, benzotriazinyl, thienopyridyl, thienopyrimidinyl, pyrazolopyrimidinyl, imidazopyridines, benzothiaxolyl, benzothienyl, quinolyl, isoquinolyl, indazolyl, pteridinyl and thiadiazolyl. "Nitrogen containing heteroaryl" refers to heteroaryl wherein any of the heteroatoms is N.

[0036] "Heteroarylene" by itself or as part of another substituent, refers to a divalent heteroaryl, where the heteroaryl is as defined herein.

[0037] "Heteroarylalkyl" refers to -(alkylene)-heteroaryl, where the alkylene group is as defined herein and has the indicated number of carbon atoms, or if unspecified having six or fewer main chain carbon atoms or four or fewer main chain carbon atoms; and heteroaryl is as defined herein.

[0038] "Heterocycloalkyl" refers to a saturated or unsaturated non-aromatic cycloalkyl group that contains from one to five heteroatoms selected from N, O, and S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized, the remaining ring atoms being C, where one or two C atoms may optionally be replaced by a

carbonyl. The heterocycloalkyl may be a monocyclic, a bicyclic or a polycylic ring system of 3 to 12, or 4 to 10 ring atoms, or 5 to 8 ring atoms in which one to five ring atoms are heteroatoms selected from –N=, -N-, -O-, -S-, -S(O)-, or $-S(O)_2-$ and further wherein one or two ring atoms are optionally replaced by a -C(O)- group. The heterocycloalkyl can also be a heterocyclic alkyl ring fused (including spirocyclic groups) with a cycloalkyl, an aryl or a heteroaryl ring. Non limiting examples of heterocycloalkyl groups include pyrrolidinyl, piperidinyl, imidazolidinyl, benzofuranyl, pyrazolidinyl, morpholinyl, oxetanyl, and the like. A heterocycloalkyl group can be attached to the remainder of the molecule through a ring carbon or a heteroatom. The term "heterocycloalkylene" refers to a divalent heterocycloalkyl, wherein the heterocycloalkyl is as defined herein. The term "heterocycloalkylsulfonyl" refers to a $-S(O)_2$-heterocycloalkyl group where heterocycloalkyl is as defined herein. "Heterocycloalkenyl" refers to a heterocycloalkyl group as defined herein that contains at least one alkenyl group as defined herein.

[0039] "Heterocycloalkylene" by itself or as part of another substituent, refers to a divalent heterocycloalkyl, where the heterocycloalkyl is as defined herein.

[0040] "Heterocycloalkylalkyl" or "heterocyclylalkyl " refers to -(alkylene)-heterocycloalkyl, where the alkylene group is as defined herein and has the indicated number of carbon atoms, or if unspecified having six or fewer main chain carbon atoms or four or fewer main chain carbon atoms; and heterocycloalkyl is as defined herein.

[0041] The term "alkylcarbonylaminoalkyl" refers to alkyl-C(O)-NH-alkylene, wherein alkyl and alkylene are as defined herein. The term "alkylsulfonyl" refers to an alkyl group attached to the parent molecular moiety through a sulfonyl group. The term "cycloalkylsulfonyl" refers to a cycloalkyl group attached to the parent molecular moiety through the sulfonyl group. The term "alkylsulfonylaminoalkyl" refers to alkyl-$S(O)_2$-NH-alkylene,wherein alkyl and alkylene are as defined herein. The term "aminocarbonylalkyl" refers to H_2N-C(O)-alkylene, wherein alkylene is as defined herein. The term "alkylaminosulfonyl" refers to an alkyl-NH-SO_2- group, wherein alkyl is as defined herein and the parent molecular moiety is attached through the sulfonyl group. The term "alkylaminoalkyl" refers to an alkyl-NH-alkylene group, wherein alkyl and alkylene are as defined herein.

[0042] "Protecting group" refers to a grouping of atoms that when attached to a reactive group in a molecule masks, reduces or prevents that reactivity. Examples of protecting groups can be found in T.W. Greene and P.G. Wuts, PROTECTIVE GROUPS IN ORGANIC CHEMISTRY, (Wiley, 4th ed. 2006), Beaucage and Iyer, *Tetrahedron* 48:2223-2311 (1992), and Harrison and Harrison *et al.*, COMPENDIUM OF SYNTHETIC ORGANIC METHODS, Vols. 1-8 (John Wiley and Sons. 1971-1996). Representative amino protecting groups include formyl, acetyl, trifluoroacetyl, benzyl,

benzyloxycarbonyl (CBZ), *tert*-butoxycarbonyl (Boc), trimethyl silyl (TMS), 2-trimethylsilyl-ethanesulfonyl (SES), trityl and substituted trityl groups, allyloxycarbonyl, 9-fluorenylmethyloxycarbonyl (FMOC), nitro-veratryloxycarbonyl (NVOC), tri-isopropylsilyl (TIPS), phenylsulphonyl and the like (see also, Boyle, A. L. (Editor), carbamates, amides, N-sulfonyl derivatives, groups of formula -C(O)OR, wherein R is, for example, methyl, ethyl, t-butyl, benzyl, phenylethyl, CH_2=$CHCH_2$-, and the like, groups of the formula -C(O)R', wherein R' is, for example, methyl, phenyl, trifluoromethyl, and the like, groups of the formula -SO_2R", wherein R" is, for example, tolyl, phenyl, trifluoromethyl, 2,2,5,7,8-pentamethylchroman-6-yl, 2,3,6-trimethyl-4-methoxyphenyl, and the like, and silanyl containing groups, such as 2-trimethylsilylethoxymethyl, t-butyldimethylsilyl, triisopropylsilyl, and the like, CURRENT PROTOCOLS IN NUCLEIC ACID CHEMISTRY, John Wiley and Sons, New York, Volume 1, 2000).

[0043] "Optional" or "optionally" as used throughout the disclosure means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, the phrase "the aromatic group is optionally substituted with one or two alkyl substituents" means that the alkyl may but need not be present, and the description includes situations where the aromatic group is substituted with an alkyl group and situations where the aromatic group is not substituted with the alkyl group.

[0044] As used herein, the term "composition" refers to a formulation suitable for administration to an intended animal subject for therapeutic purposes that contains at least one pharmaceutically active compound and at least one pharmaceutically acceptable carrier or excipient.

[0045] The term "pharmaceutically acceptable" indicates that the indicated material does not have properties that would cause a reasonably prudent medical practitioner to avoid administration of the material to a patient, taking into consideration the disease or conditions to be treated and the respective route of administration. For example, it is commonly required that such a material be essentially sterile, e.g., for injectables.

[0046] "Pharmaceutically acceptable salt" refers to a salt which is acceptable for administration to a patient, such as a mammal (e.g., salts having acceptable mammalian safety for a given dosage regime). Such salts can be derived from pharmaceutically acceptable inorganic or organic bases and from pharmaceutically-acceptable inorganic or organic acids, depending on the particular substituents found on the compounds described herein. When compounds of the present disclosure 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. 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, tertiary and quaternary 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, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, meglumine (N-methyl-glucamine) and the like. When compounds of the present disclosure 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. Salts derived from pharmaceutically acceptable acids include acetic, trifluoroacetic, propionic, ascorbic, benzenesulfonic, benzoic, camphosulfonic, citric, ethanesulfonic, fumaric, glycolic, gluconic, glucoronic, glutamic, hippuric, hydrobromic, hydrochloric, isethionic, lactic, lactobionic, maleic, malic, mandelic, methanesulfonic, mucic, naphthalenesulfonic, nicotinic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, hydroiodic, carbonic, tartaric, p-toluenesulfonic, pyruvic, aspartic, benzoic, anthranilic, mesylic, salicylic, p-hydroxybenzoic, phenylacetic, embonic (pamoic), ethanesulfonic, benzenesulfonic, 2-hydroxyethanesulfonic, sulfanilic, stearic, cyclohexylaminosulfonic, algenic, hydroxybutyric, galactaric and galacturonic acid and the like.

[0047] 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, for example, Berge, S. M. et al, "Pharmaceutical Salts", J. Pharmaceutical Science, 1977, 66:1-19). Certain specific compounds of the present disclosure contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

[0048] 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 disclosure.

[0049] As used herein in connection with compounds of the disclosure, the term "synthesizing" and like terms means chemical synthesis from one or more precursor materials.

[0050] The compounds of the present disclosure 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 radioactive isotopes, such as for example tritium (^{3}H), iodine-125 (^{125}I), carbon-14 (^{14}C), carbon-11 (^{11}C) or fluorine-18 (^{18}F). All isotopic variations of the compounds of the present disclosure, whether radioactive or not, are intended to be encompassed within the scope of the present disclosure.

[0051] The term "deuterated" as used herein alone or as part of a group, means substituted deuterium atoms. The term "deuterated analog" as used herein alone or as part of a group, means substituted deuterium atoms in place of hydrogen. The deuterated analog of the disclosure may be a fully or partially deuterium substituted derivative. In some embodiments, the deuterium substituted derivative of the disclosure holds a fully or partially deuterium substituted alkyl, aryl or heteroaryl group.

[0052] The disclosure also embraces isotopically-labeled compounds of the present disclosure which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the disclosure include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, and chlorine, such as, but not limited to ^{2}H (deuterium, D), ^{3}H (tritium), ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{18}F, ^{31}P, ^{32}P, ^{35}S, ^{36}Cl, and ^{125}I. Unless otherwise stated, when a position is designated specifically as "H" or "hydrogen", the position is understood to have hydrogen at its natural abundance isotopic composition or its isotopes, such as deuterium (D) or tritium (^{3}H). Certain isotopically-labeled compounds of the present disclosure (e.g., those labeled with ^{3}H and ^{14}C) are useful in compound and/or substrate tissue distribution assays. Tritiated (*i.e.*, ^{3}H) and carbon-14 (*i.e.*, ^{14}C) and fluorine-18 (^{18}F) isotopes are useful for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (*i.e.*, ^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased in vivo half-life or reduced dosage requirements) and hence may be preferred in some circumstances. Isotopically labeled compounds of the present disclosure can generally be prepared by following procedures analogous to those described in the Schemes and in the Examples herein below, by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

[0053] "Prodrugs" means any compound which releases an active parent drug according to Formula I *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of a

compound of Formula I are prepared by modifying functional groups present in the compound of Formula I in such a way that the modifications may be cleaved *in vivo* to release the parent compound. Prodrugs may be prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved, either in routine manipulation or in vivo, to the parent compounds. Prodrugs include compounds of Formula I wherein a hydroxy, amino, carboxyl or sulfhydryl group in a compound of Formula I is bonded to any group that may be cleaved *in vivo* to regenerate the free hydroxyl, amino, or sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to esters (*e.g.*, acetate, formate, and benzoate derivatives), amides, guanidines, carbamates (*e.g.*, N,N-dimethylaminocarbonyl) of hydroxy functional groups in compounds of Formula I, and the like. Preparation, selection, and use of prodrugs is discussed in T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series; "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985; and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, each of which are hereby incorporated by reference in their entirety.

[0054] "Tautomer" means compounds produced by the phenomenon wherein a proton of one atom of a molecule shifts to another atom. *See*, Jerry March, *Advanced Organic Chemistry: Reactions, Mechanisms and Structures*, Fourth Edition, John Wiley & Sons, pages 69-74 (1992). The tautomers also refer to one of two or more structural isomers that exist in equilibrium and are readily converted from one isomeric form to another. Examples of include keto-enol tautomers, such as acetone/propen-2-ol, imine-enamine tautomers and the like, ring-chain tautomers, such as glucose/2,3,4,5,6-pentahydroxy-hexanal and the like, the tautomeric forms of heteroaryl groups containing a -N=C(H)-NH- ring atom arrangement, such as pyrazoles, imidazoles, benzimidazoles, triazoles, and tetrazoles. Where the compound contains, for example, a keto or oxime group or an aromatic moiety, tautomeric isomerism ('tautomerism') can occur. The compounds described herein may have one or more tautomers and therefore include various isomers. A person of ordinary skill in the art would recognize that other tautomeric ring atom arrangements are possible. All such isomeric forms of these compounds are expressly included in the present disclosure.

[0055] "Isomers" mean compounds having identical molecular Formulae but differ in the nature or sequence of bonding of their atoms or in the arrangement of their atoms in space. 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, 6th edition J. March, John Wiley and Sons, New York, 2007) differ in the chirality of one or more stereocenters.

[0056] Certain compounds of the present disclosure can exist in unsolvated forms as well as solvated forms, including hydrated forms. "Hydrate" refers to a complex formed by combination of water molecules with molecules or ions of the solute. "Solvate" refers to a complex formed by combination of solvent molecules with molecules or ions of the solute. The solvent can be an organic compound, an inorganic compound, or a mixture of both. Solvate is meant to include hydrate. Some examples of solvents include, but are not limited to, methanol, N,N-dimethylformamide, tetrahydrofuran, dimethylsulfoxide, and water. In general, the solvated forms are equivalent to unsolvated forms and are encompassed within the scope of the present disclosure. Certain compounds of the present disclosure may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present disclosure and are intended to be within the scope of the present disclosure.

[0057] "Solid form" refers to a solid preparation (i.e. a preparation that is neither gas nor liquid) of a pharmaceutically active compound that is suitable for administration to an intended animal subject for therapeutic purposes. The solid form includes any complex, such as a salt, co-crystal or an amorphous complex, as well as any polymorph of the compound. The solid form may be substantially crystalline, semi-crystalline or substantially amorphous. The solid form may be administered directly or used in the preparation of a suitable composition having

improved pharmaceutical properties. For example, the solid form may be used in a formulation comprising at least one pharmaceutically acceptable carrier or excipient.

[0058] As used herein in connection with amino acid or nucleic acid sequence, the term "isolate" indicates that the sequence is separated from at least a portion of the amino acid and/or nucleic acid sequences with which it would normally be associated.

[0059] In connection with amino acid or nucleic sequences, the term "purified" indicates that the subject molecule constitutes a significantly greater proportion of the biomolecules in a composition than the proportion observed in a prior composition, e.g., in a cell culture. The greater proportion can be 2-fold, 5-fold, 10-fold, or more than 10-fold, with respect to the proportion found in the prior composition.

[0060] In the context of the use, testing, or screening of compounds that are or may be modulators, the term "contacting" means that the compound(s) are caused to be in sufficient proximity to a particular molecule, complex, cell, tissue, organism, or other specified material that potential binding interactions and/or chemical reaction between the compound and other specified material can occur.

[0061] As used herein, the term "subject" refers to a living organism that is treated with compounds as described herein, including, but not limited to, any mammal, such as a human, other primates, sports animals, animals of commercial interest such as cattle, farm animals such as horses, or pets such as dogs and cats.

[0062] The term "administering" refers to oral administration, administration as a suppository, topical contact, intravenous, intraperitoneal, intramuscular, intralesional, intranasal or subcutaneous administration, or the implantation of a slow-release device *e.g.*, a mini-osmotic pump, to a subject. Administration is by any route, including parenteral and transmucosal (*e.g.*, buccal, sublingual, palatal, gingival, nasal, vaginal, rectal, or transdermal). Parenteral administration includes, *e.g.*, intravenous, intramuscular, intra-arteriole, intradermal, subcutaneous, intraperitoneal, intraventricular, and intracranial. Other modes of delivery include, but are not limited to, the use of liposomal formulations, intravenous infusion, transdermal patches, *etc.*

[0063] In the present context, the term "therapeutically effective" or "effective amount" indicates that a compound or material or amount of the compound or material when administered is sufficient or effective to prevent, alleviate, or ameliorate one or more symptoms of a disease, disorder or medical condition being treated, and/or to prolong the survival of the subject being treated. The therapeutically effective amount will vary depending on the

compound, the disease, disorder or condition and its severity and the age, weight, etc., of the mammal to be treated. In general, satisfactory results in subjects are indicated to be obtained at a daily dosage of from about 0.1 to about 10 g/kg subject body weight. In some embodiments, a daily dose ranges from about 0.10 to 10.0 mg/kg of body weight, from about 1.0 to 3.0 mg/kg of body weight, from about 3 to 10 mg/kg of body weight, from about 3 to 150 mg/kg of body weight, from about 3 to 100 mg/kg of body weight, from about 10 to 100 mg/kg of body weight, from about 10 to 150 mg/kg of body weight, or from about 150 to 1000 mg/kg of body weight. The dosage can be conveniently administered, e.g., in divided doses up to four times a day or in sustained-release form.

[0064] By "assaying" is meant the creation of experimental conditions and the gathering of data regarding a particular result of the exposure to specific experimental conditions. For example, enzymes can be assayed based on their ability to act upon a detectable substrate. A compound can be assayed based on its ability to bind to a particular target molecule or molecules.

[0065] As used herein, the terms "ligand" and "modulator" are used equivalently to refer to a compound that changes (*i.e.*, increases or decreases) the activity of a target biomolecule, *e.g.*, an enzyme such as a kinase. Generally a ligand or modulator will be a small molecule, where "small molecule refers to a compound with a molecular weight of 1500 Daltons or less, 1000 Daltons or less, 800 Daltons or less, or 600 Daltons or less. Thus, an "improved ligand" is one that possesses better pharmacological and/or pharmacokinetic properties than a reference compound, where "better" can be defined by one skilled in the relevant art for a particular biological system or therapeutic use.

[0066] The term "binds" in connection with the interaction between a target and a potential binding compound indicates that the potential binding compound associates with the target to a statistically significant degree as compared to association with proteins generally (*i.e.*, non-specific binding). Thus, the term "binding compound" refers to a compound that has a statistically significant association with a target molecule. In some embodiments, a binding compound interacts with a specified target with a dissociation constant (K_D) of 1 mM or less, 1 μM or less, 100 nM or less, 10 nM or less, or 1 nM or less. In the context of compounds binding to a target, the terms "greater affinity" and "selective" indicates that the compound binds more tightly than a reference compound, or than the same compound in a reference condition, *i.e.*, with a lower dissociation constant. In some embodiments, the greater affinity is at least 2, 3, 4, 5, 8, 10, 50, 100, 200, 400, 500, 1000, or 10,000-fold greater affinity.

[0067] The terms "prevent", "preventing", "prevention" and grammatical variations thereof as used herein, refers to a method of partially or completely delaying or precluding the onset or recurrence of a disease, disorder or condition and/or one or more of its attendant symptoms or barring a subject from acquiring or reacquiring a disorder or condition or reducing a subject's risk of acquiring or requiring a disorder or condition or one or more of its attendant symptoms.

[0068] "Unit dosage form" refers to a composition intended for a single administration to treat a subject suffering from a disease or medical condition. Each unit dosage form typically comprises each of the active ingredients of this disclosure plus pharmaceutically acceptable excipients. Examples of unit dosage forms are individual tablets, individual capsules, bulk powders, liquid solutions, ointments, creams, eye drops, suppositories, emulsions or suspensions. Treatment of the disease or condition may require periodic administration of unit dosage forms, for example: one unit dosage form two or more times a day, one with each meal, one every four hours or other interval, or only one per day. The expression "oral unit dosage form" indicates a unit dosage form designed to be taken orally.

[0069] In addition, abbreviations as used herein have respective meanings as follows:

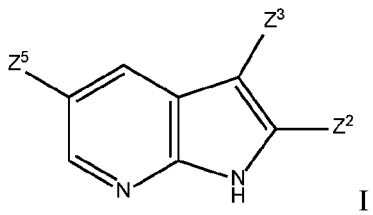
°C	Degree Celsius
AML	Acute myeloid leukemia
ATP	Adenosine triphosphate
BOC	tert-Butoxycarbonyl
BSA	Bovine serum albumin
DCM	Dichloromethane
DEAE	Diethylaminoethyl
DMEM	Dulbecco's Modified Eagle's Medium
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
DTT	Dithiothreitol
EDTA	Ethylenediaminetetraacetic acid
equiv.	equivalents
FBS	Fetal bovine serum

G	Gram
H or hr	Hour
HBTU	*N,N,N',N'*-Tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate
HEPES	4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid
HPLC	High performance liquid chromatography
IMDM	Iscove's Modified Dulbecco's Medium
L	liter
LC-MS or LC/MS	(tandem) liquid chromatography-mass spectrometry
M	Molar
Me	Methyl
MeOH	Methanol
MEM	Minimum essential medium
mg	Milligram
mL or ml	Milliliter
MLL	Mixed lineage leukemia
mM	Millimolar
mmol	Millimole
mol	Mole
MS ESI or MS (ESI)	Mass spectrometry electrospray ionization
MTBE	Methyl tert-butyl ether
N	Normal
nM	Nanomolar
NEAA	Non-essential amino acids

PBS	Phosphate buffered saline
Ph	Phenyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIPS	triisopropylsilyl
μg	Microgram
μL or μl	Microliter
μM	Micromolar

II. Compounds

[0070] Embodiment 1A of this disclosure relates to a compound of Formula I:



I

or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog thereof, wherein:

Z^2 is alkynyl optionally substituted with R^b, aryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl or heteroaryl, wherein each aryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl or heteroaryl is optionally substituted with 1-3 R^1 groups;

Z^3 is hydrogen or halo;

Z^5 is -Cy-L;

Cy is heterocycloalkylene, arylene or heteroarylene, wherein Cy is optionally substituted with 1-2 R^a groups;

L is:

$-C(O)NR^3R^4$, wherein:

R^3 is hydrogen or C_{1-6}alkyl optionally substituted with 1-3 G groups and

R^4 is cycloalkylalkyl, alkoxy, cycloalkyl, heterocycloalkyl, heteroaryl, hydroxyalkylene, cyano, cyanoalkylene, or aminocarbonylalkyl, wherein R^4 is optionally substituted with 1-3 G groups;

or R^3 and R^4, together with the N atom to which they are attached, join to form a heterocycloalkyl or heteroaryl moiety, wherein 1-2 carbon atoms of the heterocycloalkyl or heteroaryl moiety is substituted with 1-2 G groups; or

-C_1-C_3alkyl-heterocycloalkyl, -C(O)-heterocycloalkyl, -N(H)-heterocycloalkyl, -C(O)-cycloalkyl, or -O-heterocycloalkyl, each of which is optionally substituted with 1-3 G groups; or

-C(O)-N(H)-O-R^5 or –NH-C(O)-R^c, wherein:

R^5 is hydrogen, C_{1-6}alkyl or cycloalkyl; and

R^c is C_{1-6}alkyl, cycloalkyl or heterocycloalkyl;

-SO_2-NR^6R^7, -N(H)C(O)NR^6R^7, or -N(H)-SO_2-NR^6R^7, wherein:

R^6 is hydrogen, alkyl, alkylcarbonyl, alkylsulfonyl, cycloalkylamino, or cycloalkyl, wherein each of the alkyl, alkylcarbonyl, alkylsulfonyl, cycloalkylamino, and cycloalkyl are optionally substituted with 1-3 G groups,

R^7 is hydrogen or C_{1-6}alkyl optionally substituted with 1-3 G groups;

or R^6 and R^7, together with the N atom to which they are attached, join to form a heterocycloalkyl or heteoraryl moiety, wherein 1-2 carbon atoms of the heterocycloalkyl or heteroaryl moiety is substituted with 1-2 G groups; or

heterocycloalkyl substituted with 1-3 G groups;

R^1 is hydrogen, C_{1-6}alkyl, cycloalkyl, -C(O)-cycloalkyl, -C(O)alkyl, cyano, cyanoalkyl, cyanocycloalkyl, cyanocycloalkylalkyl, hydroxy, alkoxy, alkoxyalkyl, hydroxyalkyl, halo, haloalkyl, oxo, aryl, arylalkyl, cycloalkylsulfonyl, alkylsulfonyl, alkylsulfonylalkyl, alkylcarbonylaminoalkyl, alkylsulfonylaminoalkyl, heterocycloalkyl optionally substituted with 1-2 R^a, heterocycloalkylalkyl, -NR^6R^7, -C_{1-6}alkylene-NR^6R^7, -C(O)O-alkyl, heterocycloalkyl optionally substituted with 1-2 R^d groups, or heteroaryl optionally substituted with 1-2 R^e groups;

each G is independently C_{1-6}alkyl, -C_1-C_6haloalkyl, halo, amino, alkylamino, dialkylamino, alkylaminoalkyl, -(C_{1-6}alkylene)-amino, -CN, -C(O)-C_{1-6}alkyl, -C(O)-O-C_{1-6}alkyl, -CO_2H, -C(O)-N(H)-C_{1-6}alkyl, oxo, -N(H)-C(O)-C_{1-6}alkyl, -C(=NH)-NH_2, -OH, -N(H)-C(O)-O-C_{1-6}alkyl, -N(H)-C(O)-N(H)-C_{1-6}alkyl, -N(H)-S(O)$_2$- C_{1-6}alkyl , -S(O)$_2$-C_{1-6}alkyl, hydroxyalkyl, cycloalkyl, cycloalkylamino, alkoxy, heterocycloalkyl or heteroaryl,

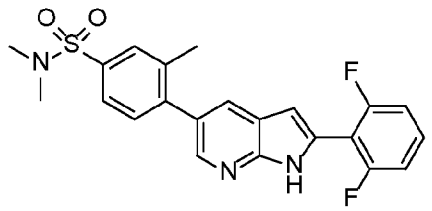
each R^a is independently alkyl, oxo, halo, or hydroxy;

R^b is halo, C_3-C_6cycloalkyl, aryl, heteroaryl, -NR^6R^7, or hydroxy;

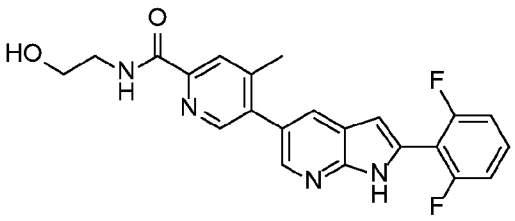
each R^d is independently C_1-C_6alkyl, halo, oxo, alkylaminosulfonyl, alkylsulfonyl, alkylcarbonyl, hydroxyalkyl, or hydroxy; and

each R^e is independently C_{1-6}alkyl, halo, or hydroxy;

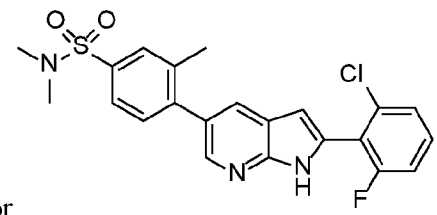
provided that when G is cycloalkyl, Z^2 is alkynyl optionally substituted with C_3-C_6cycloalkyl, -NR^6R^7, or hydroxy;



and further provided that the compound is not



, or



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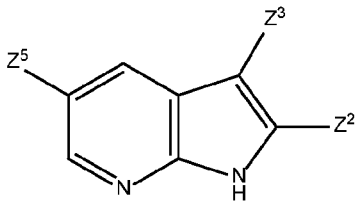
[0071] Embodiment 1B of this disclosure relates to a compound of Formula I:



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or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog thereof, wherein:

Z^2 is alkynyl optionally substituted with R^b, aryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl or heteroaryl, wherein each aryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl or heteroaryl is optionally substituted with 1-3 R^1 groups;

Z^3 is hydrogen or halo;

Z^5 is -Cy-L;

Cy is heterocycloalkylene, arylene or heteroarylene, wherein Cy is optionally substituted with 1-2 R^a groups;

L is:

-$C(O)NR^3R^4$, wherein:

R^3 is hydrogen or C_{1-6}alkyl optionally substituted with 1-3 G groups and

R^4 is alkoxy, hydroxyalkylene, cyano, cyanoalkylene, or aminocarbonylalkyl, wherein R^4 is optionally substituted with 1-3 G groups;

or R^3 and R^4, together with the N atom to which they are attached, join to form a heterocycloalkyl or heteroaryl moiety, wherein 1-2 carbon atoms of the heterocycloalkyl or heteroaryl moiety is substituted with 1-2 G groups; or

-C_{1-3}alkyl-heterocycloalkyl, -C(O)-heterocycloalkyl, -N(H)-heterocycloalkyl, -C(O)-cycloalkyl, or -O-heterocycloalkyl, each of which is optionally substituted with 1-3 G groups; or

-C(O)-N(H)-O-R^5 or –NH-C(O)-R^c, wherein:

R^5 is hydrogen, C_{1-6}alkyl or cycloalkyl; and

R^c is C_{1-6}alkyl, cycloalkyl or heterocycloalkyl; or

-SO_2-NR^6R^7, -N(H)C(O)NR^6R^7, or -N(H)-SO_2-NR^6R^7, wherein:

R^6 is hydrogen, C_{1-6}alkyl, alkylcarbonyl, alkylsulfonyl, cycloalkylamino, or cycloalkyl, wherein each of the C_{1-6}alkyl, alkylcarbonyl, alkylsulfonyl, cycloalkylamino, and cycloalkyl are optionally substituted with 1-3 G groups,

R^7 is hydrogen or C_{1-6}alkyl optionally substituted with 1-3 G groups;

or R^6 and R^7, together with the N atom to which they are attached, join to form a heterocycloalkyl or heteoraryl moiety, wherein 1-2 carbon atoms of the heterocycloalkyl or heteroaryl moiety is substituted with 1-2 G groups; or

heterocycloalkyl substituted with 1-3 G groups;

R^1 is hydrogen, C_{1-6}alkyl, cycloalkyl, -C(O)-cycloalkyl, -C(O)alkyl, cyano, cyanoalkyl, cyanocycloalkyl, cyanocycloalkylalkyl, hydroxy, alkoxy, alkoxyalkyl, hydroxyalkyl, halo, haloalkyl, oxo, aryl, arylalkyl, cycloalkylsulfonyl, alkylsulfonyl, alkylsulfonylalkyl, alkylcarbonylaminoalkyl, alkylsulfonylaminoalkyl, heterocycloalkyl optionally substituted with 1-2 R^a, heterocycloalkylalkyl, $-NR^6R^7$, $-C_{1-6}$alkylene-NR^6R^7, -C(O)O-alkyl, heterocycloalkyl optionally substituted with 1-2 R^d groups, or heteroaryl optionally substituted with 1-2 R^e groups;

each G is independently C_{1-6}alkyl, C_{1-6}haloalkyl, halo, amino, alkylamino, dialkylamino, alkylaminoalkyl, -(C_{1-6}alkylene)-amino, -CN, -C(O)-C_{1-6}alkyl, -C(O)-O-C_{1-6}alkyl, $-CO_2H$, -C(O)-N(H)-C_{1-6}alkyl, oxo, -N(H)-C(O)-C_{1-6}alkyl, -C(=NH)-NH_2, -OH, -N(H)-C(O)-O-C_{1-6}alkyl, -N(H)-C(O)-N(H)-C_{1-6}alkyl, -N(H)-$S(O)_2$-C_{1-6}alkyl , -$S(O)_2$-C_{1-6}alkyl, hydroxyalkyl, cycloalkyl, cycloalkylamino, alkoxy, heterocycloalkyl or heteroaryl,

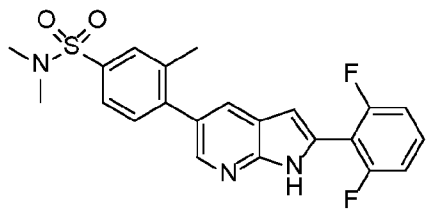
each R^a is independently alkyl, oxo, halo, or hydroxy;

R^b is halo, C_{3-6}cycloalkyl, aryl, heteroaryl, $-NR^6R^7$, or hydroxy;

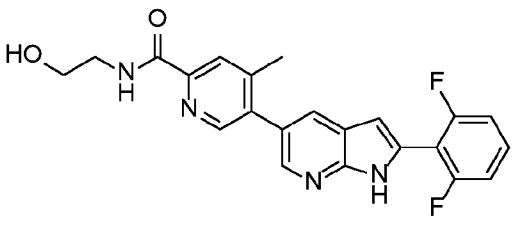
each R^d is independently C_{1-6}alkyl, halo, oxo, alkylaminosulfonyl, alkylsulfonyl, alkylcarbonyl, hydroxyalkyl, or hydroxy; and

each R^e is independently C_{1-6}alkyl, halo, or hydroxy;

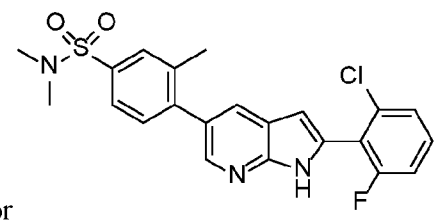
provided that when G is cycloalkyl, Z^2 is alkynyl optionally substituted with C_3-C_6cycloalkyl, $-NR^6R^7$, or hydroxy;



and further provided that the compound is not



, or



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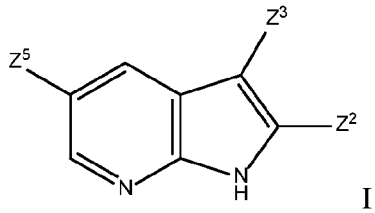
[0072] Embodiment 1C of this disclosure relates to a compound of Formula I:



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or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog thereof, wherein:

Z^2 is alkynyl optionally substituted with R^b, aryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl or heteroaryl, wherein each aryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl or heteroaryl is optionally substituted with 1-3 R^1 groups;

Z^3 is hydrogen or halo;

Z^5 is -Cy-L;

Cy is heterocycloalkylene, arylene or heteroarylene, wherein Cy is optionally substituted with 1-2 R^a groups;

L is:

-C(O)NR^3R^4, wherein:

R^3 is hydrogen or C_{1-6}alkyl optionally substituted with 1-3 G groups and

R^4 is alkoxy, hydroxyalkylene, cyano, cyanoalkylene, aminocarbonylalkyl, or -(C_0-C_3)alkyl-cycloalkyl-(C_0-C_3)alkyl-CN, wherein R^4 is optionally substituted with 1-3 G groups;

or R^3 and R^4, together with the N atom to which they are attached, join to form a heterocycloalkyl or heteroaryl moiety, wherein 1-2 carbon atoms of the heterocycloalkyl or heteroaryl moiety is substituted with 1-2 G groups; or

-C_{1-3}alkyl-heterocycloalkyl, -C(O)-heterocycloalkyl, -N(H)-heterocycloalkyl, -C(O)-cycloalkyl, or -O-heterocycloalkyl, each of which is optionally substituted with 1-3 G groups; or

-C(O)-N(H)-O-R^5 or –NH-C(O)-R^c, wherein:

R^5 is hydrogen, C_{1-6}alkyl or cycloalkyl; and

R^c is C_{1-6}alkyl, cycloalkyl or heterocycloalkyl; or

$-SO_2-NR^6R^7$, $-N(H)C(O)NR^6R^7$, or $-N(H)-SO_2-NR^6R^7$, wherein:

R^6 is hydrogen, C_{1-6}alkyl, alkylcarbonyl, alkylsulfonyl, cycloalkylamino, or cycloalkyl, wherein each of the C_{1-6}alkyl, alkylcarbonyl, alkylsulfonyl, cycloalkylamino, and cycloalkyl are optionally substituted with 1-3 G groups,

R^7 is hydrogen or C_{1-6}alkyl optionally substituted with 1-3 G groups;

or R^6 and R^7, together with the N atom to which they are attached, join to form a heterocycloalkyl or heteoraryl moiety, wherein 1-2 carbon atoms of the heterocycloalkyl or heteroaryl moiety is substituted with 1-2 G groups; or

heterocycloalkyl substituted with 1-3 G groups;

R^1 is hydrogen, C_{1-6}alkyl, cycloalkyl, -C(O)-cycloalkyl, -C(O)alkyl, cyano, cyanoalkyl, cyanocycloalkyl, cyanocycloalkylalkyl, hydroxy, alkoxy, alkoxyalkyl, hydroxyalkyl, halo, haloalkyl, oxo, aryl, arylalkyl, cycloalkylsulfonyl, alkylsulfonyl, alkylsulfonylalkyl, alkylcarbonylaminoalkyl, alkylsulfonylaminoalkyl, heterocycloalkyl optionally substituted with 1-2 R^a, heterocycloalkylalkyl, $-NR^6R^7$, $-C_{1-6}$alkylene-NR^6R^7, -C(O)O-alkyl, heterocycloalkyl optionally substituted with 1-2 R^d groups, or heteroaryl optionally substituted with 1-2 R^e groups;

each G is independently C_{1-6}alkyl, C_{1-6}haloalkyl, halo, amino, alkylamino, dialkylamino, alkylaminoalkyl, -(C_{1-6}alkylene)-amino, -CN, -C(O)-C_{1-6}alkyl, -C(O)-O-C_{1-6}alkyl, $-CO_2H$, -C(O)-N(H)-C_{1-6}alkyl, oxo, -N(H)-C(O)-C_{1-6}alkyl, $-C(=NH)-NH_2$, -OH, -N(H)-C(O)-O-C_{1-6}alkyl, -N(H)-C(O)-N(H)-C_{1-6}alkyl, -N(H)-$S(O)_2$-C_{1-6}alkyl, $-S(O)_2-C_{1-6}$alkyl, hydroxyalkyl, cycloalkyl, cycloalkylamino, alkoxy, heterocycloalkyl or heteroaryl,

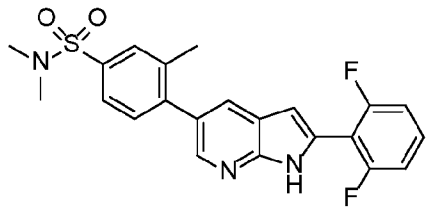
each R^a is independently alkyl, oxo, halo, or hydroxy;

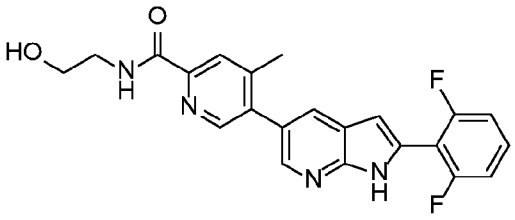
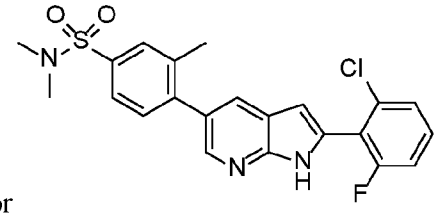
R^b is halo, C_{3-6}cycloalkyl, aryl, heteroaryl, $-NR^6R^7$, or hydroxy;

each R^d is independently C_{1-6}alkyl, halo, oxo, alkylaminosulfonyl, alkylsulfonyl, alkylcarbonyl, hydroxyalkyl, or hydroxy; and

each R^e is independently C_{1-6}alkyl, halo, or hydroxy;

provided that when G is cycloalkyl, Z^2 is alkynyl optionally substituted with C_3-C_6cycloalkyl, $-NR^6R^7$, or hydroxy;

and further provided that the compound is not  ,

 , or  .

[0073] Embodiment 2 of this disclosure relates to the compound according to Embodiment IA, IB, or IC wherein:

Z^2 is ethynylene optionally substituted with C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-6}cycloalkyl, aryl, -C_1-C_6alkylene-NR^6R^7, or hydroxyalkylene; or

Z^2 is phenyl, cyclohexanyl, cyclohexenyl , pyrazolyl, pyrimidinyl, thiazolyl, pyridyl, pyridazinyl , pyrrolyl, dihydropyrrolyl, dihydropyranyl, dihydropyradinyl, tetrahydropyridyl, dihydrothiopyranyl, dihydrothiopyranyl oxide, dihydrothiopyranyl dioxide, wherein each Z^2 is optionally substituted with 1-2 R^1 groups;

Z^3 is hydrogen or halo;

Cy is phenyl, 1H-indazolyl, pyridyl, quinolinyl, isoindolinyl, or thiophenyl, wherein Cy is optionally substituted with 1-2 R^a groups;

L is

-$C(O)NR^3R^4$, wherein:

R^3 is hydrogen or C_{1-6}alkyl;

R^4 is cyano or cyano-C_{1-6}alkylene optionally substituted with 1-3 G groups;

or R^3 and R^4, together with the N atom to which they are attached, join to form a 4-6 membered heterocycloalkyl moiety substituted with 1-2 G groups; or

-C(O)-N(H)-O-R^5, wherein

R^5 is hydrogen or C_{1-6}alkyl; or

-SO_2-NR^6R^7, -N(H)C(O)NR^6R^7, and –N(H)-SO_2-NR^6R^7, wherein:

R^6 is hydrogen, C_{1-6}alkyl or C_{3-6}cylcoalkyl;

R^7 is hydrogen or C_{1-6}alkyl;

or R^6 and R^7, together with the N atom to which they are attached, join to form a heterocycloalkyl moiety substituted with 1-2 G groups;

heterocycloalkyl substituted with 1-2 G groups; C_{1-3}alkyl-heterocycloalkyl, -C(O)-heterocycloalkyl, -N(H)-heterocycloalkyl, or -O-heterocycloalkyl;

R^1 is hydrogen, cycloalkyl, -C(O)-cycloalkyl, C_{1-6}alkyl, cyano, hydroxy, alkoxy, halo, haloalkyl, oxo, phenyl, heterocycloalkyl, heterocycloalkylalkyl, - C_{1-6}alkylene-NR^6R^7, -C(O)O-alkyl, or heteroaryl optionally substituted with 1-2 R^e groups;

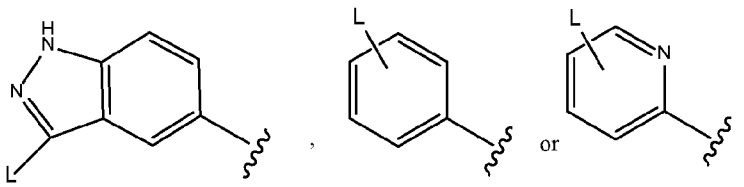
each G is independently C_{1-6}alkyl, halo, amino, -NH-C_{1-6}alkyl, -N(C_{1-6}alkyl)$_2$, -(C_{1-6}alkylene)-N(H)-C_{1-6}alkyl, -CN, -C(O)-C_{1-6}alkyl, -C(O)-N(H)-C_{1-6}alkyl, -N(H)-C(O)-C_{1-6}alkyl, -C(=NH)-NH_2, -N(H)-C(O)-O-C_{1-6}alkyl, -N(H)-C(O)-N(H)-C_{1-6}alkyl, -N(H)-S(O)$_2$-C_{1-6}alkyl, -S(O)$_2$-C_{1-6}alkyl, C_{3-6}cycloalkyl, -N(H)-C_{3-6}cycloalkyl, C_1-C_6alkoxy, 5-6 membered heterocycloalkyl or 5-6 membered heteroaryl, provided that when G is C_{3-6}cycloalkyl, Z^2 is optionally substituted with C_{1-6}alkyl, C_{3-6}cycloalkyl, - C_1-C_6alkyl-NR^6R^7, or hydroxyalkylene; and

each R^a is independently oxo, halo or hydroxy.

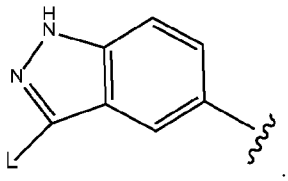
[0074] Embodiment 3 of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, or 2, wherein L is -SO_2-NR^6R^7, -C(O)NR^3R^4, -C(O)-N(H)-O-R^5, -N(H)-SO_2-NR^6R^7, or -N(H)C(O)NR^6R^7.

[0075] Embodiment 4 of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, or 2-3, wherein L is -C(O)NR^3R^4.

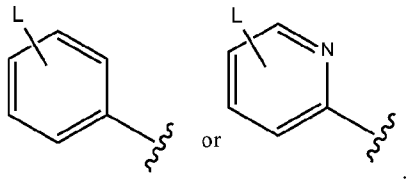
[0076] Embodiment 5(a) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, or 2-4, wherein Z^5 is



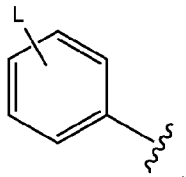
[0077] Embodiment 5(b) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4 or 5(a), wherein Z^5 is



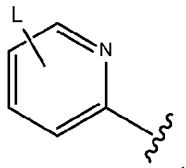
[0078] Embodiment 5(c) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4 or 5(a), wherein Z^5 is



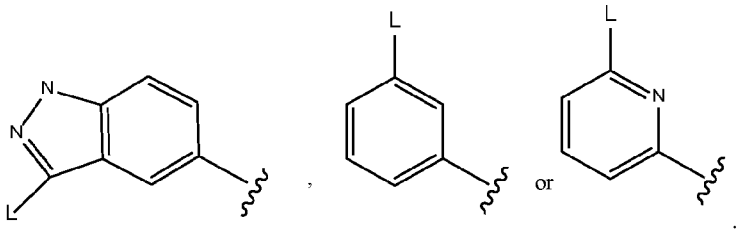
[0079] Embodiment 5(d) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4 or 5(a), wherein Z^5 is



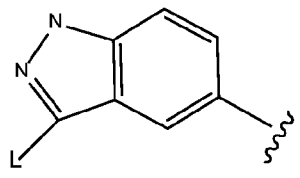
[0080] Embodiment 5(e) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4 or 5(a), wherein Z^5 is



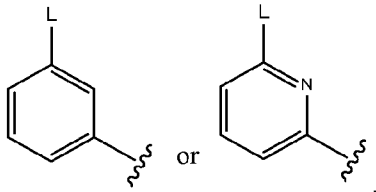
[0081] Embodiment 6(a) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4 or 5(a) wherein Z^5 is:



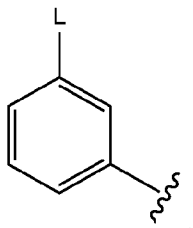
[0082] Embodiment 6(b) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a) or 6(a) wherein Z^5 is:



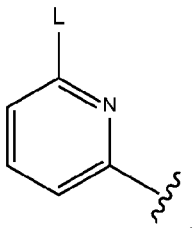
[0083] Embodiment 6(c) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a) or 6(a) wherein Z^5 is:



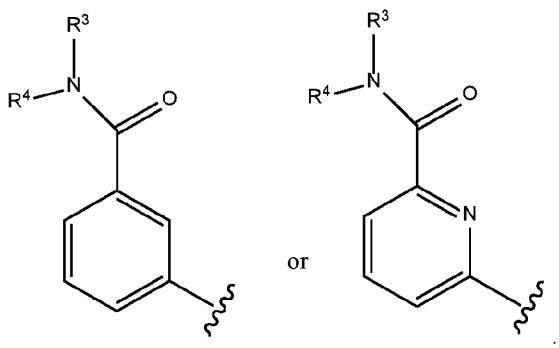
[0084] Embodiment 6(d) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a) or 6(a) wherein Z^5 is:



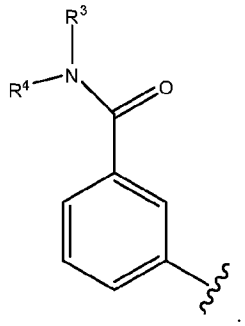
[0085] Embodiment 6(e) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a) or 6(a) wherein Z^5 is:



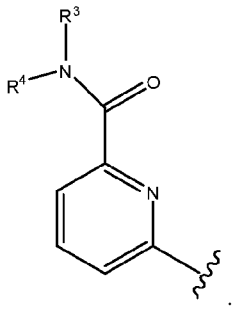
[0086] Embodiment 7(a) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a) or 6(a), wherein Z^5 is:



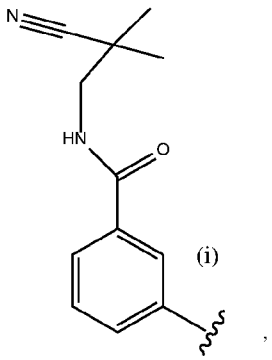
[0087] Embodiment 7(b) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a) , 6(a) or 7(a), wherein Z^5 is:



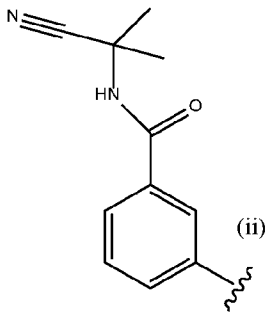
[0088] Embodiment 7(c) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a), 6(a) or 7(a), wherein Z^5 is:



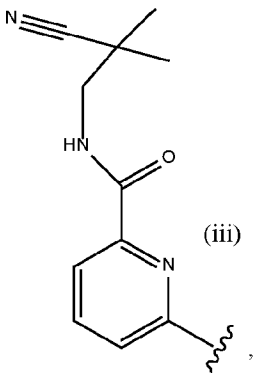
[0089] Embodiment 8(a) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C,2-4, 5(a), 6(a) or 7(a) wherein Z^5 is:



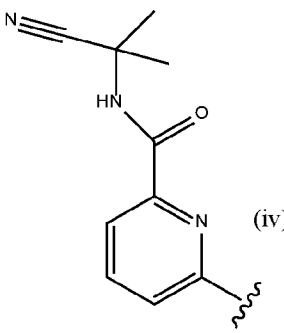
(i),



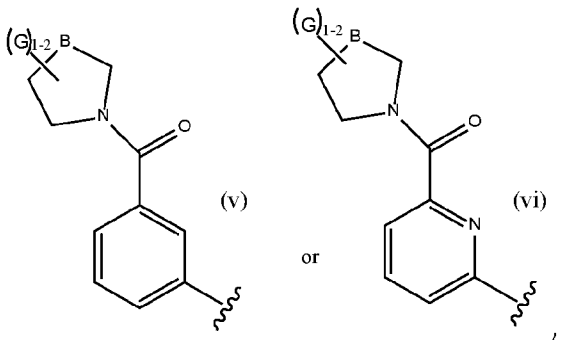
(ii),



(iii),



(iv),



wherein B is a bond, methylene or ethylene.

[0090] Embodiment 8(b) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a), 6(a), 7(a) or 8(a), wherein Z^5 is moiety (i), (ii), (iii) or (iv) in Embodiment 8(a).

[0091] Embodiment 8(c) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a), 6(a), 7(a) or 8(a), wherein Z^5 is moiety (i) or (ii) in Embodiment 8(a).

[0092] Embodiment 8(d) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a), 6(a), 7(a) or 8(a), wherein Z^5 is moiety (iii) or (iv) in Embodiment 8(a).

[0093] Embodiment 8(d) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a), 6(a), 7(a) or 8(a), wherein Z^5 is moiety (v) or (vi) in Embodiment 8(a).

[0094] Embodiment 8(e) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a), 6(a), 7(a) or 8(a), wherein Z^5 is moiety (i) in Embodiment 8(a).

[0095] Embodiment 8(f) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a), 6(a), 7(a) or 8(a), wherein Z^5 is moiety (ii) in Embodiment 8(a).

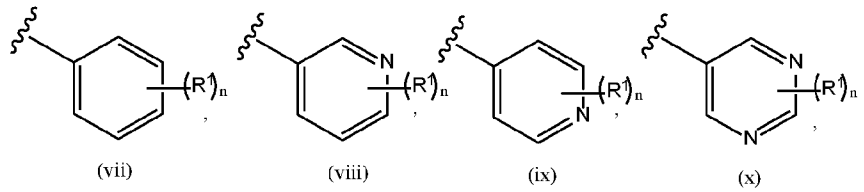
[0096] Embodiment 8(g) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a), 6(a), 7(a) or 8(a), wherein Z^5 is moiety (iii) in Embodiment 8(a).

[0097] Embodiment 8(h) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a), 6(a), 7(a) or 8(a), wherein Z^5 is moiety (iv) in Embodiment 8(a).

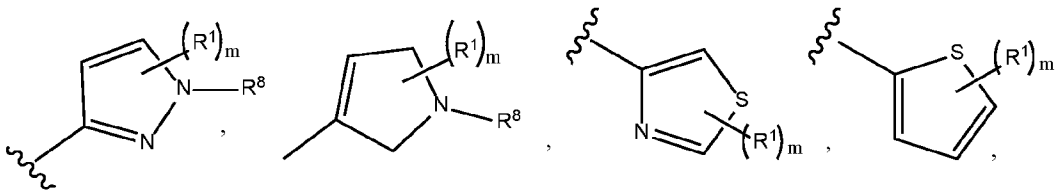
[0098] Embodiment 8(i) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a), 6(a), 7(a) or 8(a), wherein Z^5 is moiety (v) in Embodiment 8(a).

[0099] Embodiment 8(j) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a), 6(a), 7(a) or 8(a), wherein Z^5 is moiety (vi) in Embodiment 8(a).

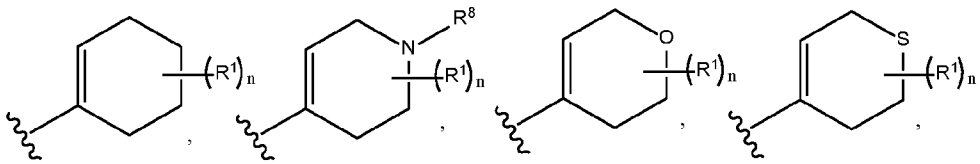
[0100] Embodiment 9(a) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a)-5(e), 6(a) -6(e), 7(a)-7(c) or 8(a)-8(j), wherein Z^2 is:



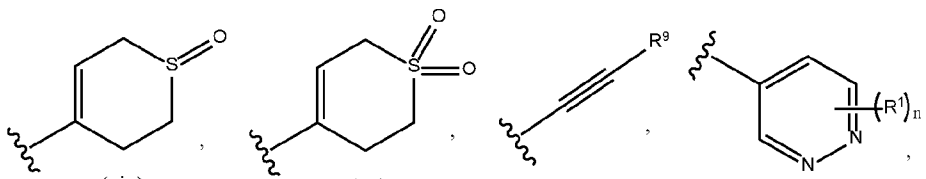
(vii) (viii) (ix) (x)



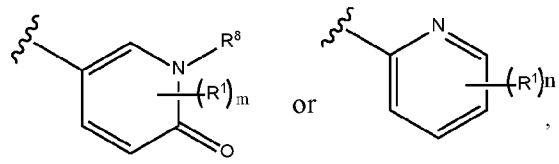
(xi) (xii) (xiii) (xiv)



(xv) (xvi) (xvii) (xviii)



(xix) (xx) (xxi) (xxii)



(xxiii) or (xxiv)

wherein

m is 0-2;

n is 0-3;

R^8 is hydrogen, C_{1-6}alkyl, -C(O)O-C_{1-6}alkyl, C_{3-6}cycloalkyl, -C(O)C_{3-6}cycloalkyl, aryl-C_{1-6}alkyl, 5-6 membered heterocycloalkyl-C_{1-6}alkyl or C_{1-6}haloalkyl; and

R^9 is C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-6}cycloalkyl, aryl, -C_{1-6}alkylene-NR^6R^7, hydroxy-C_{1-6}alkylene or hydroxy.

[0101] Embodiment 9(b) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a)-5(e), 6(a)-6(e), 7(a)-7(c), 8(a)-8(j) or (9a), wherein Z^5 is moiety (viii), (ix), (x), (xxii), (xxiii) or (xxiv) in Embodiment 9(a).

[0102] Embodiment 9(c) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a)-5(e), 6(a)-6(e), 7(a)-7(c), 8(a)-8(j) or (9a), wherein Z^5 is moiety (xi), (xii), (xiii) or (xiv) in Embodiment 9(a).

[0103] Embodiment 9(d) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a)-5(e), 6(a) 6(e), 7(a)-7(c), 8(a)-8(j) or (9a), wherein Z^5 is moiety (xv), (xvi), (xvii) or (xviii) in Embodiment 9(a).

[0104] Embodiment 9(e) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a)-5(e), 6(a)-6(e), 7(a)-7(c), 8(a)-8(j) or (9a), wherein Z^5 is moiety (vii) in Embodiment 9(a).

[0105] Embodiment 9(f) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a)-5(e), 6(a)-6(e), 7(a)-7(c), 8(a)-8(j) or (9a), wherein Z^5 is moiety (viii) in Embodiment 9(a).

[0106] Embodiment 9(g) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a)-5(e), 6(a)-6(e), 7(a)-7(c), 8(a)-8(j) or (9a), wherein Z^5 is moiety (ix) in Embodiment 9(a).

[0107] Embodiment 9(h) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a)-5(e), 6(a)-6(e), 7(a)-7(c), 8(a)-8(j) or (9a), wherein Z^5 is moiety (x) in Embodiment 9(a).

[0108] Embodiment 9(i) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a)-5(e), 6(a)-6(e), 7(a)-7(c), 8(a)-8(j) or (9a), wherein Z^5 is moiety (xi) in Embodiment 9(a).

[0109] Embodiment 9(j) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a)-5(e), 6(a)-6(e), 7(a)-7(c), 8(a)-8(j) or (9a), wherein Z^5 is moiety (xii) in Embodiment 9(a).

[0110] Embodiment 9(k) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a)-5(e), 6(a)-6(e), 7(a)-7(c), 8(a)-8(j) or (9a), wherein Z^5 is moiety (xiii) in Embodiment 9(a).

[0111] Embodiment 9(l) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a)-5(e), 6(a)-6(e), 7(a)-7(c), 8(a)-8(j) or (9a), wherein Z^5 is moiety (xiv) in Embodiment 9(a).

[0112] Embodiment 9(m) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a)-5(e), 6(a)-6(e), 7(a)-7(c), 8(a)-8(j) or (9a), wherein Z^5 is moiety (xv) in Embodiment 9(a).

[0113] Embodiment 9(n) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a)-5(e), 6(a)-6(e), 7(a)-7(c), 8(a)-8(j) or (9a), wherein Z^5 is moiety (xvi) in Embodiment 9(a).

[0114] Embodiment 9(o) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a)-5(e), 6(a)-6(e), 7(a)-7(c), 8(a)-8(j) or (9a), wherein Z^5 is moiety (xvii) in Embodiment 9(a).

[0115] Embodiment 9(p) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a)-5(e), 6(a)-6(e), 7(a)-7(c), 8(a)-8(j) or (9a), wherein Z^5 is moiety (xviii) in Embodiment 9(a).

[0116] Embodiment 9(q) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a)-5(e), 6(a)-6(e), 7(a)-7(c), 8(a)-8(j) or (9a), wherein Z^5 is moiety (xix) in Embodiment 9(a).

[0117] Embodiment 9(r) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a)-5(e), 6(a)-6(e), 7(a)-7(c), 8(a)-8(j) or (9a), wherein Z^5 is moiety (xx) in Embodiment 9(a).

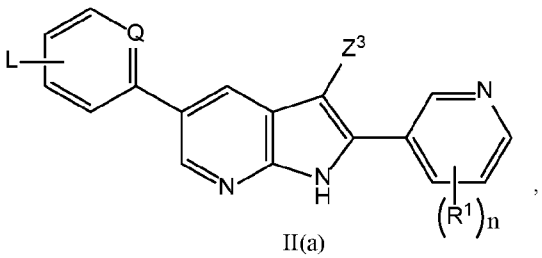
[0118] Embodiment 9(s) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a)-5(e), 6(a)-6(e), 7(a)-7(c), 8(a)-8(j) or (9a), wherein Z^5 is moiety (xxi) in Embodiment 9(a).

[0119] Embodiment 9(t) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a)-5(e), 6(a)-6(e), 7(a)-7(c), 8(a)-8(j) or (9a), wherein Z^5 is moiety (xxii) in Embodiment 9(a).

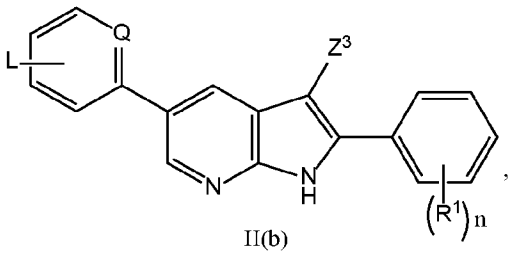
[0120] Embodiment 9(u) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a)-5(e), 6(a)-6(e), 7(a)-7(c), 8(a)-8(j) or (9a), wherein Z^5 is moiety (xiii) in Embodiment 9(a).

[0121] Embodiment 9(v) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a)-5(e), 6(a)-6(e), 7(a)-7(c), 8(a)-8(j) or (9a), wherein Z^5 is moiety (xxiv) in Embodiment 9(a).

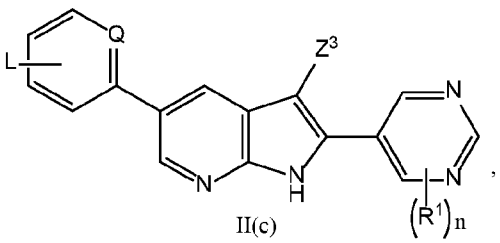
[0122] Embodiment 10(a) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a), or (9a), having one of the following Formulae:



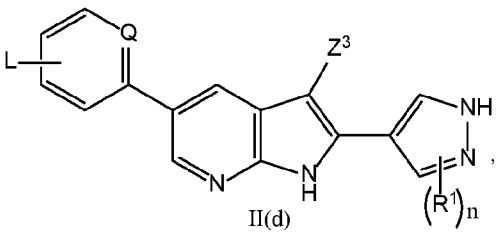
II(a)



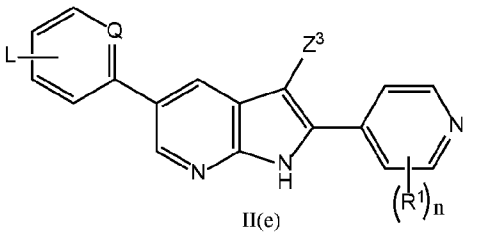
II(b)



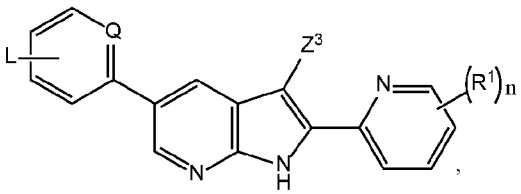
II(c)



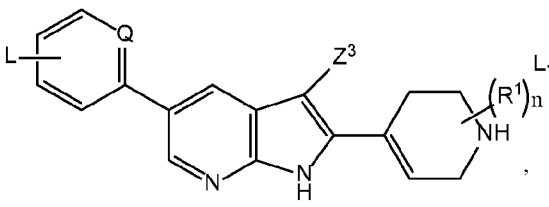
II(d)



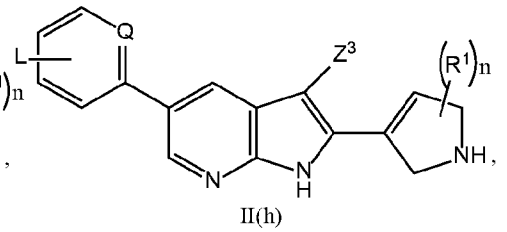
II(e)



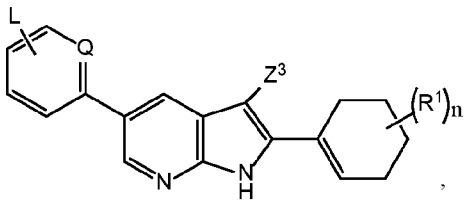
II(f)



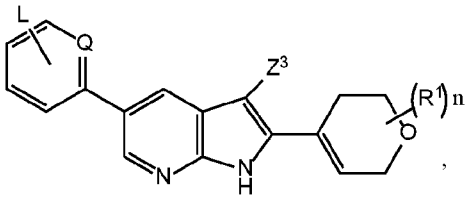
II(g)



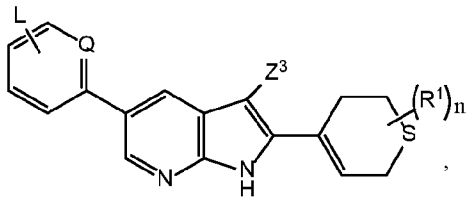
II(h)



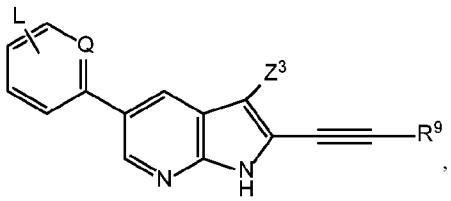
II(i)



II(j)



II(k)



II(l)

or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog of any one of the above Formulae, wherein:

Q is N or CH; and

n is 0-2.

[0123] Embodiment 10(b) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a), (9a), or 10(a) having one of Formulae II(a), II(c), II(e), II(f) or II(g), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog of Formulae II(a), II(c), II(e), II(f) or II(g).

[0124] Embodiment 10(c) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a), (9a), or 10(a) having one of Formulae II(j) or II(k), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog of Formulae II(j) or II(k).

[0125] Embodiment 10(d) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a), (9a), or 10(a) having one of Formulae II(b) or II(i), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog of Formulae II(b) or II(i).

[0126] Embodiment 10(e) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a), (9a), or 10(a) having one of Formulae II(d) or II(h), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog of Formulae II(d) or II(h).

[0127] Embodiment 10(f) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a), (9a), or 10(a) having Formulae II(l), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog thereof.

[0128] Embodiment 10(g) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a), (9a), or 10(a) having Formulae II(a), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog thereof.

[0129] Embodiment 10(h) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a), (9a), or 10(a) having Formulae II(b), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog thereof.

[0130] Embodiment 10(i) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a), (9a), or 10(a) having Formulae II(c), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog thereof.

[0131] Embodiment 10(k) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a), (9a), or 10(a) having Formulae II(d), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog thereof.

[0132] Embodiment 10(m) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a), (9a), or 10(a) having Formulae II(e), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog thereof.

[0133] Embodiment 10(n) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a), (9a), or 10(a) having Formulae II(f), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog thereof.

[0134] Embodiment 10(o) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a), (9a), or 10(a) having Formulae II(g), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog thereof.

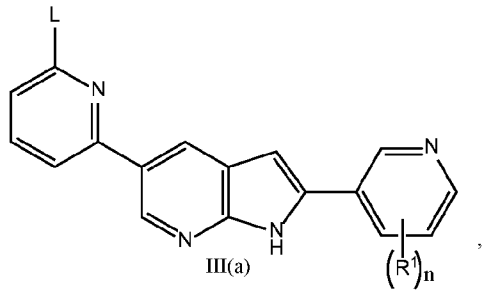
[0135] Embodiment 10(p) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a), (9a), or 10(a) having Formulae II(h), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog thereof.

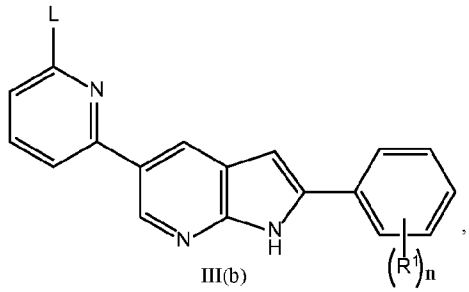
[0136] Embodiment 10(q) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a), (9a), or 10(a) having Formulae II(i), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog thereof.

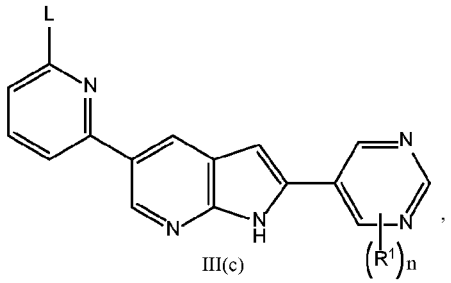
[0137] Embodiment 10(r) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a), (9a), or 10(a) having Formulae II(j), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog thereof.

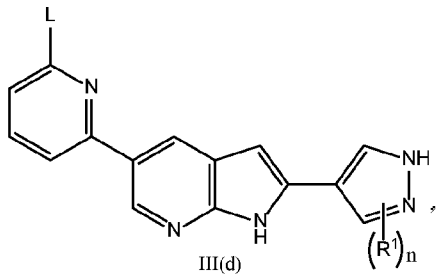
[0138] Embodiment 10(s) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a), (9a), or 10(a) having Formulae II(k), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog thereof.

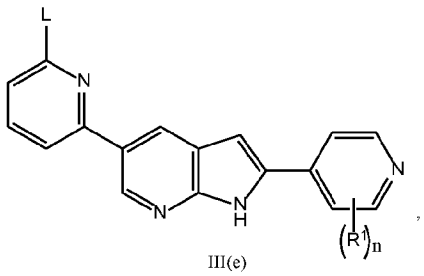
[0139] Embodiment 11(a) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a), 6(a), (9a), or 10(a) having one of the following Formulae:

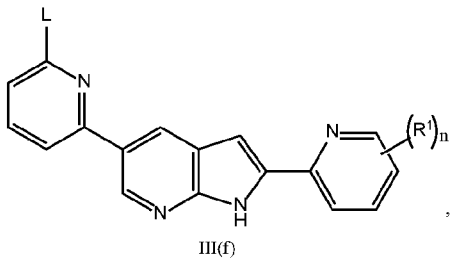

III(a)

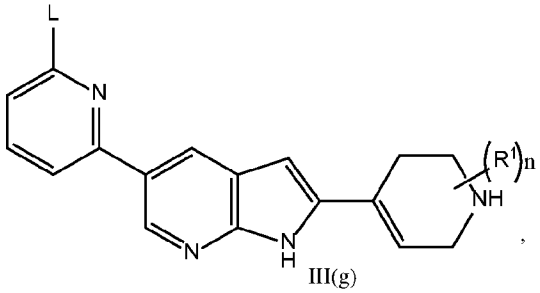

III(b)

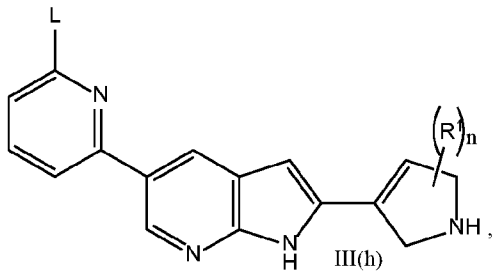

III(c)

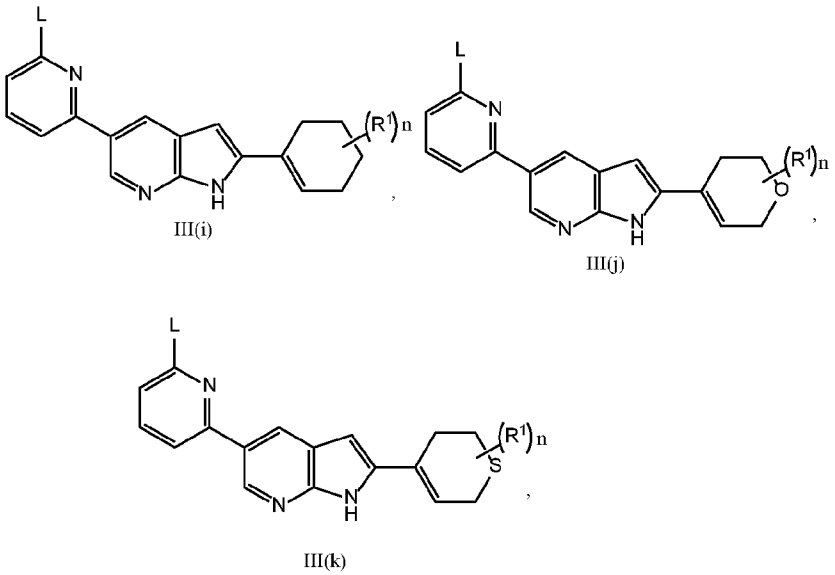

III(d)


III(e)


III(f)


III(g)


III(h)



or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog of any one of the above Formulae, wherein:

n is 0-2;

L is $-C(O)NR^3R^4$;

R^3 is hydrogen or C_{1-6}alkyl;

R^4 is cyano or cyano-C_{1-6}alkylene optionally substituted with halo or hydroxy;

or R^3 and R^4, together with the N atom to which they are attached, join to form a 4-6 membered heterocycloalkyl moiety substituted with 1-2 G groups.

[0140] Embodiment 11(b) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a), 6(a), (9a), 10(a) or 11(a) having one of Formulae III(a), III(c), III(e), III(f) or III(g), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog of Formulae III(a), III(c), III(e), III(f) or III(g).

[0141] Embodiment 11(c) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a), 6(a), (9a), 10(a) or 11(a) having one of Formulae III(b) or III(i), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog of Formulae III(b) or III(i).

[0142] Embodiment 11(d) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a), 6(a), (9a), 10(a) or 11(a) having one of Formulae III(j) or III(k), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog of Formulae III(j) or III(k).

[0143] Embodiment 11(e) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a), 6(a), (9a), 10(a) or 11(a) having one of Formulae III(b) or III(i), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog of Formulae III(b) or III(i).

[0144] Embodiment 11(f) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a), 6(a), (9a), 10(a) or 11(a) having one of Formulae III(d) or III(h), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog of Formulae III(d) or III(h).

[0145] Embodiment 11(g) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a), 6(a), (9a), 10(a) or 11(a) having Formulae III(a), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog thereof.

[0146] Embodiment 11(h) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a), 6(a), (9a), 10(a) or 11(a) having Formulae III(b), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog thereof.

[0147] Embodiment 11(i) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a), 6(a), (9a), 10(a) or 11(a) having Formulae III(c), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog thereof.

[0148] Embodiment 11(j) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a), 6(a), (9a), 10(a) or 11(a) having Formulae III(d), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog thereof.

[0149] Embodiment 11(k) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a), 6(a), (9a), 10(a) or 11(a) having Formulae III(e), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog thereof.

[0150] Embodiment 11(l) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a), 6(a), (9a), 10(a) or 11(a) having Formulae III(f), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog thereof.

[0151] Embodiment 11(m) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a), 6(a), (9a), 10(a) or 11(a) having Formulae III(g), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog thereof.

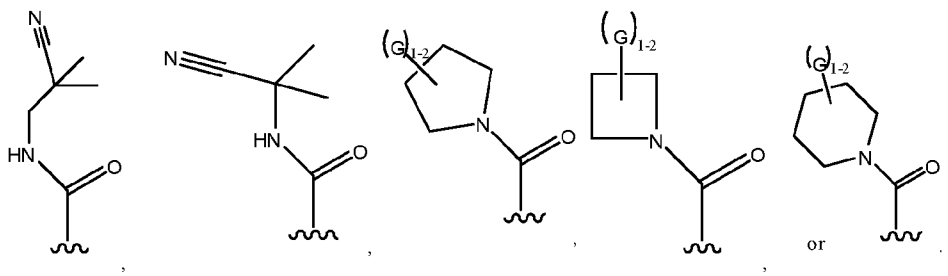
[0152] Embodiment 11(n) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a), 6(a), (9a), 10(a) or 11(a) having Formulae III(h), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog thereof.

[0153] Embodiment 11(o) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a), 6(a), (9a), 10(a) or 11(a) having Formulae III(i), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog thereof.

[0154] Embodiment 11(p) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a), 6(a), (9a), 10(a) or 11(a) having Formulae III(j), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog thereof.

[0155] Embodiment 11(q) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a), 6(a), (9a), 10(a) or 11(a) having Formulae III(k), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog thereof.

[0156] Embodiment 12(a) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a)-5(e), 6(a) -6(e), 7(a)-7(c), 8(a)-8(j), (9a)-9(v), 10(a)-10(s), or 11(a)-11(q), wherein L is one of the following moieties:



[0157] Embodiment 12(b) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a)-5(e), 6(a) -6(e), 7(a)-7(c), 8(a)-8(j), (9a)-9(v), 10(a)-10(s), 11(a)-11(q), or 12(a), wherein L is moiety (xxv) or (xxvi) in Embodiment 12(a).

[0158] Embodiment 12(c) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a)-5(e), 6(a) -6(e), 7(a)-7(c), 8(a)-8(j), (9a)-9(v), 10(a)-10(s), 11(a)-11(q), or 12(a), wherein L is moiety (xxvii), (xxviii) or (xxix) in Embodiment 12(a).

[0159] Embodiment 12(d) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a)-5(e), 6(a) -6(e), 7(a)-7(c), 8(a)-8(j), (9a)-9(v), 10(a)-10(s), 11(a)-11(q), or 12(a), wherein L is moiety (xxv), in Embodiment 12(a).

[0160] Embodiment 12(e) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a)-5(e), 6(a) -6(e), 7(a)-7(c), 8(a)-8(j), (9a)-9(v), 10(a)-10(s), 11(a)-11(q), or 12(a), wherein L is moiety (xxvi) in Embodiment 12(a).

[0161] Embodiment 12(f) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a)-5(e), 6(a) -6(e), 7(a)-7(c), 8(a)-8(j), (9a)-9(v), 10(a)-10(s), 11(a)-11(q), or 12(a), wherein L is moiety (xxvii) in Embodiment 12(a).

[0162] Embodiment 12(g) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a)-5(e), 6(a) -6(e), 7(a)-7(c), 8(a)-8(j), (9a)-9(v), 10(a)-10(s), 11(a)-11(q), or 12(a), wherein L is moiety (xxviii) in Embodiment 12(a).

[0163] Embodiment 12(h) of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a)-5(e), 6(a) -6(e), 7(a)-7(c), 8(a)-8(j), (9a)-9(v), 10(a)-10(s), 11(a)-11(q), or 12(a), wherein L is moiety (xxix) in Embodiment 12(a).

[0164] Embodiment 13 of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a)-5(e), 6(a) -6(e), 7(a)-7(c), 8(a)-8(j), (9a)-9(v), 10(a)-10(s), 11(a)-11(q), or 12(a)-12(h), wherein R^1 is C_{1-3}alkyl, C_{1-3}haloalkyl, C_{3-6}cycloalkyl, -C_{1-3}alkylene-CN, cyano, -(C_{1-3}alkylene)-C_{1-3}alkoxy, heterocycloalkyl, -C(O)-C_{3-6}cycloalkyl.

[0165] Embodiment 14(a) of this disclosure relates to the compound according toany one of Embodiments 1A, 1B, 1C, 2-4, 5(a)-5(e), 6(a) -6(e), 7(a)-7(c), 8(a)-8(j), (9a)-9(v), 10(a)-10(s), 11(a)-11(q), or 12(a)-12(h) or 13, wherein R^1 is -CH_3, -CHF_2, -CH_2F, -CF_3, cyclopropyl, -C_{1-3}alkylene-CN, cyano, methoxy-(C_{1-3}alkylene)-, piperidinyl, morpholinyl, tetrahydrofuranyl, or -C(O)-cyclopropyl.

[0166] Embodiment 14(b) of this disclosure relates to the compound according toany one of Embodiments 1A, 1B, 1C, 2-4, 5(a)-5(e), 6(a) -6(e), 7(a)-7(c), 8(a)-8(j), (9a)-9(v), 10(a)-10(s), 11(a)-11(q), or 12(a)-12(h), 13 or 14(a), wherein R^1 is -CH_3, -CHF_2, -CH_2F or -CF_3.

[0167] Embodiment 14(c) of this disclosure relates to the compound according toany one of Embodiments 1A, 1B, 1C, 2-4, 5(a)-5(e), 6(a) -6(e), 7(a)-7(c), 8(a)-8(j), (9a)-9(v), 10(a)-10(s), 11(a)-11(q), or 12(a)-12(h), 13 or 14(a), wherein R^1 is $-CH_3$.

[0168] Embodiment 14(d) of this disclosure relates to the compound according toany one of Embodiments 1A, 1B, 1C, 2-4, 5(a)-5(e), 6(a) -6(e), 7(a)-7(c), 8(a)-8(j), (9a)-9(v), 10(a)-10(s), 11(a)-11(q), or 12(a)-12(h), 13 or 14(a), wherein R^1 is $-CHF_2$.

[0169] Embodiment 14(e) of this disclosure relates to the compound according toany one of Embodiments 1A, 1B, 1C, 2-4, 5(a)-5(e), 6(a) -6(e), 7(a)-7(c), 8(a)-8(j), (9a)-9(v), 10(a)-10(s), 11(a)-11(q), or 12(a)-12(h), 13 or 14(a), wherein R^1 is $-CH_2F$.

[0170] Embodiment 14(f) of this disclosure relates to the compound according toany one of Embodiments 1A, 1B, 1C, 2-4, 5(a)-5(e), 6(a) -6(e), 7(a)-7(c), 8(a)-8(j), (9a)-9(v), 10(a)-10(s), 11(a)-11(q), or 12(a)-12(h), 13 or 14(a), wherein R^1 is $-CF_3$.

[0171] Embodiment 14(g) of this disclosure relates to the compound according toany one of Embodiments 1A, 1B, 1C, 2-4, 5(a)-5(e), 6(a) -6(e), 7(a)-7(c), 8(a)-8(j), (9a)-9(v), 10(a)-10(s), 11(a)-11(q), or 12(a)-12(h) or 13, wherein R^1 is cyclopropyl.

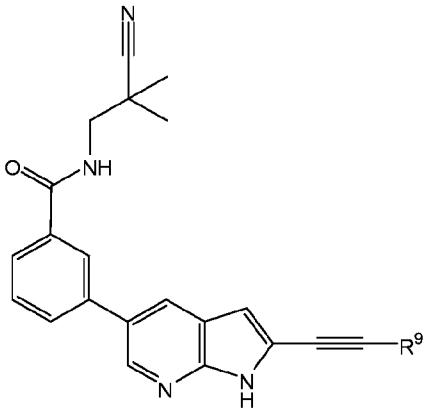
[0172] Embodiment 14(h) of this disclosure relates to the compound according toany one of Embodiments 1A, 1B, 1C, 2-4, 5(a)-5(e), 6(a) -6(e), 7(a)-7(c), 8(a)-8(j), (9a)-9(v), 10(a)-10(s), 11(a)-11(q), or 12(a)-12(h) or 13, wherein R^1 -$(C_1$-$C_3)$alkylene-CN or cyano.

[0173] Embodiment 14(i) of this disclosure relates to the compound according toany one of Embodiments 1A, 1B, 1C, 2-4, 5(a)-5(e), 6(a) -6(e), 7(a)-7(c), 8(a)-8(j), (9a)-9(v), 10(a)-10(s), 11(a)-11(q), or 12(a)-12(h) or 13, wherein R^1 is methoxy-$(C_1$-$C_3)$alkylene-.

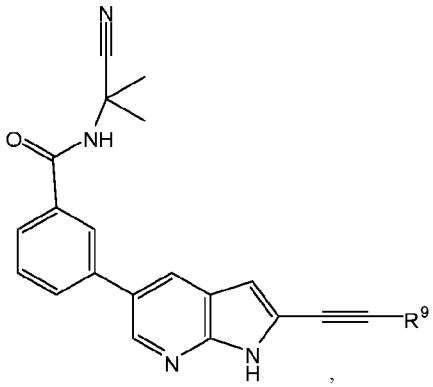
[0174] Embodiment 14(j) of this disclosure relates to the compound according toany one of Embodiments 1A, 1B, 1C, 2-4, 5(a)-5(e), 6(a) -6(e), 7(a)-7(c), 8(a)-8(j), (9a)-9(v), 10(a)-10(s), 11(a)-11(q), or 12(a)-12(h) or 13, wherein R^1 is piperidinyl, morpholinyl, or tetrahydrofuranyl.

[0175] Embodiment 14(k) of this disclosure relates to the compound according toany one of Embodiments 1A, 1B, 1C, 2-4, 5(a)-5(e), 6(a) -6(e), 7(a)-7(c), 8(a)-8(j), (9a)-9(v), 10(a)-10(s), 11(a)-11(q), or 12(a)-12(h) or 13, wherein R^1 is -C(O)-cyclopropyl.

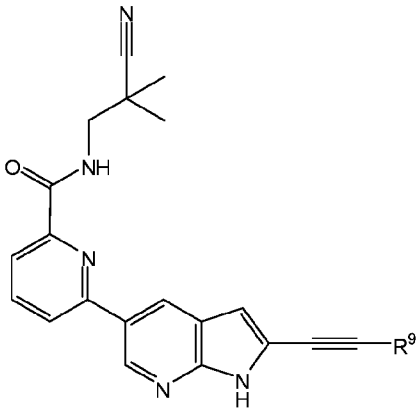
[0176] Embodiment 15 of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 9(a) or 12(a) having one of the following Formulae:



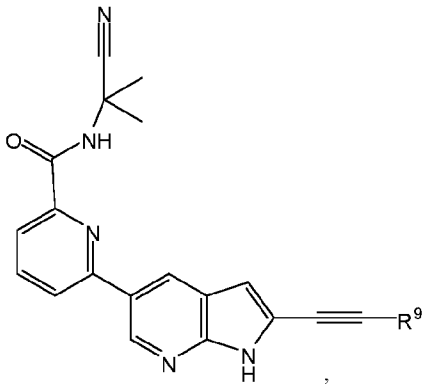
IV(a)



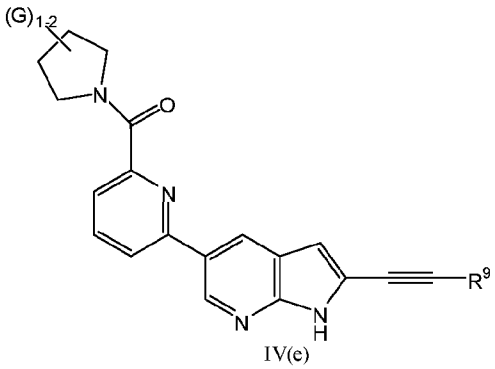
IV(b)



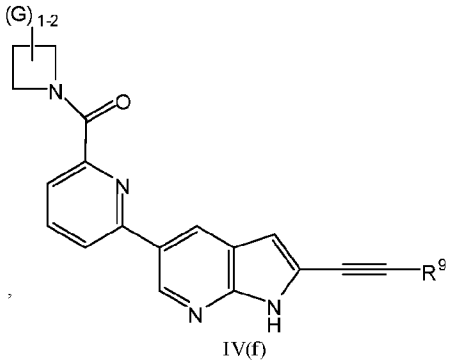
IV(c)



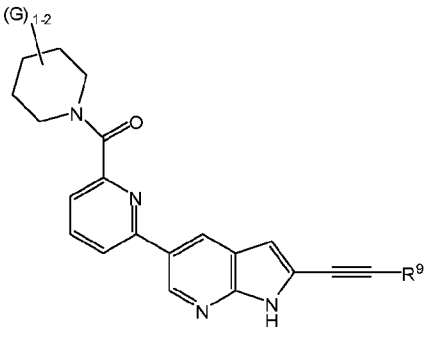
IV(d)



IV(e)



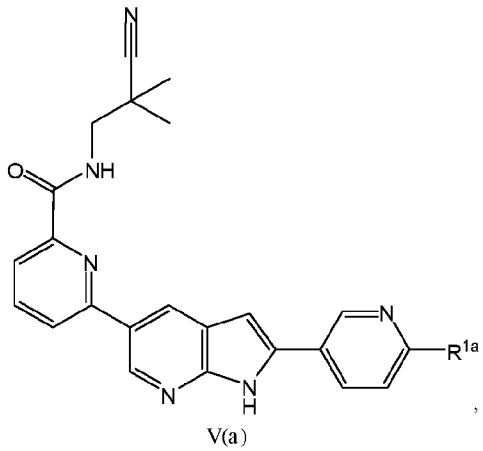
IV(f)



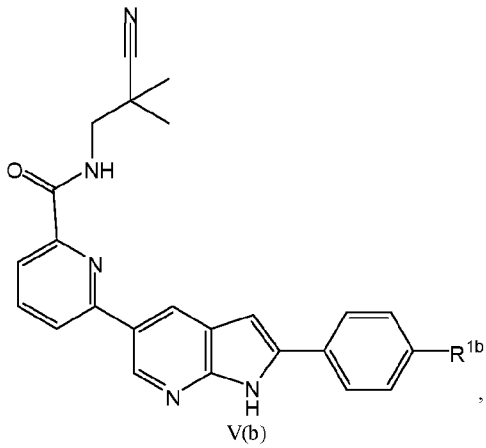
IV(g)

or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog thereof, wherein R^9 is C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-6}cycloalkyl, phenyl, -(C_{1-6}alkylene)-NR^6R^7, or hydroxy-C_{1-4}alkylene.

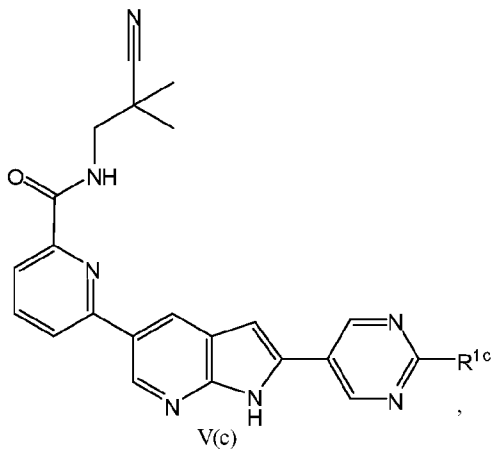
[0177] Embodiment 16 of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a)-5(e), 6(a) -6(e), 7(a)-7(c), 8(a)-8(j), (9a)-9(v), 10(a)-10(s), 11(a)-11(q), or 12(a)-12(h), 13, or 14(a)–14(k) having one of the following Formulae:



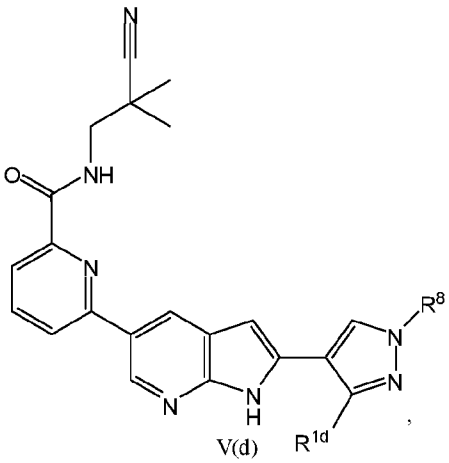
V(a)



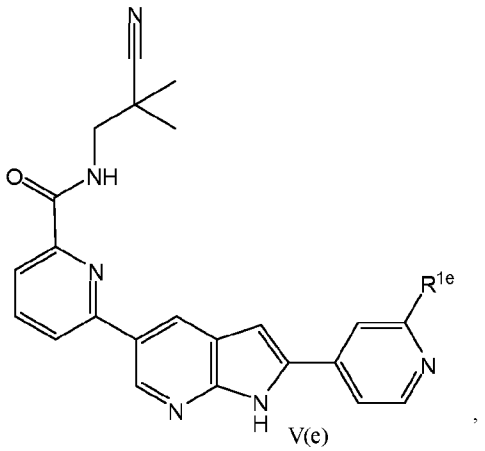
V(b)



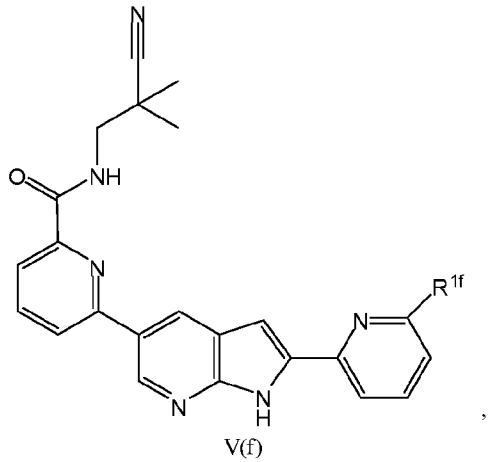
V(c)



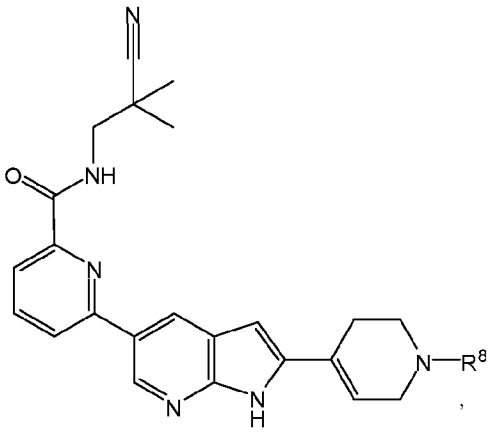
V(d)



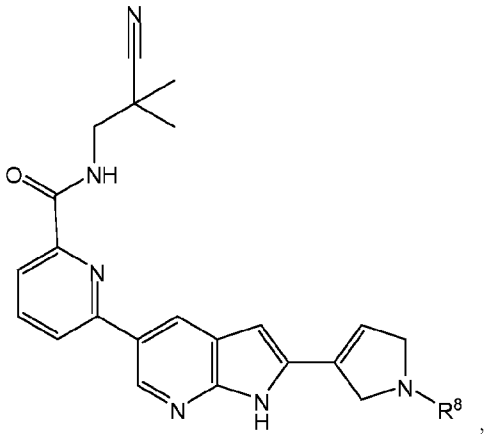
V(e)



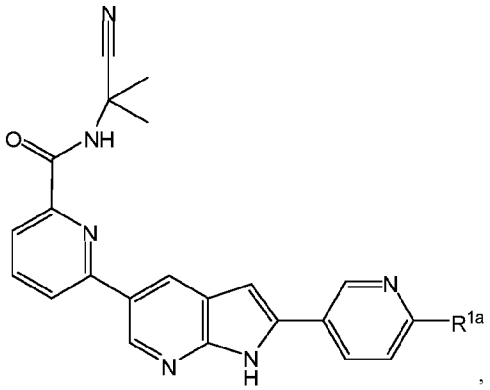
V(f)



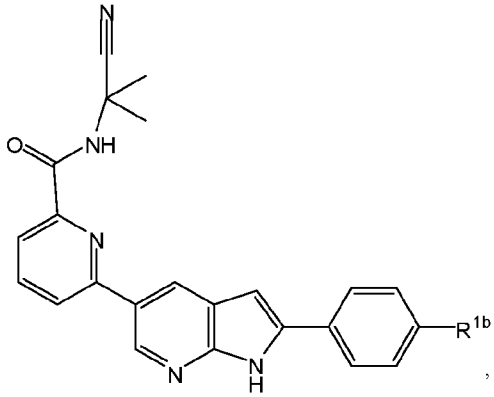
V(g)



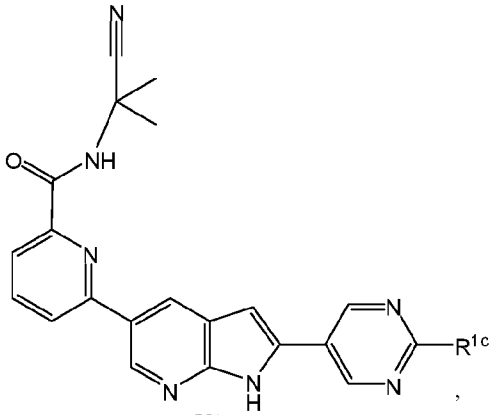
V(h)



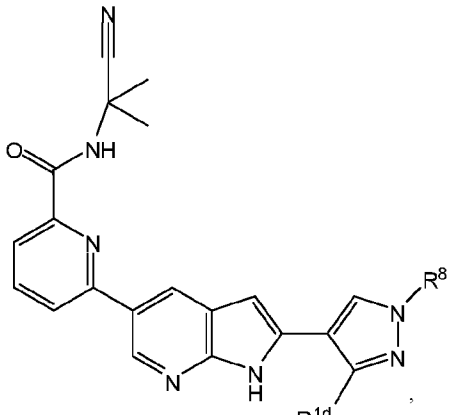
V(aa)



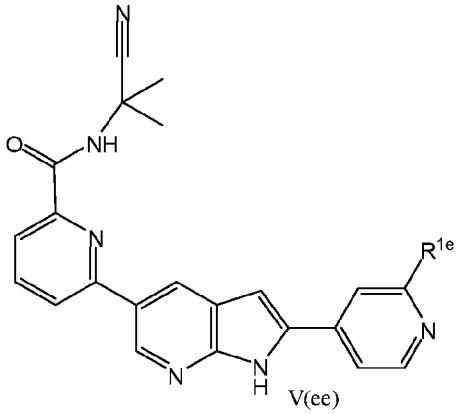
V(bb)



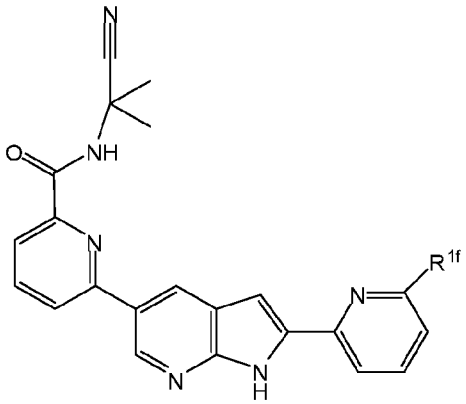
V(cc),



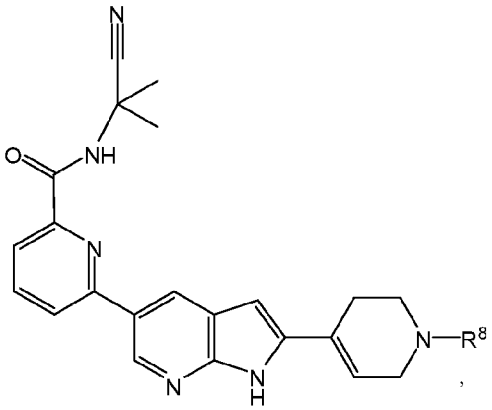
V(dd),



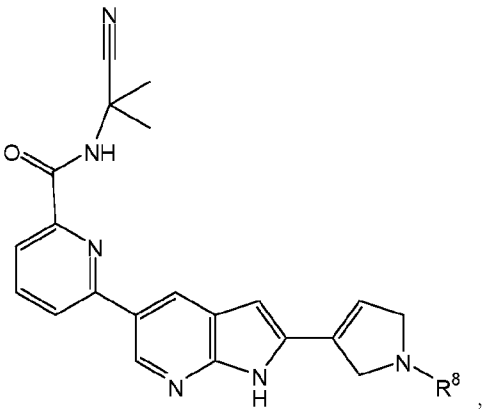
V(ee),



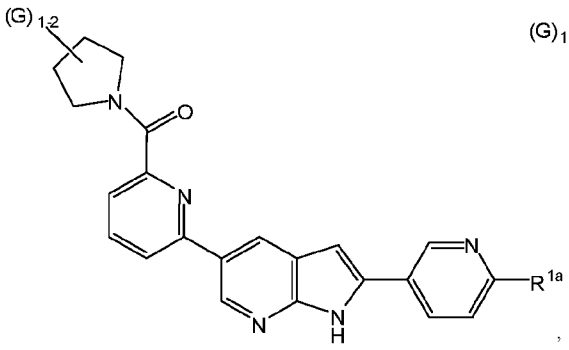
V(ff),



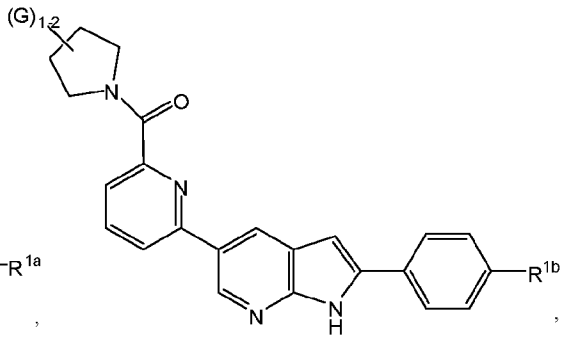
V(gg),



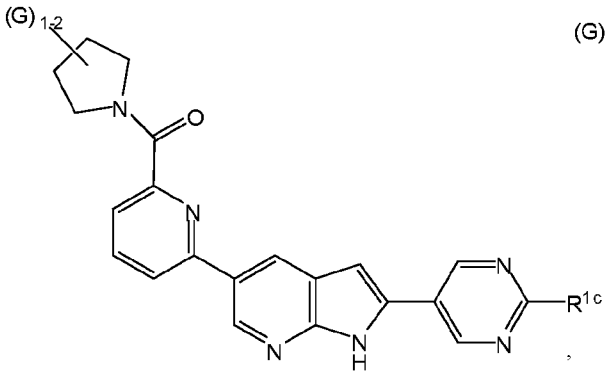
V(hh),



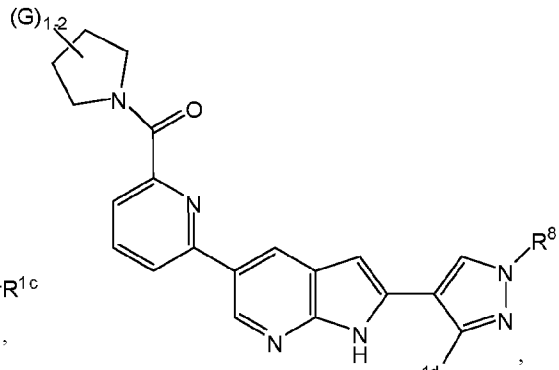
VI(a)



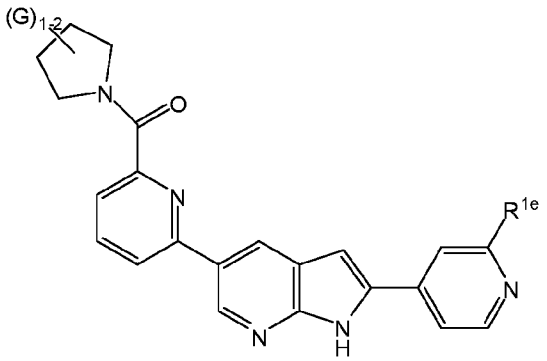
VI(b)



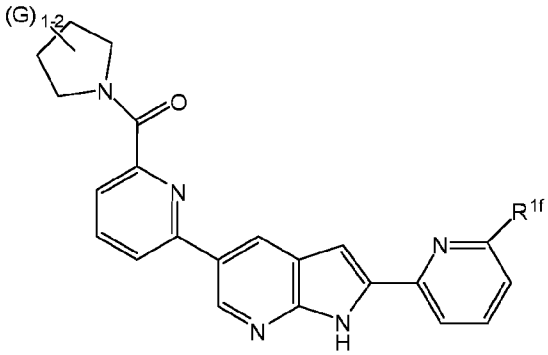
VI(c)



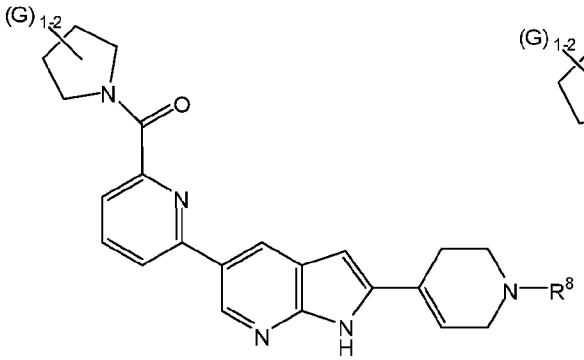
VI(d)



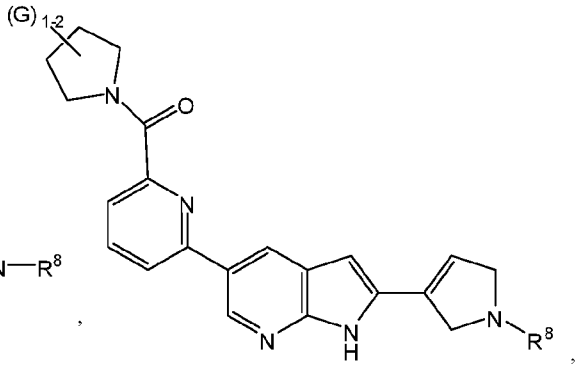
VI(e)



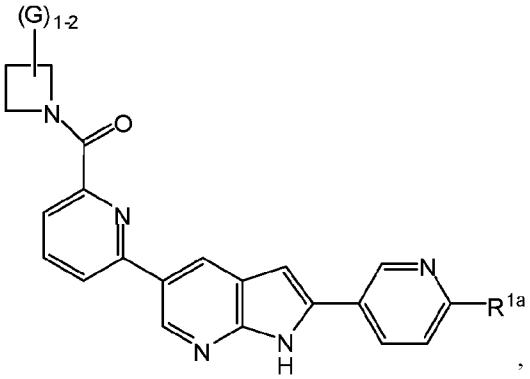
VI(f)



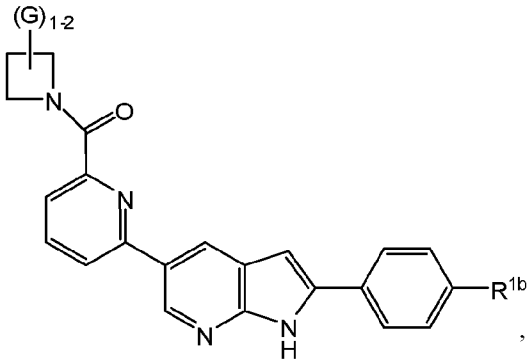
VI(g)



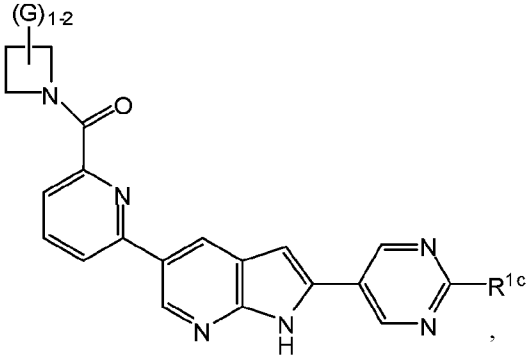
VI(h)



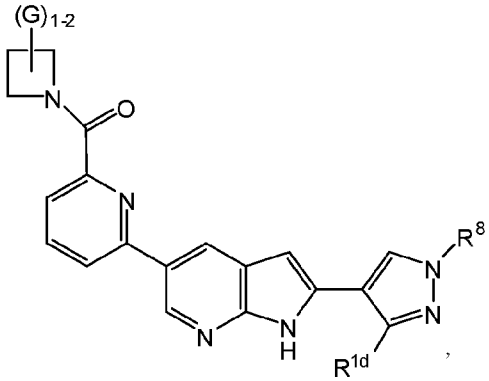
VII(a)



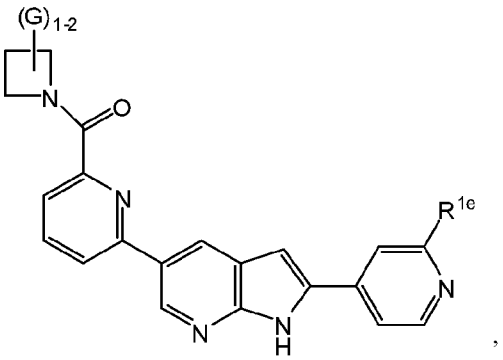
VII(b)



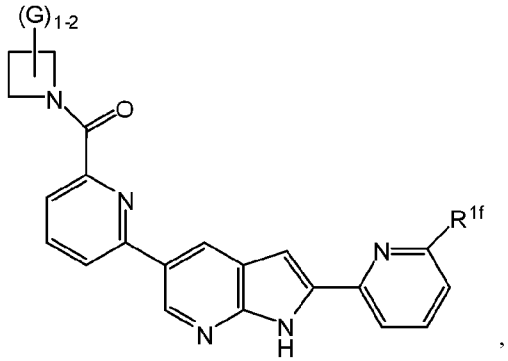
VII(c)



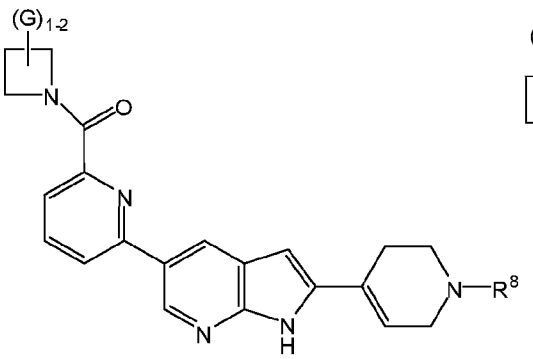
VII(d)



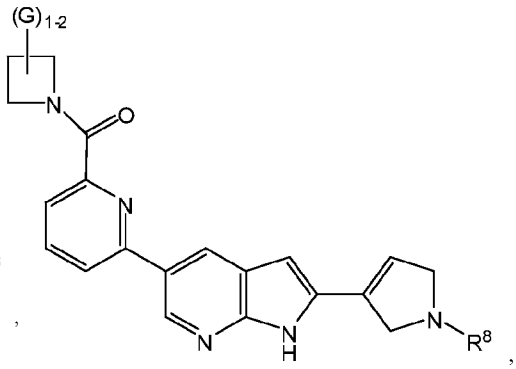
VII(e)



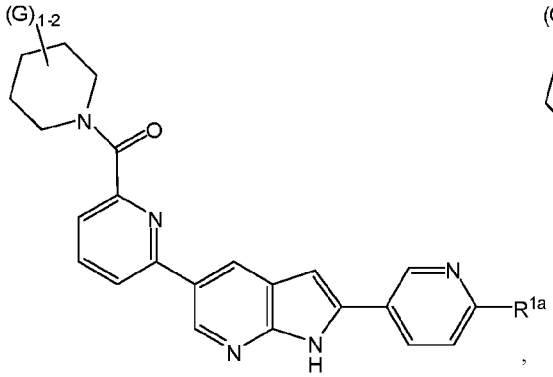
VII(f)



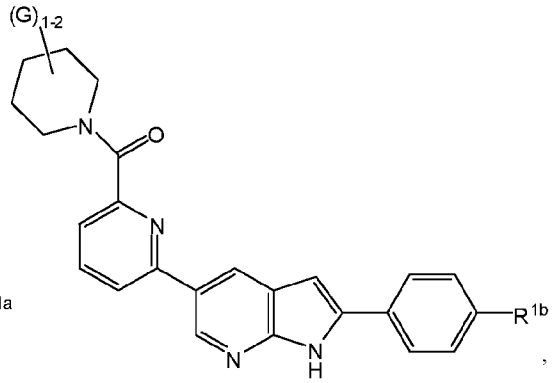
VII(g)



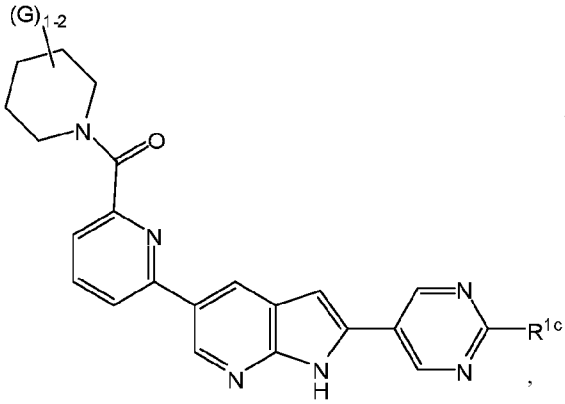
VII(h)



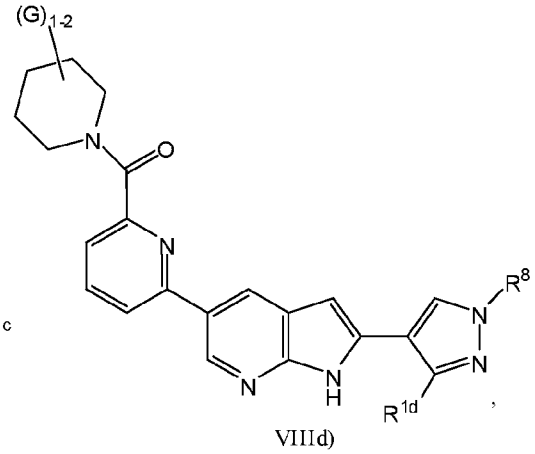
VIII(a)



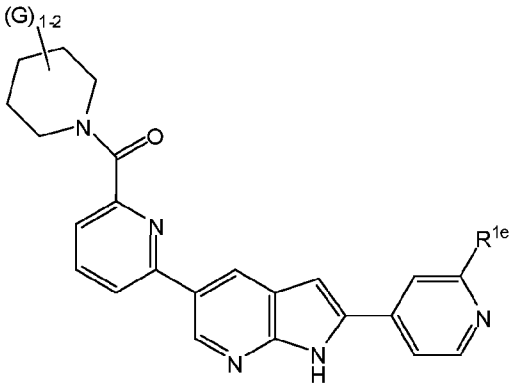
VIII(b)



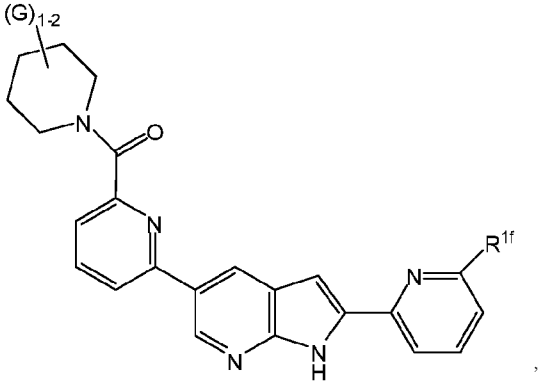
VIII(c)



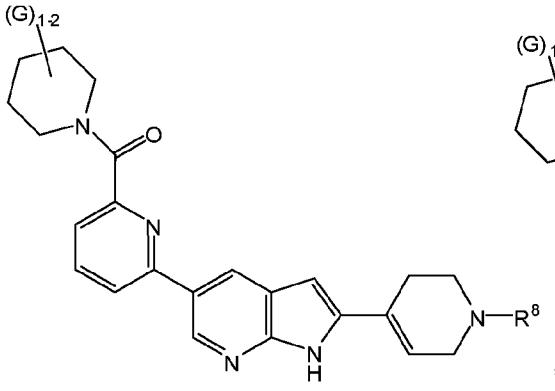
VIIId)



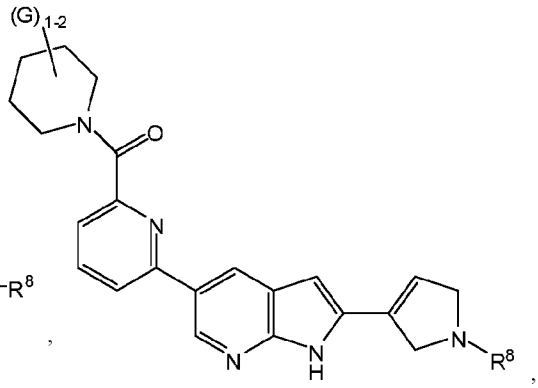
VIII(e)



VIII(f)



VIII(g)



VIII(h)

or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog thereof, wherein each of R^{1a}, R^{1b}, R^{1c}, R^{1d}, R^{1e}, and R^{1f} are as defined as R^1 in any one of Embodiments 1A, 1B, 1C, 2-4, 5(a)-5(e), 6(a) -6(e), 7(a)-7(c), 8(a)-8(j), (9a)-9(v), 10(a)-10(s), 11(a)-11(q), 12(a)-12(h), 13, or 14(a)–14(k).

[0178] Embodiment 17(a) of this disclosure relates to the compound according to Embodiment 16 having one of Formulae V(a), V(b), V(c), V(d), V(e), V(f), V(g), V(h), V(aa), V(bb), V(cc), V(dd), V(ee), V(ff), V(gg), V(hh), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog of any one of Formulae V(a), V(b), V(c), V(d), V(e), V(f), V(g), V(h), V(aa), V(bb), V(cc), V(dd), V(ee), V(ff), V(gg), V(hh).

[0179] Embodiment 17(b) of this disclosure relates to the compound according to Embodiment 16 having Formulae V(a), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog thereof.

[0180] Embodiment 17(c) of this disclosure relates to the compound according to Embodiment 16 having Formulae V(b), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog thereof.

[0181] Embodiment 17(d) of this disclosure relates to the compound according to Embodiment 16 having Formulae V(c), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog thereof.

[0182] Embodiment 17(e) of this disclosure relates to the compound according to Embodiment 16 having Formulae V(d), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog thereof.

[0183] Embodiment 17(f) of this disclosure relates to the compound according to Embodiment 16 having Formulae V(e), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog thereof.

[0184] Embodiment 17(g) of this disclosure relates to the compound according to Embodiment 16 having Formulae V(f), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog thereof.

[0185] Embodiment 17(h) of this disclosure relates to the compound according to Embodiment 16 having Formulae V(g), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog thereof.

[0186] Embodiment 17(i) of this disclosure relates to the compound according to Embodiment 16 having Formulae V(h), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog thereof.

[0187] Embodiment 17(j) of this disclosure relates to the compound according to Embodiment 16 having Formulae V(aa), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog thereof.

[0188] Embodiment 17(k) of this disclosure relates to the compound according to Embodiment 16 having Formulae V(bb), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog thereof.

[0189] Embodiment 17(l) of this disclosure relates to the compound according to Embodiment 16 having Formulae V(cc), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog thereof.

[0190] Embodiment 17(m) of this disclosure relates to the compound according to Embodiment 16 having Formulae V(dd), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog thereof.

[0191] Embodiment 17(n) of this disclosure relates to the compound according to Embodiment 16 having Formulae V(ee), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog thereof.

[0192] Embodiment 17(o) of this disclosure relates to the compound according to Embodiment 16 having Formulae V(ff), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog thereof.

[0193] Embodiment 17(p) of this disclosure relates to the compound according to Embodiment 16 having Formulae V(gg), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog thereof.

[0194] Embodiment 17(q) of this disclosure relates to the compound according to Embodiment 16 having Formulae V(hh), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog thereof.

[0195] Embodiment 18(a) of this disclosure relates to the compound according to Embodiment 16 having one of Formulae VI(a), VI(b), VI(c), VI(d), VI(e), VI(f), VI(g), VI(h), VII(a), VII(b), VII(c), VII(d), VII(e), VII(f), VII(g), VII(h), VIII(a), VIII(b), VIII(c), VIII(d), VIII(e), VIII(f), VIII(g), VIII(h), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer,or a deuterated analog of any one of Formulae VI(a), VI(b), VI(c), VI(d), VI(e), VI(f), VI(g), VI(h), VII(a), VII(b), VII(c), VII(d), VII(e), VII(f), VII(g), VII(h), VIII(a), VIII(b), VIII(c), VIII(d), VIII(e), VIII(f), VIII(g) or VIII(h).

[0196] Embodiment 18(b) of this disclosure relates to the compound according to Embodiment 16 having Formulae VI(a), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog thereof.

[0197] Embodiment 18(c) of this disclosure relates to the compound according to Embodiment 16 having Formulae VI(b), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog thereof.

[0198] Embodiment 18(d) of this disclosure relates to the compound according to Embodiment 16 having Formulae VI(c), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog thereof.

[0199] Embodiment 18(e) of this disclosure relates to the compound according to Embodiment 16 having Formulae VI(d), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog thereof.

[0200] Embodiment 18(f) of this disclosure relates to the compound according to Embodiment 16 having Formulae VI(e), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog thereof.

[0201] Embodiment 18(g) of this disclosure relates to the compound according to Embodiment 16 having Formulae VI(f), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog thereof.

[0202] Embodiment 18(h) of this disclosure relates to the compound according to Embodiment 16 having Formulae VI(g), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog thereof.

[0203] Embodiment 18(i) of this disclosure relates to the compound according to Embodiment 16 having Formulae VI(h), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog thereof.

[0204] Embodiment 18(j) of this disclosure relates to the compound according to Embodiment 16 having Formulae VII(a), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog thereof.

[0205] Embodiment 18(k) of this disclosure relates to the compound according to Embodiment 16 having Formulae VII(b), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog thereof.

[0206] Embodiment 18(l) of this disclosure relates to the compound according to Embodiment 16 having Formulae VII(c), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog thereof.

[0207] Embodiment 18(m) of this disclosure relates to the compound according to Embodiment 16 having Formulae VII(d), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog thereof.

[0208] Embodiment 18(n) of this disclosure relates to the compound according to Embodiment 16 having Formulae VII(e), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog thereof.

[0209] Embodiment 18(o) of this disclosure relates to the compound according to Embodiment 16 having Formulae VII(f), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog thereof.

[0210] Embodiment 18(p) of this disclosure relates to the compound according to Embodiment 16 having Formulae VII(g), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog thereof.

[0211] Embodiment 18(q) of this disclosure relates to the compound according to Embodiment 16 having Formulae VII(h), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog thereof.

[0212] Embodiment 18(r) of this disclosure relates to the compound according to Embodiment 16 having Formulae VIII(a), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog thereof.

[0213] Embodiment 18(s) of this disclosure relates to the compound according to Embodiment 16 having Formulae VIII(b), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog thereof.

[0214] Embodiment 18(t) of this disclosure relates to the compound according to Embodiment 16 having Formulae VIII(c), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog thereof.

[0215] Embodiment 18(u) of this disclosure relates to the compound according to Embodiment 16 having Formulae VIII(d), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog thereof.

[0216] Embodiment 18(v) of this disclosure relates to the compound according to Embodiment 16 having Formulae VIII(e), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog thereof.

[0217] Embodiment 18(w) of this disclosure relates to the compound according to Embodiment 16 having Formulae VIII(f), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog thereof.

[0218] Embodiment 18(x) of this disclosure relates to the compound according to Embodiment 16 having Formulae VIII(g), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog thereof.

[0219] Embodiment 18(y) of this disclosure relates to the compound according to Embodiment 16 having Formulae VIII(h), or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog thereof.

[0220] Embodiment 19 of this disclosure relates to the compound according to any one of Embodiments 16, 17(a) or 18(a) wherein:

R^{1a} is hydrogen, cyclopropyl, $-OC(H)(CH_3)_2$, morpholinyl, $-CF_3$, $-CHF_2$ or F;

R^{1b} is hydrogen, F, cyano, cyclopropyl or cyanocyclopropyl;

R^{1c} is hydrogen, cyclopropyl, methoxy, $-OC(H)(CH_3)_2$, pyrrolidinyl, ethoxy, $-CH_3$, $-CF_3$ or $-CHF_2$;

R^{1d} is hydrogen or $-CH_3$;

R^{1e} is hydrogen, methoxy, cyclopropyl, methoxy, morpholinyl, $-CF_3$, $-CHF_2$, $-CH_3$, pyrrolidinyl or F;

R^{1f} is hydrogen or cyclopropyl; and

R^8 is hydrogen, -$CH(CH_3)_2$, -$C(O)OC(CH_3)_3$, cyclopropyl, -C(O)cyclopropyl, -$(CH_2)_{0-2}$-phenyl, -$(CH_2)_{0-2}$-morpholinyl, -$(CH_2)_{0-2}$-tetrahydrofuranyl, -$(CH_2)_{0-2}$-piperidinyl, CH_3, $-CF_3$ or $-CHF_2$.

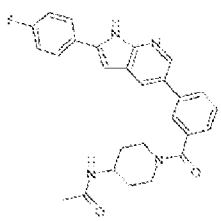
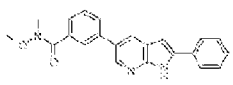
[0221] Embodiment 20 of this disclosure relates to the compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a)-5(e), 6(a) -6(e), 7(a)-7(c), 8(a), (9a), 10(a), 11(a), or 12(a), 13, 14(a) , 15, 16, 17(a), 18(a)-18(y) or 19, wherein G is $–NH_2$, -N(H)C(O)-C_{1-6}alkyl, -C(O)-N(H)-C_{1-6}alkyl, -N(H)-C(O)-N(H)-C_{1-6}alkyl, -N(H)-$S(O)_2$-C_{1-6}alkyl, –N(H)-C_{1-6}alkyl, –N(C_{1-6}alkyl)$_2$, -C(=NH)-NH_2, -OH, C_{1-6}alkyl, C_{1-6}haloalkyl, halo, -N(H)-C_{3-6}cycloalkyl, -C_{1-6}alkoxy, -C_{4-6}heterocycloalkyl, -C_{5-6}heteroaryl, -CN, -C(O)-C_{1-6}alkyl, or -C_{1-3}alkylene-N(H)-C_{1-3}alkyl.

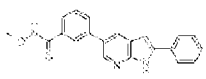
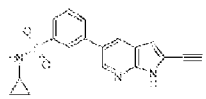
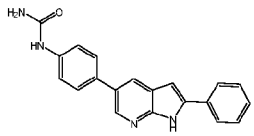
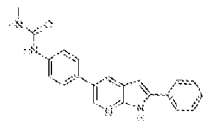
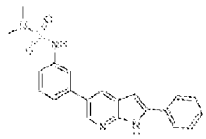
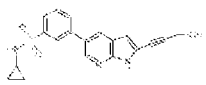
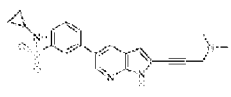
[0222] Embodiment 21 of this disclosure relates to the compound according to Embodiment 20, wherein G is $–NH_2$, –N(H)C(O)-C_{1-4}alkyl, -C(O)-N(H)-C_{1-4}alkyl, -N(H)-C(O)-N(H)-C_{1-4}alkyl, -N(H)-$S(O)_2$-C_{1-3}alkyl, $–N(H)-CH_3$, $–N(CH_3)_2$, -C(=NH)-NH_2, -OH, -C_{1-3}alkyl, $-CF_3$, fluoro, -N(H)-C_{3-6}cycloalkyl, -C_{1-3}alkoxy, morpholinyl, imidazolyl, -CN, -C(O)-C_{1-3}alkyl, or -C_{1-2}alkylene-N(H)-CH_3.

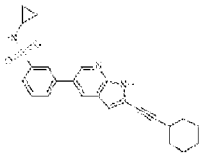
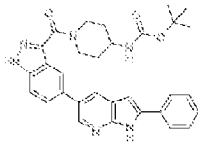
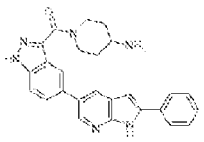
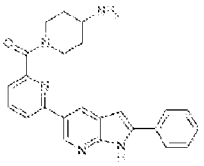
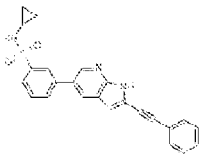
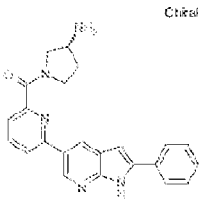
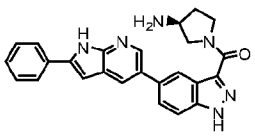
[0223] Embodiment 22 of this disclosure relates to a compound according to any of the embodiments described herein, wherein R^a is oxo, fluoro, chloro, or hydroxy.

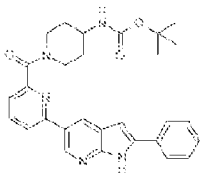
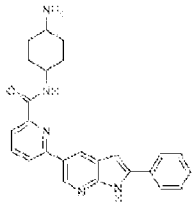
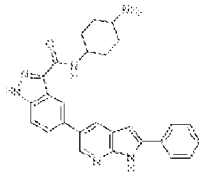
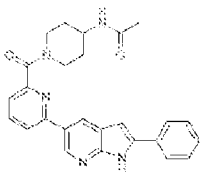
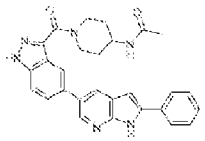
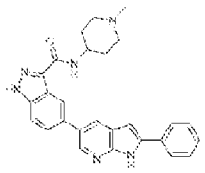
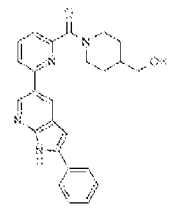
[0224] Embodiment 23(a) of this disclosure relates to a compound of Table 1:

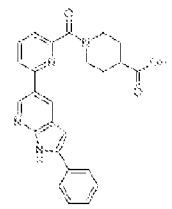
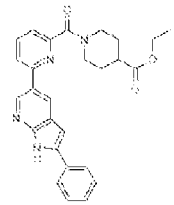
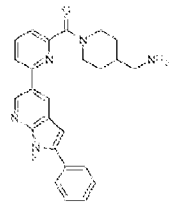
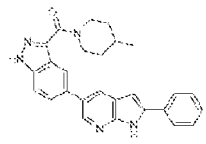
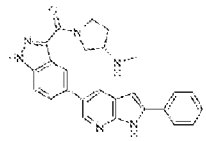
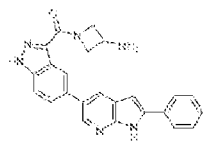
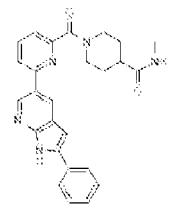
TABLE 1

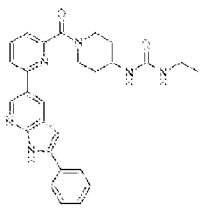
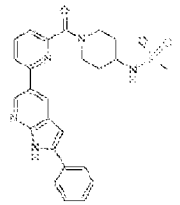
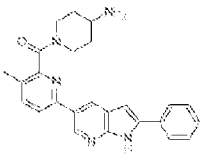
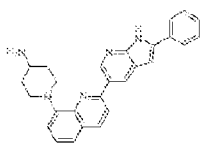
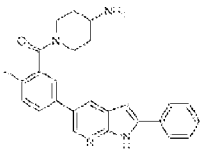
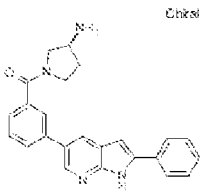
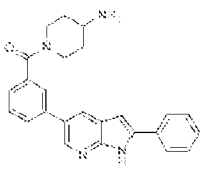
Structure	Compound Name	(M+H)+	P Values
	N-[1-[3-[2-(4-fluorophenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]benzoyl]-4-piperidyl]acetamide	**457.30**	**P-0001**
	N-methoxy-N-methyl-3-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)benzamide	**358.15**	**P-0002**

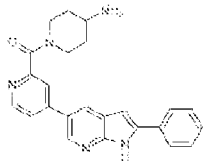
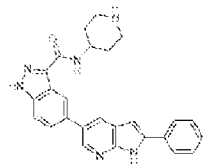
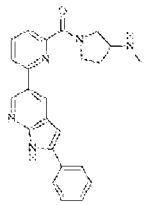
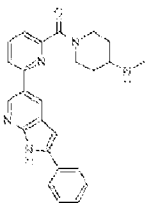
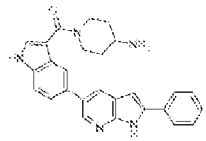
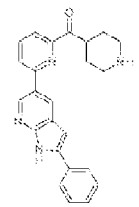
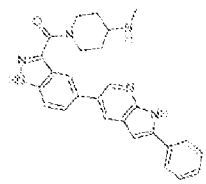
	N-methoxy-3-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)benzamide	**344.10**	**P-0003**
	N-cyclopropyl-3-(2-ethynyl-1H-pyrrolo[2,3-b]pyridin-5-yl)benzenesulfonamide	**338.10**	**P-0004**
	[4-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)phenyl]urea	**329.12**	**P-0005**
	1-methyl-3-[4-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)phenyl]urea	**343.23**	**P-0006**
	5-[3-(dimethylsulfamoylamino)phenyl]-2-phenyl-1H-pyrrolo[2,3-b]pyridine	**393.4**	**P-0007**
	N-cyclopropyl-3-[2-(3-hydroxyprop-1-ynyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]benzenesulfonamide	**367.95**	**P-0008**
	N-cyclopropyl-3-[2-[3-(dimethylamino)prop-1-ynyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]benzenesulfonamide	**395.20**	**P-0009**

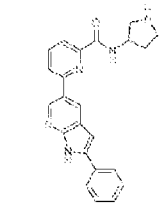
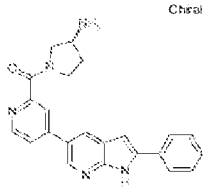
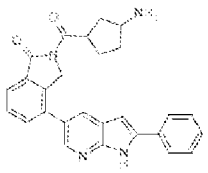
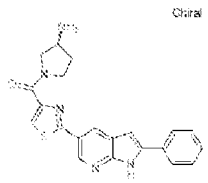
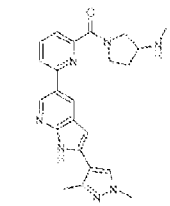
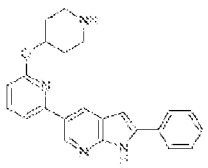
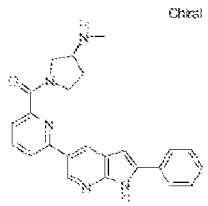
	3-[2-(2-cyclohexylethynyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]-N-cyclopropyl-benzenesulfonamide	**420.25**	**P-0010**
	tert-butyl N-[1-[5-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-indazole-3-carbonyl]-4-piperidyl]carbamate	**537.00**	**P-0011**
	(4-amino-1-piperidyl)-[5-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-indazol-3-yl]methanone	**436.90**	**P-0012**
	(4-amino-1-piperidyl)-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]methanone	**397.90**	**P-0013**
	N-cyclopropyl-3-[2-(2-phenylethynyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]benzenesulfonamide	**414.20**	**P-0014**
	[(3S)-3-aminopyrrolidin-1-yl]-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]methanone	**383.85**	**P-0015**
	[(3S)-3-aminopyrrolidin-1-yl]-[5-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-indazol-3-yl]methanone	**422.90**	**P-0016**

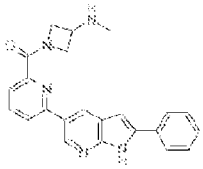
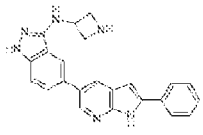
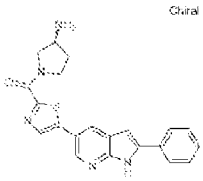
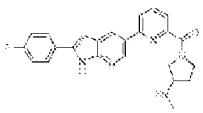
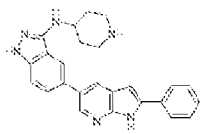
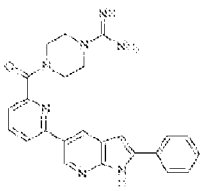
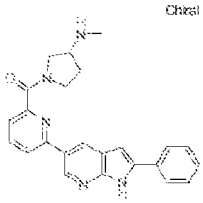
	tert-butyl N-[1-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carbonyl]-4-piperidyl]carbamate	**498.00**	**P-0017**
	N-(4-aminocyclohexyl)-6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carboxamide	**411.95**	**P-0018**
	N-(4-aminocyclohexyl)-5-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-indazole-3-carboxamide	**450.95**	**P-0019**
	N-[1-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carbonyl]-4-piperidyl]acetamide	**439.90**	**P-0020**
	N-[1-[5-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-indazole-3-carbonyl]-4-piperidyl]acetamide	**478.95**	**P-0021**
	N-(1-methyl-4-piperidyl)-5-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-indazole-3-carboxamide	**451.15**	**P-0022**
	[4-(hydroxymethyl)-1-piperidyl]-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]methanone	**413.25**	**P-0023**

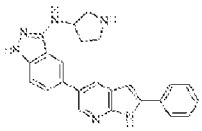
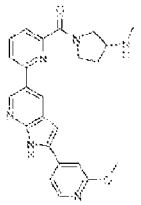
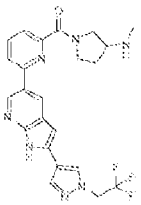
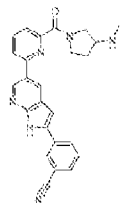
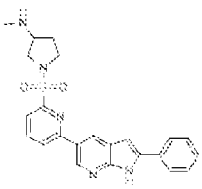
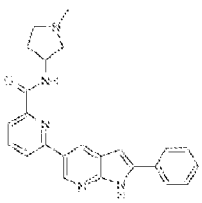
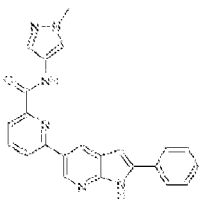
	1-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carbonyl]piperidine-4-carboxylic acid	**427.25**	**P-0024**
	ethyl 1-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carbonyl]piperidine-4-carboxylate	**455.25**	**P-0025**
	[4-(aminomethyl)-1-piperidyl]-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]methanone	**412.25**	**P-0026**
	(4-methyl-1-piperidyl)-[5-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-indazol-3-yl]methanone	**435.95**	**P-0027**
	[3-(methylamino)pyrrolidin-1-yl]-[5-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-indazol-3-yl]methanone	**436.9**	**P-0028**
	(3-aminoazetidin-1-yl)-[5-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-indazol-3-yl]methanone	**409.20**	**P-0029**
	N-methyl-1-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carbonyl]piperidine-4-carboxamide	**440.30**	**P-0030**

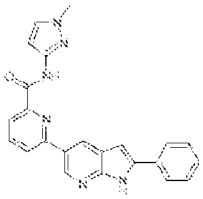
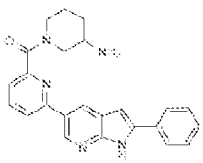
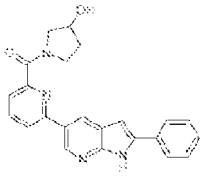
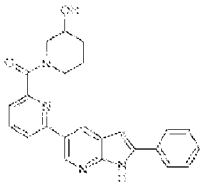
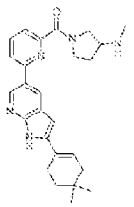
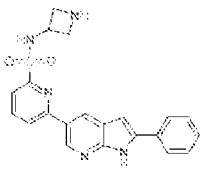
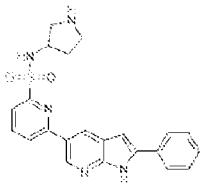
	1-ethyl-3-[1-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carbonyl]-4-piperidyl]urea		**P-0031**
	N-[1-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carbonyl]-4-piperidyl]methanesulfonamide	**476.30**	**P-0032**
	(4-amino-1-piperidyl)-[3-methyl-6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]methanone	**411.90**	**P-0033**
	1-[2-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-8-quinolyl]piperidin-4-amine	**420.25**	**P-0034**
	(4-amino-1-piperidyl)-[2-methyl-5-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)phenyl]methanone	**410.95**	**P-0035**
	[(3S)-3-aminopyrrolidin-1-yl]-[3-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)phenyl]methanone	**382.85**	**P-0036**
	(4-amino-1-piperidyl)-[3-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)phenyl]methanone	**396.90**	**P-0037**

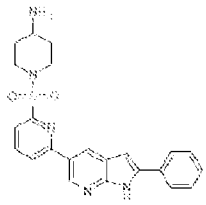
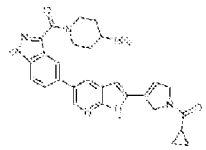
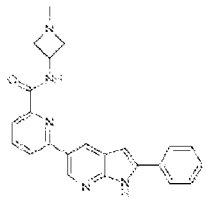
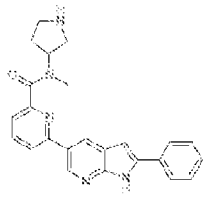
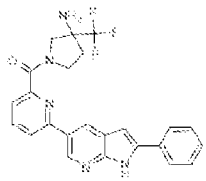
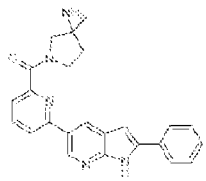
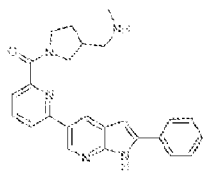
	(4-amino-1-piperidyl)-[4-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]methanone	**397.90**	**P-00038**
	5-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-N-(4-piperidyl)-1H-indazole-3-carboxamide	**436.95**	**P-0039**
	[3-(methylamino)pyrrolidin-1-yl]-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]methanone	**398.25**	**P-0040**
	[4-(methylamino)-1-piperidyl]-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]methanone	**412.30**	**P-0041**
	(4-amino-1-piperidyl)-[5-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-indol-3-yl]methanone	**435.90**	**P-0042**
	[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]-(4-piperidyl)methanone	**383.25**	**P-0043**
	[4-(methylamino)-1-piperidyl]-[5-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-indazol-3-yl]methanone	**451.25**	**P-0044**

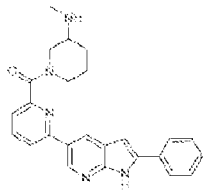
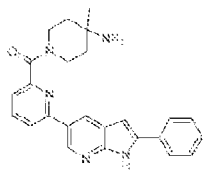
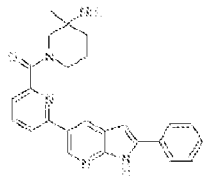
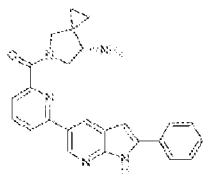
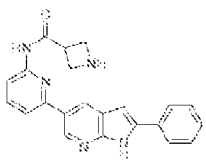
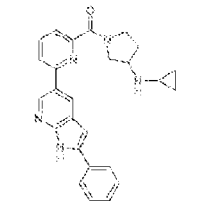
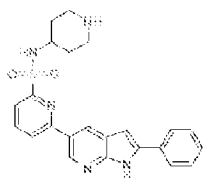
	6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-N-pyrrolidin-3-yl-pyridine-2-carboxamide	**384.20**	**P-0045**
	[(3S)-3-aminopyrrolidin-1-yl]-[4-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]methanone	**383.90**	**P-0046**
	2-(3-aminocyclopentanecarbonyl)-4-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)isoindolin-1-one	**437.47**	**P-0047**
	[(3S)-3-aminopyrrolidin-1-yl]-[2-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)thiazol-4-yl]methanone	**389.80**	**P-0048**
	[6-[2-(1,3-dimethylpyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]-2-pyridyl]-[3-(methylamino)pyrrolidin-1-yl]methanone	**416.30**	**P-0049**
	2-phenyl-5-[6-(4-piperidyloxy)-2-pyridyl]-1H-pyrrolo[2,3-b]pyridine	**372.05**	**P-0050**
	[(3S)-3-(methylamino)pyrrolidin-1-yl]-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]methanone	**398.25**	**P-0051**

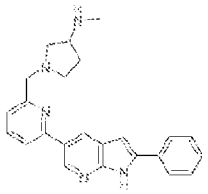
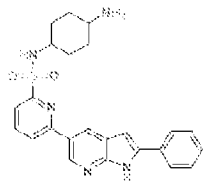
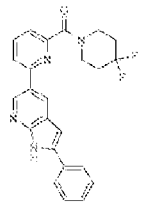
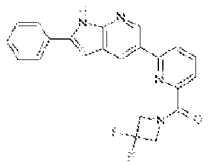
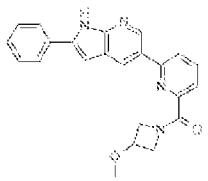
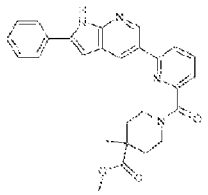
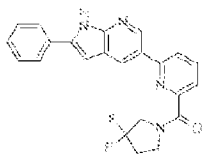
	[3-(methylamino)azetidin-1-yl]-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]methanone	**384.25**	**P-0052**
	N-(azetidin-3-yl)-5-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-indazol-3-amine	**381.85**	**P-0053**
	[(3S)-3-aminopyrrolidin-1-yl]-[5-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)thiazol-2-yl]methanone	**389.80**	**P-0054**
	[6-[2-(4-fluorophenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]-2-pyridyl]-[3-(methylamino)pyrrolidin-1-yl]methanone	**416.25**	**P-0055**
	5-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-N-(4-piperidyl)-1H-indazol-3-amine	**408.90**	**P-0056**
	4-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carbonyl]piperazine-1-carboxamidine	**426.3**	**P-0057**
	[(3R)-3-(methylamino)pyrrolidin-1-yl]-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]methanone	**398.25**	**P-0058**

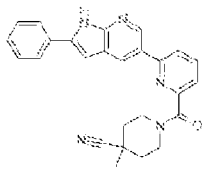
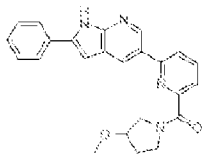
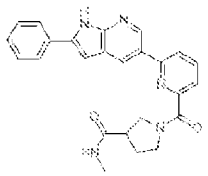
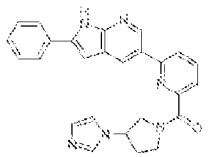
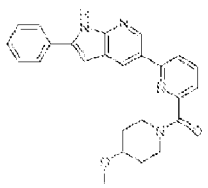
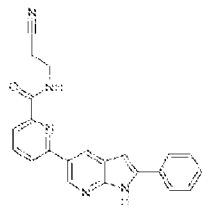
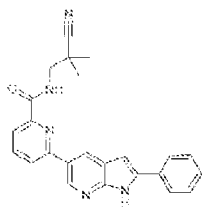
	5-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-N-pyrrolidin-3-yl-1H-indazol-3-amine	**396.10**	**P-0059**
	[6-[2-(2-methoxy-4-pyridyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]-2-pyridyl]-[3-(methylamino)pyrrolidin-1-yl]methanone	**429.30**	**P-0060**
	[3-(methylamino)pyrrolidin-1-yl]-[6-[2-[1-(2,2,2-trifluoroethyl)pyrazol-4-yl]-1H-pyrrolo[2,3-b]pyridin-5-yl]-2-pyridyl]methanone	**470.30**	**P-0061**
	3-[5-[6-[3-(methylamino)pyrrolidine-1-carbonyl]-2-pyridyl]-1H-pyrrolo[2,3-b]pyridin-2-yl]benzonitrile	**423.30**	**P-0062**
	N-methyl-1-[[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]sulfonyl]pyrrolidin-3-amine	**434.20**	**P-0063**
	N-(1-methylpyrrolidin-3-yl)-6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carboxamide	**398.15**	**P-0064**
	N-(1-methylpyrazol-4-yl)-6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carboxamide	**395.15**	**P-0065**

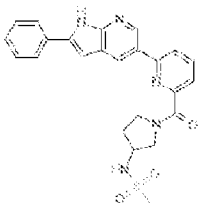
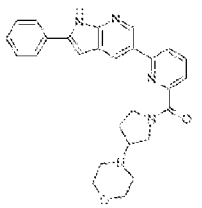
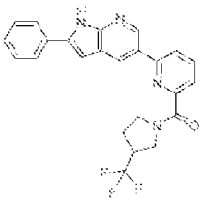
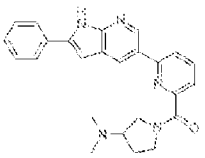
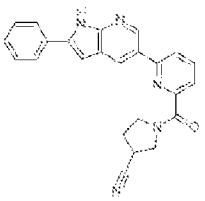
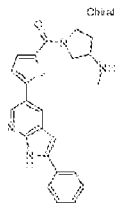
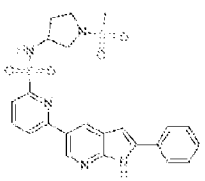
	N-(1-methylpyrazol-3-yl)-6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carboxamide	**395.15**	**P-0066**
	(3-amino-1-piperidyl)-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]methanone	**398.15**	**P-0067**
	(3-hydroxypyrrolidin-1-yl)-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]methanone	**385.55**	**P-0068**
	(3-hydroxy-1-piperidyl)-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]methanone	**399.35**	**P-0069**
	[6-[2-(4,4-dimethylcyclohexen-1-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]-2-pyridyl]-[3-(methylamino)pyrrolidin-1-yl]methanone	**430.35**	**P-0070**
	N-(azetidin-3-yl)-6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-sulfonamide	**406.00**	**P-0071**
	6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-N-pyrrolidin-3-yl-pyridine-2-sulfonamide	**420.10**	**P-0072**

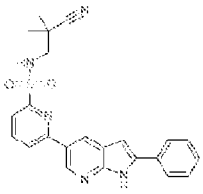
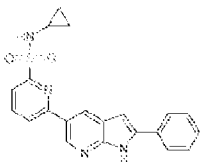
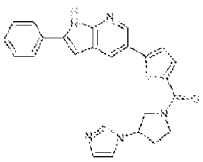
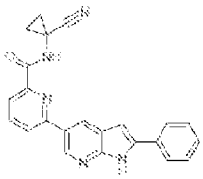
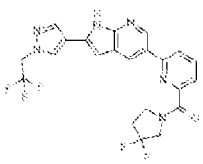
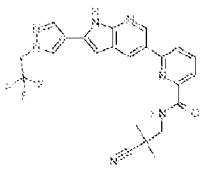
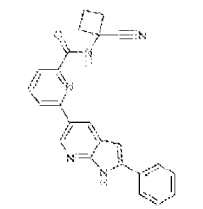
	1-[[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]sulfonyl]piperidin-4-amine	**433.85**	**P-0073**
	(4-amino-1-piperidyl)-[5-[2-[1-(cyclopropanecarbonyl)-2,5-dihydropyrrol-3-yl]-1H-pyrrolo[2,3-b]pyridin-5-yl]-1H-indazol-3-yl]methanone	**496.05**	**P-0074**
	N-(1-methylazetidin-3-yl)-6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carboxamide	**384.3**	**P-0075**
	N-methyl-6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-N-pyrrolidin-3-yl-pyridine-2-carboxamide	**398.2**	**P-0076**
	[3-amino-3-(trifluoromethyl)pyrrolidin-1-yl]-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]methanone	**452.2**	**P-0077**
	(3-amino-3-methyl-pyrrolidin-1-yl)-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]methanone	**398.2**	**P-0078**
	[3-(methylaminomethyl)pyrrolidin-1-yl]-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]methanone	**412.6**	**P-0079**

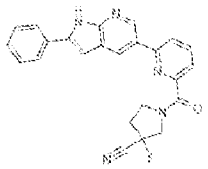
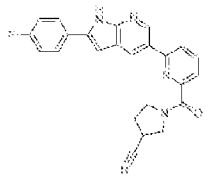
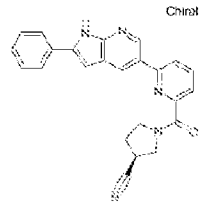
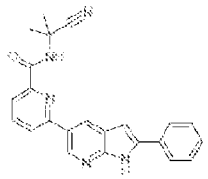
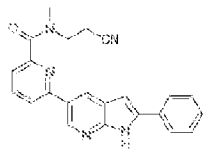
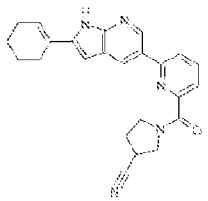
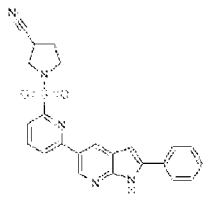
	[3-(methylamino)-1-piperidyl]-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]methanone	**412.6**	**P-0080**
	(4-amino-4-methyl-1-piperidyl)-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]methanone	**412.3**	**P-0081**
	(3-amino-3-methyl-1-piperidyl)-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]methanone	**412.3**	**P-0082**
	[(7S)-7-amino-5-azaspiro[2.4]heptan-5-yl]-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]methanone	**410.5**	**P-0083**
	N-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]azetidine-3-carboxamide	**369.85**	**P-0084**
	[3-(cyclopropylamino)pyrrolidin-1-yl]-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]methanone	**424.30**	**P-0085**
	6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-N-(4-piperidyl)pyridine-2-sulfonamide	**433.90**	**P-0086**

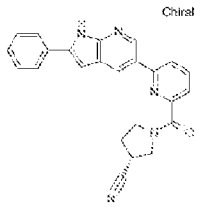
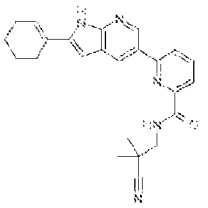
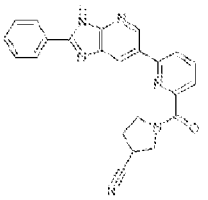
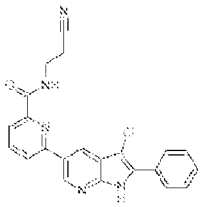
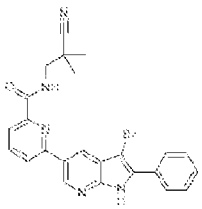
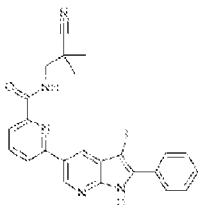
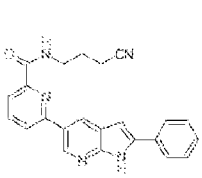
	N-methyl-1-[[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]methyl]pyrrolidin-3-amine	**383.95**	**P-0087**
	N-(4-aminocyclohexyl)-6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-sulfonamide	**447.95**	**P-0088**
	(4,4-difluoro-1-piperidyl)-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]methanone	**419.25**	**P-0089**
	(3,3-difluoroazetidin-1-yl)-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]methanone	**391.15**	**P-0090**
	(3-methoxyazetidin-1-yl)-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]methanone	**385.20**	**P-0091**
	methyl 4-methyl-1-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carbonyl]piperidine-4-carboxylate	**455.30**	**P-0092**
	(3,3-difluoropyrrolidin-1-yl)-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]methanone	**405.2**	**P-0093**

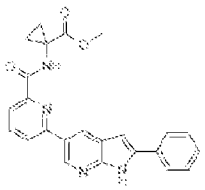
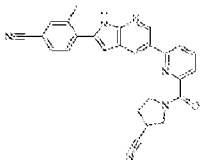
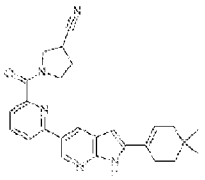
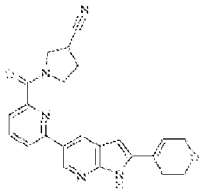
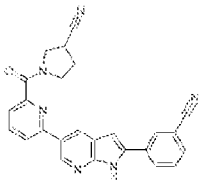
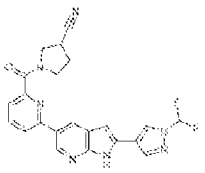
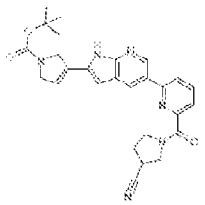
	4-methyl-1-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carbonyl]piperidine-4-carbonitrile	**422.30**	**P-0094**
	(3-methoxypyrrolidin-1-yl)-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]methanone	**399.25**	**P-0095**
	N-methyl-1-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carbonyl]pyrrolidine-3-carboxamide	**426.30**	**P-0096**
	(3-imidazol-1-ylpyrrolidin-1-yl)-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]methanone	**435.30**	**P-0097**
	(4-methoxy-1-piperidyl)-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]methanone	**413.30**	**P-0098**
	N-(2-cyanoethyl)-6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carboxamide	**368.1**	**P-0099**
	N-(2-cyano-2-methyl-propyl)-6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carboxamide	**396.4**	**P-0100**

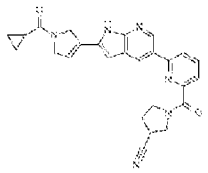
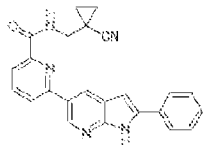
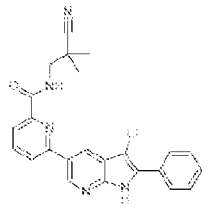
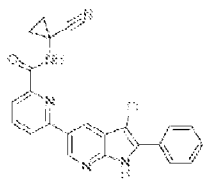
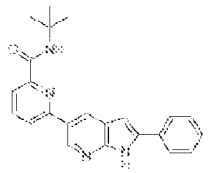
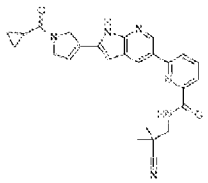
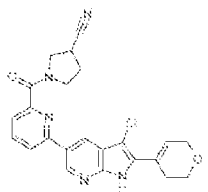
	N-[1-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carbonyl]pyrrolidin-3-yl]methanesulfonamide	**462.25**	**P-0101**
	(3-morpholinopyrrolidin-1-yl)-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]methanone	**452.25**	**P-0102**
	[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]-[3-(trifluoromethyl)pyrrolidin-1-yl]methanone	**437.25**	**P-0103**
	[3-(dimethylamino)pyrrolidin-1-yl]-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]methanone	**411.90**	**P-0104**
	1-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carbonyl]pyrrolidine-3-carbonitrile	**394.20**	**P-0105**
	[(3R)-3-(methylamino)pyrrolidin-1-yl]-[5-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-thienyl]methanone	**402.95**	**P-0106**
	N-(1-methylsulfonylpyrrolidin-3-yl)-6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-sulfonamide	**497.95**	**P-0107**

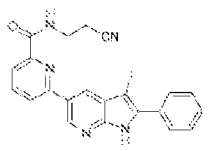
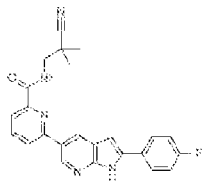
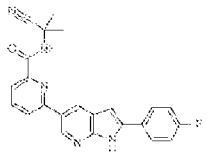
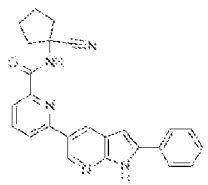
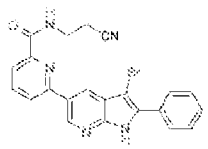
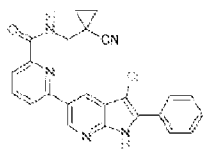
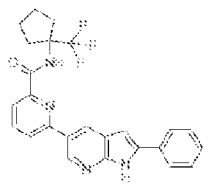
	N-(2-cyano-2-methyl-propyl)-6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-sulfonamide	**431.90**	**P-0108**
	N-cyclopropyl-6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-sulfonamide	**391.00**	**P-0109**
	(3-imidazol-1-ylpyrrolidin-1-yl)-[5-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-thienyl]methanone	**440.25**	**P-0110**
	N-(1-cyanocyclopropyl)-6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carboxamide	**379.80**	**P-0111**
	(3,3-difluoropyrrolidin-1-yl)-[6-[2-[1-(2,2,2-trifluoroethyl)pyrazol-4-yl]-1H-pyrrolo[2,3-b]pyridin-5-yl]-2-pyridyl]methanone	**477.25**	**P-0112**
	N-(2-cyano-2-methyl-propyl)-6-[2-[1-(2,2,2-trifluoroethyl)pyrazol-4-yl]-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide	**468.25**	**P-0113**
	N-(1-cyanocyclobutyl)-6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carboxamide	**394.10**	**P-0114**

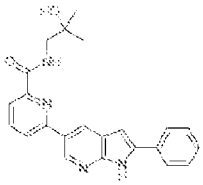
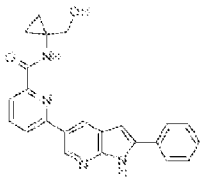
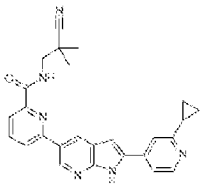
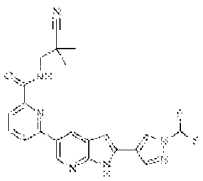
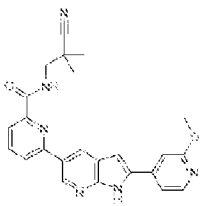
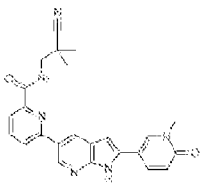
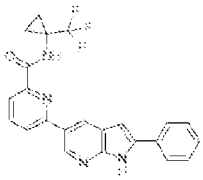
	3-fluoro-1-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carbonyl]pyrrolidine-3-carbonitrile	**412.25**	**P-0115**
	1-[6-[2-(4-fluorophenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carbonyl]pyrrolidine-3-carbonitrile	**412.25**	**P-0116**
	(3S)-1-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carbonyl]pyrrolidine-3-carbonitrile	**394.20**	**P-0117**
	N-(1-cyano-1-methyl-ethyl)-6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carboxamide	**381.90**	**P-0118**
	N-(2-cyanoethyl)-N-methyl-6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carboxamide	**382.05**	**P-0119**
	1-[6-[2-(cyclohexen-1-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carbonyl]pyrrolidine-3-carbonitrile	**398.30**	**P-0120**
	1-[[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]sulfonyl]pyrrolidine-3-carbonitrile	**430.25**	**P-0121**

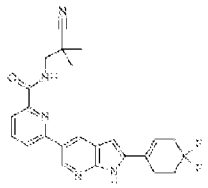
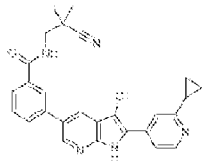
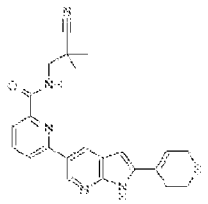
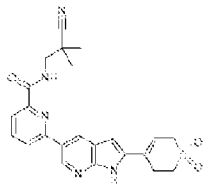
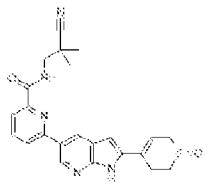
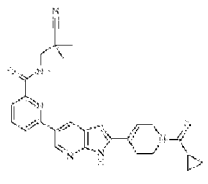
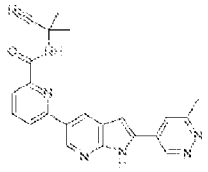
	(3R)-1-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carbonyl]pyrrolidine-3-carbonitrile	**394.25**	**P-0122**
	N-(2-cyano-2-methyl-propyl)-6-[2-(cyclohexen-1-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide	**400.30**	**P-0123**
	1-[6-(2-phenyl-3H-imidazo[4,5-b]pyridin-6-yl)pyridine-2-carbonyl]pyrrolidine-3-carbonitrile	**395.25**	**P-0124**
	6-(3-chloro-2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-N-(2-cyanoethyl)pyridine-2-carboxamide	**401.80**	**P-0125**
	6-(3-bromo-2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-N-(2-cyano-2-methyl-propyl)pyridine-2-carboxamide	**475.65**	**P-0126**
	N-(2-cyano-2-methyl-propyl)-6-(3-iodo-2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carboxamide	**521.80**	**P-0127**
	N-(3-cyanopropyl)-6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carboxamide	**382.30**	**P-0128**

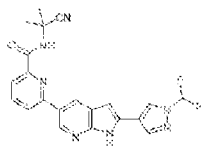
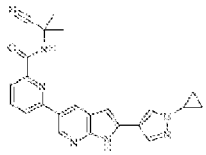
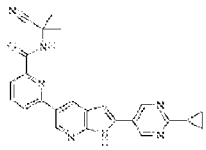
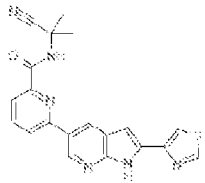
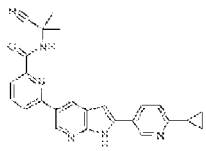
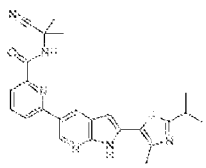
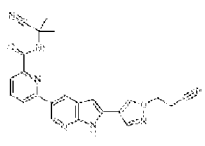
	methyl 1-[[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carbonyl]amino]cyclopropanecarboxylate	**412.90**	**P-0129**
	1-[6-[2-(4-cyano-2-methyl-phenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carbonyl]pyrrolidine-3-carbonitrile	**433.25**	**P-0130**
	1-[6-[2-(4,4-dimethylcyclohexen-1-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carbonyl]pyrrolidine-3-carbonitrile	**426.00**	**P-0131**
	1-[6-[2-(3,6-dihydro-2H-pyran-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carbonyl]pyrrolidine-3-carbonitrile	**399.90**	**P-0132**
	1-[6-[2-(3-cyanophenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carbonyl]pyrrolidine-3-carbonitrile	**418.95**	**P-0133**
	1-[6-[2-[1-(difluoromethyl)pyrazol-4-yl]-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carbonyl]pyrrolidine-3-carbonitrile	**434.10**	**P-0134**
	tert-butyl 3-[5-[6-(3-cyanopyrrolidine-1-carbonyl)-2-pyridyl]-1H-pyrrolo[2,3-b]pyridin-2-yl]-2,5-dihydropyrrole-1-carboxylate	**485.30**	**P-0135**

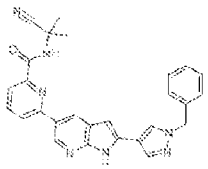
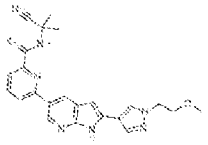
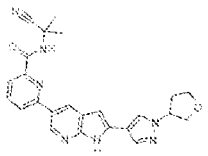
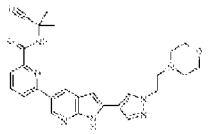
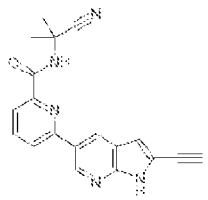
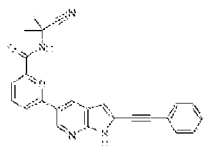
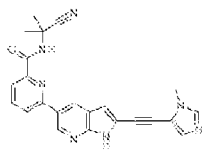
	1-[6-[2-[1-(cyclopropanecarbonyl)-2,5-dihydropyrrol-3-yl]-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carbonyl]pyrrolidine-3-carbonitrile	**453.30**	**P-0136**
	N-[(1-cyanocyclopropyl)methyl]-6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carboxamide	**393.85**	**P-0137**
	6-(3-chloro-2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-N-(2-cyano-2-methyl-propyl)pyridine-2-carboxamide	**429.85**	**P-0138**
	6-(3-chloro-2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-N-(1-cyanocyclopropyl)pyridine-2-carboxamide	**413.85**	**P-0139**
	N-tert-butyl-6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carboxamide	**370.90**	**P-0140**
	N-(2-cyano-2-methyl-propyl)-6-[2-[1-(cyclopropanecarbonyl)-2,5-dihydropyrrol-3-yl]-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide	**455.3**	**P-0141**
	1-[6-[3-chloro-2-(3,6-dihydro-2H-pyran-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carbonyl]pyrrolidine-3-carbonitrile	**433.85**	**P-0142**

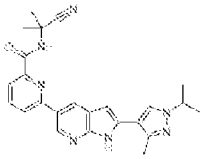
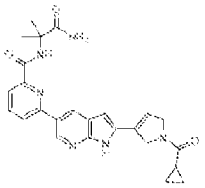
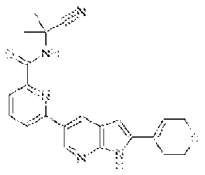
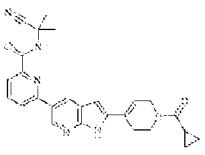
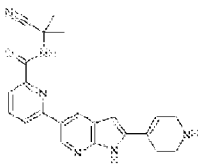
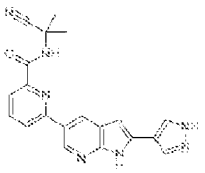
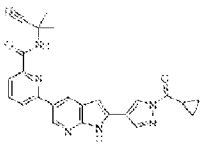
	N-(2-cyanoethyl)-6-(3-iodo-2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carboxamide	**494.05**	**P-0143**
	N-(2-cyano-2-methyl-propyl)-6-[2-(4-fluorophenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide	**413.90**	**P-0144**
	N-(1-cyano-1-methyl-ethyl)-6-[2-(4-fluorophenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide	**399.90**	**P-0145**
	N-(1-cyanocyclopentyl)-6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carboxamide	**407.90**	**P-0146**
	6-(3-bromo-2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-N-(2-cyanoethyl)pyridine-2-carboxamide	**448.95**	**P-0147**
	6-(3-chloro-2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-N-[(1-cyanocyclopropyl)methyl]pyridine-2-carboxamide	**427.80**	**P-0148**
	6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-N-[1-(trifluoromethyl)cyclopentyl]pyridine-2-carboxamide	**450.90**	**P-0149**

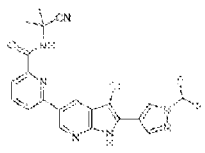
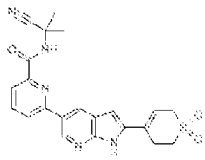
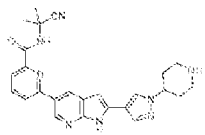
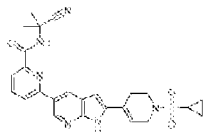
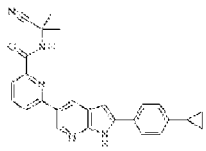
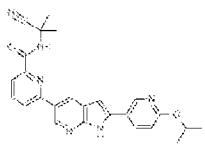
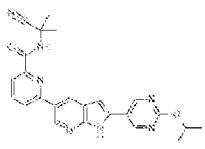
	N-(2-hydroxy-2-methyl-propyl)-6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carboxamide	**387.25**	**P-0150**
	N-[1-(hydroxymethyl)cyclopropyl]-6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carboxamide	**384.90**	**P-0151**
	N-(2-cyano-2-methyl-propyl)-6-[2-(2-cyclopropyl-4-pyridyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide	**437.3**	**P-0152**
	N-(2-cyano-2-methyl-propyl)-6-[2-[1-(difluoromethyl)pyrazol-4-yl]-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide	**436.15**	**P-0153**
	N-(2-cyano-2-methyl-propyl)-6-[2-(2-methoxy-4-pyridyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide	**427.25**	**P-0154**
	N-(2-cyano-2-methyl-propyl)-6-[2-(1-methyl-6-oxo-3-pyridyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide	**427.25**	**P-0155**
	6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide	**422.90**	**P-0156**

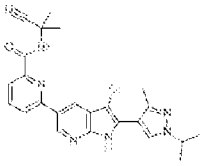
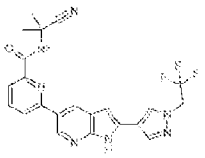
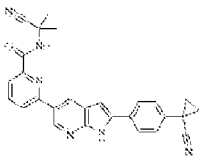
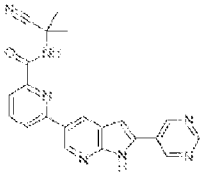
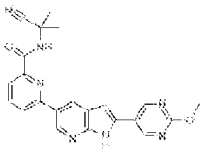
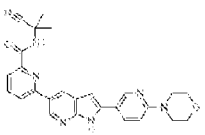
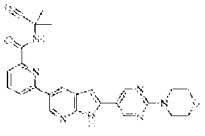
	N-(2-cyano-2-methyl-propyl)-6-[2-(4,4-difluorocyclohexen-1-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide	**436.25**	**P-0157**
	3-[3-chloro-2-(2-cyclopropyl-4-pyridyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]-N-(2-cyano-2-methyl-propyl)benzamide	**471.25**	**P-0158**
	N-(2-cyano-2-methyl-propyl)-6-[2-(3,6-dihydro-2H-thiopyran-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide	**417.90**	**P-0159**
	N-(2-cyano-2-methyl-propyl)-6-[2-(1,1-dioxo-3,6-dihydro-2H-thiopyran-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide	**449.95**	**P-0160**
	N-(2-cyano-2-methyl-propyl)-6-[2-(1-oxo-3,6-dihydro-2H-thiopyran-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide	**433.90**	**P-0161**
	N-(2-cyano-2-methyl-propyl)-6-[2-[1-(cyclopropanecarbonyl)-3,6-dihydro-2H-pyridin-4-yl]-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide	**469.30**	**P-0162**
	N-(1-cyano-1-methyl-ethyl)-6-[2-(6-methylpyridazin-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide	**398.25**	**P-0163**

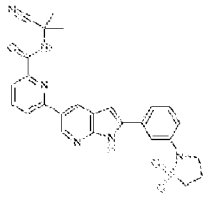
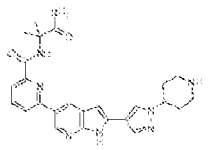
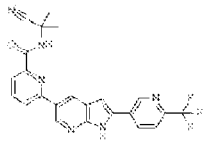
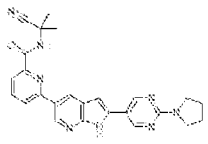
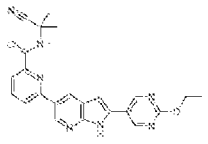
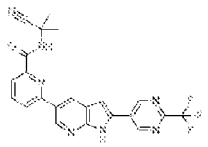
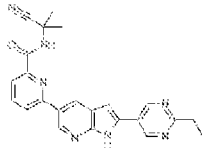
	N-(1-cyano-1-methyl-ethyl)-6-[2-[1-(difluoromethyl)pyrazol-4-yl]-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide	**421.90**	**P-0164**
	N-(1-cyano-1-methyl-ethyl)-6-[2-(1-cyclopropylpyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide	**412.30**	**P-0165**
	N-(1-cyano-1-methyl-ethyl)-6-[2-(2-cyclopropylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide	**424.30**	**P-0166**
	N-(1-cyano-1-methyl-ethyl)-6-(2-thiazol-4-yl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carboxamide	**389.20**	**P-0167**
	N-(1-cyano-1-methyl-ethyl)-6-[2-(6-cyclopropyl-3-pyridyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide	**423.25**	**P-0168**
	N-(1-cyano-1-methyl-ethyl)-6-[2-(2-isopropyl-4-methyl-thiazol-5-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide	**445.25**	**P-0169**
	6-[2-[1-(2-cyanoethyl)pyrazol-4-yl]-1H-pyrrolo[2,3-b]pyridin-5-yl]-N-(1-cyano-1-methyl-ethyl)pyridine-2-carboxamide	**424.95**	**P-0170**

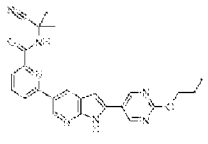
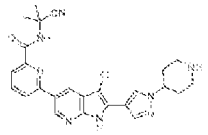
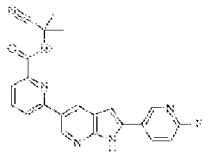
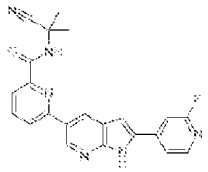
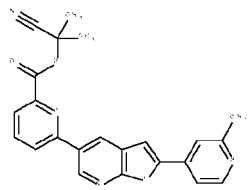
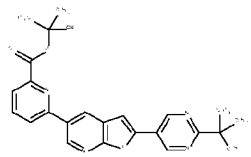
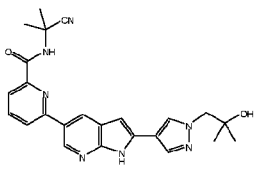
	6-[2-(1-benzylpyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]-N-(1-cyano-1-methyl-ethyl)pyridine-2-carboxamide	**462.30**	**P-0171**
	N-(1-cyano-1-methyl-ethyl)-6-[2-[1-(2-methoxyethyl)pyrazol-4-yl]-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide	**430.30**	**P-0172**
	N-(1-cyano-1-methyl-ethyl)-6-[2-(1-tetrahydrofuran-3-ylpyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide	**442.30**	**P-0173**
	N-(1-cyano-1-methyl-ethyl)-6-[2-[1-(2-morpholinoethyl)pyrazol-4-yl]-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide	**485.45**	**P-0174**
	N-(1-cyano-1-methyl-ethyl)-6-(2-ethynyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carboxamide	**329.80**	**P-0175**
	N-(1-cyano-1-methyl-ethyl)-6-[2-(2-phenylethynyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide	**406.25**	**P-0176**
	N-(1-cyano-1-methyl-ethyl)-6-[2-[2-(3-methylimidazol-4-yl)ethynyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide	**409.90**	**P-0177**

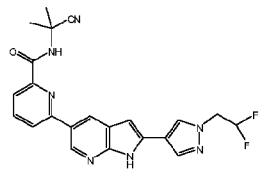
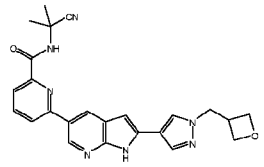
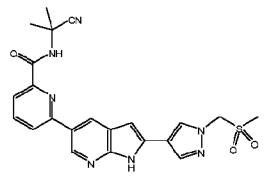
	N-(1-cyano-1-methyl-ethyl)-6-[2-(1-isopropyl-3-methyl-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide	**428.00**	**P-0178**
	N-(2-amino-1,1-dimethyl-2-oxo-ethyl)-6-[2-[1-(cyclopropanecarbonyl)-2,5-dihydropyrrol-3-yl]-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide	**460.25**	**P-0179**
	N-(1-cyano-1-methyl-ethyl)-6-[2-(3,6-dihydro-2H-thiopyran-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide	**404.2**	**P-0180**
	N-(1-cyano-1-methyl-ethyl)-6-[2-[1-(cyclopropanecarbonyl)-3,6-dihydro-2H-pyridin-4-yl]-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide	**455.30**	**P-0181**
	N-(1-cyano-1-methyl-ethyl)-6-[2-(1,2,3,6-tetrahydropyridin-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide	**387.25**	**P-0182**
	N-(1-cyano-1-methyl-ethyl)-6-[2-(1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide	**372.25**	**P-0183**
	N-(1-cyano-1-methyl-ethyl)-6-[2-[1-(cyclopropanecarbonyl)pyrazol-4-yl]-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide	**440.25**	**P-0184**

	6-[3-chloro-2-[1-(difluoromethyl)pyrazol-4-yl]-1H-pyrrolo[2,3-b]pyridin-5-yl]-N-(1-cyano-1-methyl-ethyl)pyridine-2-carboxamide	**455.85**	**P-0185**
	N-(1-cyano-1-methyl-ethyl)-6-[2-(1,1-dioxo-3,6-dihydro-2H-thiopyran-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide	**436.25**	**P-0186**
	N-(1-cyano-1-methyl-ethyl)-6-[2-[1-(4-piperidyl)pyrazol-4-yl]-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide	**455.05**	**P-0187**
	N-(1-cyano-1-methyl-ethyl)-6-[2-(1-cyclopropylsulfonyl-3,6-dihydro-2H-pyridin-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide	**491.30**	**P-0188**
	N-(1-cyano-1-methyl-ethyl)-6-[2-(4-cyclopropylphenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide	**422.25**	**P-0189**
	N-(1-cyano-1-methyl-ethyl)-6-[2-(6-isopropoxy-3-pyridyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide	**441.30**	**P-0190**
	N-(1-cyano-1-methyl-ethyl)-6-[2-(2-isopropoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide	**442.30**	**P-0191**

	6-[3-chloro-2-(1-isopropyl-3-methyl-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]-N-(1-cyano-1-methyl-ethyl)pyridine-2-carboxamide	**461.95**	**P-0192**
	N-(1-cyano-1-methyl-ethyl)-6-[2-[1-(2,2,2-trifluoroethyl)pyrazol-4-yl]-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide	**454.25**	**P-0193**
	6-[2-[4-(1-cyanocyclopropyl)phenyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]-N-(1-cyano-1-methyl-ethyl)pyridine-2-carboxamide	**447.25**	**P-0194**
	N-(1-cyano-1-methyl-ethyl)-6-(2-pyrimidin-5-yl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carboxamide	**384.20**	**P-0195**
	N-(1-cyano-1-methyl-ethyl)-6-[2-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide	**414.25**	**P-0196**
	N-(1-cyano-1-methyl-ethyl)-6-[2-(6-morpholino-3-pyridyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide	**468.40**	**P-0197**
	N-(1-cyano-1-methyl-ethyl)-6-[2-(2-morpholinopyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide	**469.30**	**P-0198**

	N-(1-cyano-1-methyl-ethyl)-6-[2-[3-(1,1-dioxo-1,2-thiazolidin-2-yl)phenyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide	**501.25**	**P-0199**
	N-(2-amino-1,1-dimethyl-2-oxo-ethyl)-6-[2-[1-(4-piperidyl)pyrazol-4-yl]-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide	**473.05**	**P-0200**
	N-(1-cyano-1-methyl-ethyl)-6-[2-[6-(trifluoromethyl)-3-pyridyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide	**451.25**	**P-0201**
	N-(1-cyano-1-methyl-ethyl)-6-[2-(2-pyrrolidin-1-ylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide	**453.35**	**P-0202**
	N-(1-cyano-1-methyl-ethyl)-6-[2-(2-ethoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide	**428.25**	**P-0203**
	N-(1-cyano-1-methyl-ethyl)-6-[2-[2-(trifluoromethyl)pyrimidin-5-yl]-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide	**452.25**	**P-0204**
	N-(1-cyano-1-methyl-ethyl)-6-[2-(2-ethylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide	**412.25**	**P-0205**

	N-(1-cyano-1-methyl-ethyl)-6-[2-(2-propoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide	**442.25**	**P-0206**
	6-[3-chloro-2-[1-(4-piperidyl)pyrazol-4-yl]-1H-pyrrolo[2,3-b]pyridin-5-yl]-N-(1-cyano-1-methyl-ethyl)pyridine-2-carboxamide	**489.35**	**P-0207**
	N-(1-cyano-1-methyl-ethyl)-6-[2-(6-fluoro-3-pyridyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide	**401.20**	**P-0208**
	N-(1-cyano-1-methyl-ethyl)-6-[2-(2-fluoro-4-pyridyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide	**401.20**	**P-0209**
	N-(1-cyano-1-methyl-ethyl)-6-[2-(2-methyl-4-pyridyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide	**397.30**	**P-0210**
	N-(1-cyano-1-methyl-ethyl)-6-[2-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide	**442.30**	**P-0211**
	N-(2-cyanopropan-2-yl)-6-(2-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)picolinamide	**444.10**	**P-0212**

	N-(2-cyanopropan-2-yl)-6-(2-(1-(2,2-difluoroethyl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)picolinamide	**436.10**	**P-0213**
	N-(2-cyanopropan-2-yl)-6-(2-(1-(oxetan-3-ylmethyl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)picolinamide	**441.485**	**P-0214**
	N-(2-cyanopropan-2-yl)-6-(2-(1-((methylsulfonyl)methyl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)picolinamide	**463.512**	**P-0215**

or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer, or a deuterated analog of any of the above compounds.

[0225] Embodiment 23(b) of this disclosure relates to a compound of Table 2:

TABLE 2

N-[1-[3-[2-(4-fluorophenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]benzoyl]-4-piperidyl]acetamide;	**P-0001**
N-methoxy-N-methyl-3-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)benzamide;	**P-0002**
N-methoxy-3-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)benzamide;	**P-0003**
N-cyclopropyl-3-(2-ethynyl-1H-pyrrolo[2,3-b]pyridin-5-yl)benzenesulfonamide;	**P-0004**
[4-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)phenyl]urea;	**P-0005**
1-methyl-3-[4-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)phenyl]urea;	**P-0006**
5-[3-(dimethylsulfamoylamino)phenyl]-2-phenyl-1H-pyrrolo[2,3-b]pyridine;	**P-0007**
N-cyclopropyl-3-[2-(3-hydroxyprop-1-ynyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]benzenesulfonamide;	**P-0008**
N-cyclopropyl-3-[2-[3-(dimethylamino)prop-1-ynyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]benzenesulfonamide;	**P-0009**
3-[2-(2-cyclohexylethynyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]-N-cyclopropyl-benzenesulfonamide;	**P-0010**
tert-butyl N-[1-[5-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-indazole-3-carbonyl]-4-piperidyl]carbamate;	**P-0011**

(4-amino-1-piperidyl)-[5-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-indazol-3-yl]methanone;	**P-0012**
(4-amino-1-piperidyl)-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]methanone;	**P-0013**
N-cyclopropyl-3-[2-(2-phenylethynyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]benzenesulfonamide;	**P-0014**
[(3S)-3-aminopyrrolidin-1-yl]-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]methanone;	**P-0015**
[(3S)-3-aminopyrrolidin-1-yl]-[5-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-indazol-3-yl]methanone;	**P-0016**
tert-butyl N-[1-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carbonyl]-4-piperidyl]carbamate;	**P-0017**
N-[1-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carbonyl]-4-piperidyl]acetamide;	**P-0020**
N-[1-[5-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-indazole-3-carbonyl]-4-piperidyl]acetamide;	**P-0021**
[4-(hydroxymethyl)-1-piperidyl]-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]methanone;	**P-0023**
1-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carbonyl]piperidine-4-carboxylic acid;	**P-0024**
ethyl 1-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carbonyl]piperidine-4-carboxylate;	**P-0025**
[4-(aminomethyl)-1-piperidyl]-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]methanone;	**P-0026**
(4-methyl-1-piperidyl)-[5-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-indazol-3-yl]methanone;	**P-0027**
[3-(methylamino)pyrrolidin-1-yl]-[5-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-indazol-3-yl]methanone;	**P-0028**
(3-aminoazetidin-1-yl)-[5-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-indazol-3-yl]methanone;	**P-0029**
N-methyl-1-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carbonyl]piperidine-4-carboxamide;	**P-0030**
1-ethyl-3-[1-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carbonyl]-4-piperidyl]urea;	**P-0031**
N-[1-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carbonyl]-4-piperidyl]methanesulfonamide;	**P-0032**
(4-amino-1-piperidyl)-[3-methyl-6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]methanone;	**P-0033**
1-[2-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-8-quinolyl]piperidin-4-amine;	**P-0034**
(4-amino-1-piperidyl)-[2-methyl-5-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)phenyl]methanone;	**P-0035**
[(3S)-3-aminopyrrolidin-1-yl]-[3-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)phenyl]methanone;	**P-0036**
(4-amino-1-piperidyl)-[3-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)phenyl]methanone;	**P-0037**
(4-amino-1-piperidyl)-[4-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]methanone;	**P-0038**

[3-(methylamino)pyrrolidin-1-yl]-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]methanone;	**P-0040**
[4-(methylamino)-1-piperidyl]-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]methanone;	**P-0041**
(4-amino-1-piperidyl)-[5-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-indol-3-yl]methanone;	**P-0042**
[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]-(4-piperidyl)methanone	**P-0043**
[4-(methylamino)-1-piperidyl]-[5-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-indazol-3-yl]methanone;	**P-0044**
[(3S)-3-aminopyrrolidin-1-yl]-[4-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]methanone;	**P-0046**
2-(3-aminocyclopentanecarbonyl)-4-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)isoindolin-1-one;	**P-0047**
[(3S)-3-aminopyrrolidin-1-yl]-[2-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)thiazol-4-yl]methanone;	**P-0048**
[6-[2-(1,3-dimethylpyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]-2-pyridyl]-[3-(methylamino)pyrrolidin-1-yl]methanone;	**P-0049**
2-phenyl-5-[6-(4-piperidyloxy)-2-pyridyl]-1H-pyrrolo[2,3-b]pyridine;	**P-0050**
[(3S)-3-(methylamino)pyrrolidin-1-yl]-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]methanone;	**P-0051**
[3-(methylamino)azetidin-1-yl]-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]methanone;	**P-0052**
[(3S)-3-aminopyrrolidin-1-yl]-[5-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)thiazol-2-yl]methanone;	**P-0054**
[6-[2-(4-fluorophenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]-2-pyridyl]-[3-(methylamino)pyrrolidin-1-yl]methanone;	**P-0055**
5-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-N-(4-piperidyl)-1H-indazol-3-amine;	**P-0056**
4-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carbonyl]piperazine-1-carboxamidine;	**P-0057**
[(3R)-3-(methylamino)pyrrolidin-1-yl]-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]methanone;	**P-0058**
5-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-N-pyrrolidin-3-yl-1H-indazol-3-amine;	**P-0059**
[6-[2-(2-methoxy-4-pyridyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]-2-pyridyl]-[3-(methylamino)pyrrolidin-1-yl]methanone;	**P-0060**
[3-(methylamino)pyrrolidin-1-yl]-[6-[2-[1-(2,2,2-trifluoroethyl)pyrazol-4-yl]-1H-pyrrolo[2,3-b]pyridin-5-yl]-2-pyridyl]methanone;	**P-0061**
3-[5-[6-[3-(methylamino)pyrrolidine-1-carbonyl]-2-pyridyl]-1H-pyrrolo[2,3-b]pyridin-2-yl]benzonitrile;	**P-0062**
N-methyl-1-[[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]sulfonyl]pyrrolidin-3-amine;	**P-0063**
(3-amino-1-piperidyl)-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]methanone;	**P-0067**
(3-hydroxypyrrolidin-1-yl)-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]methanone;	**P-0068**

(3-hydroxy-1-piperidyl)-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]methanone;	**P-0069**
[6-[2-(4,4-dimethylcyclohexen-1-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]-2-pyridyl]-[3-(methylamino)pyrrolidin-1-yl]methanone;	**P-0070**
N-(azetidin-3-yl)-6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-sulfonamide;	**P-0071**
6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-N-pyrrolidin-3-yl-pyridine-2-sulfonamide;	**P-0072**
1-[[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]sulfonyl]piperidin-4-amine;	**P-0073**
(4-amino-1-piperidyl)-[5-[2-[1-(cyclopropanecarbonyl)-2,5-dihydropyrrol-3-yl]-1H-pyrrolo[2,3-b]pyridin-5-yl]-1H-indazol-3-yl]methanone;	**P-0074**
[3-amino-3-(trifluoromethyl)pyrrolidin-1-yl]-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]methanone;	**P-0077**
(3-amino-3-methyl-pyrrolidin-1-yl)-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]methanone;	**P-0078**
[3-(methylaminomethyl)pyrrolidin-1-yl]-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]methanone;	**P-0079**
[3-(methylamino)-1-piperidyl]-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]methanone;	**P-0080**
(4-amino-4-methyl-1-piperidyl)-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]methanone;	**P-0081**
(3-amino-3-methyl-1-piperidyl)-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]methanone;	**P-0082**
[(7S)-7-amino-5-azaspiro[2.4]heptan-5-yl]-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]methanone;	**P-0083**
N-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]azetidine-3-carboxamide;	**P-0084**
[3-(cyclopropylamino)pyrrolidin-1-yl]-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]methanone;	**P-0085**
6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-N-(4-piperidyl)pyridine-2-sulfonamide;	**P-0086**
N-methyl-1-[[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]methyl]pyrrolidin-3-amine;	**P-0087**
N-(4-aminocyclohexyl)-6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-sulfonamide;	**P-0088**
(4,4-difluoro-1-piperidyl)-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]methanone;	**P-0089**
(3,3-difluoroazetidin-1-yl)-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]methanone;	**P-0090**
(3-methoxyazetidin-1-yl)-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]methanone;	**P-0091**
methyl 4-methyl-1-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carbonyl]piperidine-4-carboxylate;	**P-0092**
(3,3-difluoropyrrolidin-1-yl)-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]methanone;	**P-0093**
4-methyl-1-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carbonyl]piperidine-4-carbonitrile;	**P-0094**

(3-methoxypyrrolidin-1-yl)-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]methanone	**P-0095**
N-methyl-1-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carbonyl]pyrrolidine-3-carboxamide;	**P-0096**
(3-imidazol-1-ylpyrrolidin-1-yl)-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]methanone;	**P-0097**
(4-methoxy-1-piperidyl)-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]methanone;	**P-0098**
N-(2-cyanoethyl)-6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carboxamide;	**P-0099**
N-(2-cyano-2-methyl-propyl)-6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carboxamide;	**P-0100**
N-[1-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carbonyl]pyrrolidin-3-yl]methanesulfonamide;	**P-0101**
(3-morpholinopyrrolidin-1-yl)-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]methanone;	**P-0102**
[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]-[3-(trifluoromethyl)pyrrolidin-1-yl]methanone;	**P-0103**
[3-(dimethylamino)pyrrolidin-1-yl]-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]methanone;	**P-0104**
1-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carbonyl]pyrrolidine-3-carbonitrile;	**P-0105**
[(3R)-3-(methylamino)pyrrolidin-1-yl]-[5-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-thienyl]methanone;	**P-0106**
N-(1-methylsulfonylpyrrolidin-3-yl)-6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-sulfonamide;	**P-0107**
N-(2-cyano-2-methyl-propyl)-6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-sulfonamide;	**P-0108**
N-cyclopropyl-6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-sulfonamide;	**P-0109**
(3,3-difluoropyrrolidin-1-yl)-[6-[2-[1-(2,2,2-trifluoroethyl)pyrazol-4-yl]-1H-pyrrolo[2,3-b]pyridin-5-yl]-2-pyridyl]methanone;	**P-0112**
N-(2-cyano-2-methyl-propyl)-6-[2-[1-(2,2,2-trifluoroethyl)pyrazol-4-yl]-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0113**
3-fluoro-1-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carbonyl]pyrrolidine-3-carbonitrile;	**P-0115**
1-[6-[2-(4-fluorophenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carbonyl]pyrrolidine-3-carbonitrile;	**P-0116**
(3S)-1-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carbonyl]pyrrolidine-3-carbonitrile;	**P-0117**
N-(1-cyano-1-methyl-ethyl)-6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carboxamide;	**P-0118**
N-(2-cyanoethyl)-N-methyl-6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carboxamide;	**P-0119**
1-[6-[2-(cyclohexen-1-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carbonyl]pyrrolidine-3-carbonitrile;	**P-0120**
1-[[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]sulfonyl]pyrrolidine-3-carbonitrile;	**P-0121**

(3R)-1-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carbonyl]pyrrolidine-3-carbonitrile;	**P-0122**
N-(2-cyano-2-methyl-propyl)-6-[2-(cyclohexen-1-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0123**
1-[6-(2-phenyl-3H-imidazo[4,5-b]pyridin-6-yl)pyridine-2-carbonyl]pyrrolidine-3-carbonitrile;	**P-0124**
6-(3-chloro-2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-N-(2-cyanoethyl)pyridine-2-carboxamide;	**P-0125**
6-(3-bromo-2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-N-(2-cyano-2-methyl-propyl)pyridine-2-carboxamide;	**P-0126**
N-(2-cyano-2-methyl-propyl)-6-(3-iodo-2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carboxamide;	**P-0127**
N-(3-cyanopropyl)-6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carboxamide;	**P-0128**
1-[6-[2-(4-cyano-2-methyl-phenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carbonyl]pyrrolidine-3-carbonitrile;	**P-0130**
1-[6-[2-(4,4-dimethylcyclohexen-1-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carbonyl]pyrrolidine-3-carbonitrile;	**P-0131**
1-[6-[2-(3,6-dihydro-2H-pyran-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carbonyl]pyrrolidine-3-carbonitrile;	**P-0132**
1-[6-[2-(3-cyanophenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carbonyl]pyrrolidine-3-carbonitrile;	**P-0133**
1-[6-[2-[1-(difluoromethyl)pyrazol-4-yl]-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carbonyl]pyrrolidine-3-carbonitrile;	**P-0134**
tert-butyl 3-[5-[6-(3-cyanopyrrolidine-1-carbonyl)-2-pyridyl]-1H-pyrrolo[2,3-b]pyridin-2-yl]-2,5-dihydropyrrole-1-carboxylate;	**P-0135**
1-[6-[2-[1-(cyclopropanecarbonyl)-2,5-dihydropyrrol-3-yl]-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carbonyl]pyrrolidine-3-carbonitrile;	**P-0136**
6-(3-chloro-2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-N-(2-cyano-2-methyl-propyl)pyridine-2-carboxamide;	**P-0138**
N-(2-cyano-2-methyl-propyl)-6-[2-[1-(cyclopropanecarbonyl)-2,5-dihydropyrrol-3-yl]-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0141**
1-[6-[3-chloro-2-(3,6-dihydro-2H-pyran-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carbonyl]pyrrolidine-3-carbonitrile;	**P-0142**
N-(2-cyanoethyl)-6-(3-iodo-2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carboxamide;	**P-0143**
N-(2-cyano-2-methyl-propyl)-6-[2-(4-fluorophenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0144**
N-(1-cyano-1-methyl-ethyl)-6-[2-(4-fluorophenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0145**
6-(3-bromo-2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-N-(2-cyanoethyl)pyridine-2-carboxamide;	**P-0147**
N-(2-hydroxy-2-methyl-propyl)-6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carboxamide;	**P-0150**
N-(2-cyano-2-methyl-propyl)-6-[2-(2-cyclopropyl-4-pyridyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0152**
N-(2-cyano-2-methyl-propyl)-6-[2-[1-(difluoromethyl)pyrazol-4-yl]-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0153**

N-(2-cyano-2-methyl-propyl)-6-[2-(2-methoxy-4-pyridyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0154**
N-(2-cyano-2-methyl-propyl)-6-[2-(1-methyl-6-oxo-3-pyridyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0155**
N-(2-cyano-2-methyl-propyl)-6-[2-(4,4-difluorocyclohexen-1-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0157**
3-[3-chloro-2-(2-cyclopropyl-4-pyridyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]-N-(2-cyano-2-methyl-propyl)benzamide;	**P-0158**
N-(2-cyano-2-methyl-propyl)-6-[2-(3,6-dihydro-2H-thiopyran-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0159**
N-(2-cyano-2-methyl-propyl)-6-[2-(1,1-dioxo-3,6-dihydro-2H-thiopyran-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0160**
N-(2-cyano-2-methyl-propyl)-6-[2-(1-oxo-3,6-dihydro-2H-thiopyran-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0161**
N-(2-cyano-2-methyl-propyl)-6-[2-[1-(cyclopropanecarbonyl)-3,6-dihydro-2H-pyridin-4-yl]-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0162**
N-(1-cyano-1-methyl-ethyl)-6-[2-(6-methylpyridazin-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0163**
N-(1-cyano-1-methyl-ethyl)-6-[2-[1-(difluoromethyl)pyrazol-4-yl]-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0164**
N-(1-cyano-1-methyl-ethyl)-6-[2-(1-cyclopropylpyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0165**
N-(1-cyano-1-methyl-ethyl)-6-[2-(2-cyclopropylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0166**
N-(1-cyano-1-methyl-ethyl)-6-(2-thiazol-4-yl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carboxamide;	**P-0167**
N-(1-cyano-1-methyl-ethyl)-6-[2-(6-cyclopropyl-3-pyridyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0168**
N-(1-cyano-1-methyl-ethyl)-6-[2-(2-isopropyl-4-methyl-thiazol-5-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0169**
6-[2-[1-(2-cyanoethyl)pyrazol-4-yl]-1H-pyrrolo[2,3-b]pyridin-5-yl]-N-(1-cyano-1-methyl-ethyl)pyridine-2-carboxamide;	**P-0170**
6-[2-(1-benzylpyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]-N-(1-cyano-1-methyl-ethyl)pyridine-2-carboxamide;	**P-0171**
N-(1-cyano-1-methyl-ethyl)-6-[2-[1-(2-methoxyethyl)pyrazol-4-yl]-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0172**
N-(1-cyano-1-methyl-ethyl)-6-[2-(1-tetrahydrofuran-3-ylpyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0173**
N-(1-cyano-1-methyl-ethyl)-6-[2-[1-(2-morpholinoethyl)pyrazol-4-yl]-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0174**
N-(1-cyano-1-methyl-ethyl)-6-(2-ethynyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carboxamide;	**P-0175**
N-(1-cyano-1-methyl-ethyl)-6-[2-(2-phenylethynyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0176**
N-(1-cyano-1-methyl-ethyl)-6-[2-[2-(3-methylimidazol-4-yl)ethynyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0177**
N-(1-cyano-1-methyl-ethyl)-6-[2-(1-isopropyl-3-methyl-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0178**

N-(2-amino-1,1-dimethyl-2-oxo-ethyl)-6-[2-[1-(cyclopropanecarbonyl)-2,5-dihydropyrrol-3-yl]-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0179**
N-(1-cyano-1-methyl-ethyl)-6-[2-(3,6-dihydro-2H-thiopyran-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0180**
N-(1-cyano-1-methyl-ethyl)-6-[2-[1-(cyclopropanecarbonyl)-3,6-dihydro-2H-pyridin-4-yl]-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0181**
N-(1-cyano-1-methyl-ethyl)-6-[2-(1,2,3,6-tetrahydropyridin-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0182**
N-(1-cyano-1-methyl-ethyl)-6-[2-(1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0183**
N-(1-cyano-1-methyl-ethyl)-6-[2-[1-(cyclopropanecarbonyl)pyrazol-4-yl]-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0184**
6-[3-chloro-2-[1-(difluoromethyl)pyrazol-4-yl]-1H-pyrrolo[2,3-b]pyridin-5-yl]-N-(1-cyano-1-methyl-ethyl)pyridine-2-carboxamide;	**P-0185**
N-(1-cyano-1-methyl-ethyl)-6-[2-(1,1-dioxo-3,6-dihydro-2H-thiopyran-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0186**
N-(1-cyano-1-methyl-ethyl)-6-[2-[1-(4-piperidyl)pyrazol-4-yl]-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0187**
N-(1-cyano-1-methyl-ethyl)-6-[2-(1-cyclopropylsulfonyl-3,6-dihydro-2H-pyridin-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0188**
N-(1-cyano-1-methyl-ethyl)-6-[2-(4-cyclopropylphenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0189**
N-(1-cyano-1-methyl-ethyl)-6-[2-(6-isopropoxy-3-pyridyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0190**
N-(1-cyano-1-methyl-ethyl)-6-[2-(2-isopropoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0191**
6-[3-chloro-2-(1-isopropyl-3-methyl-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]-N-(1-cyano-1-methyl-ethyl)pyridine-2-carboxamide;	**P-0192**
N-(1-cyano-1-methyl-ethyl)-6-[2-[1-(2,2,2-trifluoroethyl)pyrazol-4-yl]-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0193**
6-[2-[4-(1-cyanocyclopropyl)phenyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]-N-(1-cyano-1-methyl-ethyl)pyridine-2-carboxamide;	**P-0194**
N-(1-cyano-1-methyl-ethyl)-6-(2-pyrimidin-5-yl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carboxamide;	**P-0195**
N-(1-cyano-1-methyl-ethyl)-6-[2-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0196**
N-(1-cyano-1-methyl-ethyl)-6-[2-(6-morpholino-3-pyridyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0197**
N-(1-cyano-1-methyl-ethyl)-6-[2-(2-morpholinopyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0198**
N-(1-cyano-1-methyl-ethyl)-6-[2-[3-(1,1-dioxo-1,2-thiazolidin-2-yl)phenyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0199**
N-(2-amino-1,1-dimethyl-2-oxo-ethyl)-6-[2-[1-(4-piperidyl)pyrazol-4-yl]-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0200**
N-(1-cyano-1-methyl-ethyl)-6-[2-[6-(trifluoromethyl)-3-pyridyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0201**
N-(1-cyano-1-methyl-ethyl)-6-[2-(2-pyrrolidin-1-ylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0202**

N-(1-cyano-1-methyl-ethyl)-6-[2-(2-ethoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0203**
N-(1-cyano-1-methyl-ethyl)-6-[2-[2-(trifluoromethyl)pyrimidin-5-yl]-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0204**
N-(1-cyano-1-methyl-ethyl)-6-[2-(2-ethylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0205**
N-(1-cyano-1-methyl-ethyl)-6-[2-(2-propoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0206**
6-[3-chloro-2-[1-(4-piperidyl)pyrazol-4-yl]-1H-pyrrolo[2,3-b]pyridin-5-yl]-N-(1-cyano-1-methyl-ethyl)pyridine-2-carboxamide;	**P-0207**
N-(1-cyano-1-methyl-ethyl)-6-[2-(6-fluoro-3-pyridyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0208**
N-(1-cyano-1-methyl-ethyl)-6-[2-(2-fluoro-4-pyridyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0209**
N-(1-cyano-1-methyl-ethyl)-6-[2-(2-methyl-4-pyridyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0210**
N-(1-cyano-1-methyl-ethyl)-6-[2-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0211**
N-(2-cyanopropan-2-yl)-6-(2-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)picolinamide;	**P-0212**
N-(2-cyanopropan-2-yl)-6-(2-(1-(2,2-difluoroethyl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)picolinamide;	**P-0213**
N-(2-cyanopropan-2-yl)-6-(2-(1-(oxetan-3-ylmethyl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)picolinamide;	**P-0214**
N-(2-cyanopropan-2-yl)-6-(2-(1-((methylsulfonyl)methyl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)picolinamide;	**P-0215**

or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer,or a deuterated analog of any of the above compounds.

[0226] Embodiment 24(a) of this disclosure relates to a pharmaceutical composition according to the compound in any one of Embodiments 1A, 1B, 1C, 2-4, 5(a)-5(e), 6(a) -6(e), 7(a)-7(c), 8(a)-8(j), (9a)-9(v), 10(a)-10(s), 11(a)-11(q), 12(a)-12(h), 13, 14(a) –14(k), 15, 16, 17(a)-17(q), 18(a)-18(y), 19, 20, 21, 22, 23a, or 23b and a pharmaceutically acceptable carrier. Embodiment 24(b) of this disclosure relates to a pharmaceutical composition according to the compound in any one of Embodiments 1A, 1B, 1C, 2-4, 5(a)-5(e), 6(a) -6(e), 7(a)-7(c), 8(a)-8(j), (9a)-9(v), 10(a)-10(s), 11(a)-11(q), 12(a)-12(h), 13, 14(a) –14(k), 15, 16, 17(a)-17(q), 18(a)-18(y), 19, 20, 21, 22, or 23b and a pharmaceutically acceptable carrier.

[0227] Embodiment 25 of this disclosure relates to the pharmaceutical composition of Embodiment 24(a) or Embodiment 24(b) further comprising a second pharmaceutical agent selected from the group consisting of an anti-proliferative agent, an anti-inflammatory agent, an immunomodulatory agent and an immunosuppressive agent.

[0228] Embodiment 26 of this disclosure relates to the pharmaceutical composition of Embodiment 25, wherein the second pharmaceutical agent is i) an alkylating agent selected from adozelesin, altretamine, bizelesin, busulfan, carboplatin, carboquone, carmustine, chlorambucil, cisplatin, cyclophosphamide, dacarbazine, estramustine, fotemustine, hepsulfam, ifosfamide, improsulfan, irofulven, lomustine, mechlorethamine, melphalan, oxaliplatin, piposulfan, semustine, streptozocin, temozolomide, thiotepa, and treosulfan; ii) an antibiotic selected from bleomycin, dactinomycin, daunorubicin, doxorubicin, epirubicin, idarubicin, menogaril, mitomycin, mitoxantrone, neocarzinostatin, pentostatin, and plicamycin; an antimetabolite, including, but not limited to, azacitidine, capecitabine, cladribine, clofarabine, cytarabine, decitabine, floxuridine, fludarabine, 5-fluorouracil, ftorafur, gemcitabine, hydroxyurea, mercaptopurine, methotrexate, nelarabine, pemetrexed, raltitrexed, thioguanine, and trimetrexate; iii) an antibody therapy agent selected from alemtuzumab, bevacizumab, cetuximab, galiximab, gemtuzumab, panitumumab, pembrolizumab, pertuzumab, rituximab, tositumomab, trastuzumab, and 90 Y ibritumomab tiuxetan; a hormone or hormone antagonist, including, but not limited to, anastrozole, androgens, buserelin, diethylstilbestrol, exemestane, flutamide, fulvestrant, goserelin, idoxifene, letrozole, leuprolide, magestrol, raloxifene, tamoxifen, and toremifene; iv) a taxane selected from DJ-927, docetaxel, TPI 287, paclitaxel and DHA-paclitaxel; v) a retinoid selected from alitretinoin, bexarotene, fenretinide, isotretinoin, and tretinoin; vi) an alkaloid selected from etoposide, homoharringtonine, teniposide, vinblastine, vincristine, vindesine, and vinorelbine; vii) an antiangiogenic agent selected from AE-941 (GW786034, Neovastat), ABT-510, 2-methoxyestradiol, lenalidomide, and thalidomide; viii) a topoisomerase inhibitor selected from amsacrine, edotecarin, exatecan, irinotecan (also active metabolite SN-38 (7-ethyl-10-hydroxy-camptothecin)), rubitecan, topotecan, and 9-aminocamptothecin; ix) a kinase inhibitor selected from erlotinib, gefitinib, flavopiridol, imatinib mesylate, lapatinib, sorafenib, sunitinib malate, AEE-788, AG-013736, AMG 706, AMN107, BMS-354825, BMS-599626, UCN-01 (7-hydroxystaurosporine), vemurafenib, dabrafenib, trametinib, cobimetinib selumetinib and vatalanib; x) a targeted signal transduction inhibitor selected from bortezomib, geldanamycin, and rapamycin; xi) a biological response modifier selected from imiquimod, interferon-.alpha., and interleukin-2; xii) an IDO inhibitor (e.g. indoximod); and xiii) a chemotherapeutic agent selected from 3-AP (3-amino-2-carboxyaldehyde thiosemicarbazone), altrasentan, aminoglutethimide, anagrelide, asparaginase, bryostatin-1, cilengitide, elesclomol, eribulin mesylate (E7389), ixabepilone, lonidamine, masoprocol, mitoguanazone, oblimersen, sulindac, testolactone, tiazofurin, mTOR inhibitors (e.g. sirolimus, temsirolimus, everolimus, deforolimus), PI3K inhibitors (e.g. BEZ235, GDC-0941, XL147, XL765), Cdk4 inhibitors (e.g. PD-332991), Akt inhibitors, Hsp90 inhibitors (e.g.

geldanamycin, radicicol, tanespimycin), farnesyltransferase inhibitors (e.g. tipifarnib) and Aromatase inhibitors (anastrozole letrozole exemestane); xiii) a Mek inhibitor; xiv) a tyrosine kinase inhibitor as described herein; or xv) an EGFR inhibitor.

[0229] Embodiment 27 of this disclosure relates to a method for treatment of a disease or condition modulated by a FLT3 protein kinase, wherein the disease is an inflammatory disease, an inflammatory condition, an autoimmune disease or cancer, said method comprising administering to a subject suffering from the disease a therapeutically effective amount of a compound of any one of Embodiments 1A, 1B, 1C, 2-4, 5(a)-5(e), 6(a) -6(e), 7(a)-7(c), 8(a)-8(j), (9a)-9(v), 10(a)-10(s), 11(a)-11(q), 12(a)-12(h), 13, 14(a) – 14(k), 15, 16, 17(a)-17(q), 18(a)-18(y), 19, 20, 21, 22, 23a, or 23b or a pharmaceutical composition of any one of Embodiments 24(a)-26.

[0230] Embodiment 28 of this disclosure relates to a method for treating a subject with a disease or condition mediated by a FLT3 protein kinase, said method comprising administering to the subject an effective amount of a compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a)-5(e), 6(a) -6(e), 7(a)-7(c), 8(a)-8(j), (9a)-9(v), 10(a)-10(s), 11(a)-11(q), 12(a)-12(h), 13, 14(a) – 14(k), 15, 16, 17(a)-17(q), 18(a)-18(y), 19, 20, 21, 22, 23a, or 23b or a pharmaceutically acceptable salt, deuterated analog, a tautomer or an isomer thereof, or a pharmaceutical composition according to any one of Embodiments 24(a)-26, wherein the disease or condition is acute myeloid leukemia, stem cell ablation and myelopreparation for stem cell transplant, primary progressive multiple sclerosis, complex regional pain syndrome, reflex sympathetic dystrophy, muscular dystrophy, duchenne muscular dystrophy, causalgia, neuro-inflammation, neuroinflammatory disorders, benign forgetfulness, HIV, binswager type dementia, dementia with lewy bodie, prosencephaly, microencepahy, cerebral palsy, congenital hydrocephalus, abdominal dropsy, progressive supranuclear palsy, glaucoma, addiction disorders, dependencies, alcoholism, tremors, Wilson's disease, vascular dementias, multi infarct dementia, fronto temporal dementia, pseudo-dementia, bladder cancer, basal cell carcinoma, cholangiocarcinoma, colon cancer, endometrial cancer, esophageal cancer, Ewing's sarcoma, gastric cancer, glioma, hepatocellular carcinoma, Hodgkin lymphoma, laryngeal carcinoma, leukemia, liver cancer, lung cancer, melanoma, mesothelioma, pancreatic cancer, rectal cancer, renal cancer, squamous cell carcinoma, t cell lymphoma, thyroid cancer, monocytic leukemia, pheochromocytoma, malignant peripheral nerve cell tumors, malignant peripheral nerve sheath tumors (MPNST), cutaneous and plexiform neurofibromas, leiomyoadenomatoid tumor, fibroids, uterine fibroids, leiomyosarcoma, papillary thyroid cancer, anaplastic thyroid cancer, medullary thyroid cancer, follicular thyroid cancer, hurthle cell carcinoma, thyroid cancer,

ascites, malignant ascites, mesothelioma, salivary gland tumors, mucoepidermoid carcinoma of the salivary gland, acinic cell carcinoma of the salivary gland, gastrointestinal stromal tumors (GIST), tumors that cause effusions in potential spaces of the body, pleural effusions, pericardial effusions, peritoneal effusions aka ascites, giant cell tumors (GCT), GCT of bone other sarcomas, tumor angiogenesis, or paracrine tumor growth.

[0231] Embodiment 29 of this disclosure relates to a method for treating a subject with a disease or condition mediated by a FLT3 protein kinase, said method comprising administering to the subject an effective amount of a compound according to any one of Embodiments 1A, 1B, 1C, 2-4, 5(a)-5(e), 6(a) -6(e), 7(a)-7(c), 8(a)-8(j), (9a)-9(v), 10(a)-10(s), 11(a)-11(q), 12(a)-12(h), 13, 14(a) – 14(k), 15, 16, 17(a)-17(q), 18(a)-18(y), 19, 20, 21, 22, 23a, or 23b or a pharmaceutically acceptable salt, deuterated analog, a tautomer or an isomer thereof, or a pharmaceutical composition according to any one of Embodiments 24(a)-26, wherein the disease or condition is lysosomal storage selected from the group consisting of mucolipodosis, alpha-mannosidosis; aspartylglucosaminuria; Batten disease; beta-mannosidosis; cystinosis; Danon disease; Fabry disease; Farber disease; fucosidosis; galactosialidosis; Gaucher disease; gangliosidosis; Krabbe disease; metachromatic leukodystrophy; mucopolysaccharidoses disorders; aspartylglucosaminuria; Batten disease; beta-mannosidosis; cystinosis; Danon disease; Fabry disease; Farber disease; fucosidosis; galactosialidosis; Gaucher disease; gangliosidosis; Krabbe disease; metachromatic leukodystrophy; mucopolysaccharidoses disorders; mucolipidosis type I (Sialidosis); Mucolipidosis type II (I-Cell disease); Mucolipidosis type III (Pseudo-Hurler polydystrophy); Mucolipidosis type IV; multiple sulfatase deficiency; Niemann–Pick types A, B, C; Pompe disease (glycogen storage disease); pycnodysostosis; Sandhoff disease; Schindler disease; Salla disease/sialic acid storage disease; Tay–Sachs; and Wolman disease.

[0232] Embodiment 30 of this disclosure relates to the method according to any one of Embodiments 27-29, wherein FLT3 protein kinase is a mutated form comprising a FLT3 internal tandem duplication (ITD) mutation.

[0233] Embodiment 31 of this disclosure relates to the method according to Embodiment 30, wherein mutated FLT3 protein kinase further comprises a D835 mutation, a F691L mutation, or both D835 and F691L mutations.

[0234] Embodiment 32 of this disclosure relates to the method according to Embodiment 31, wherein mutated FLT3 protein kinase further comprises a D835Y mutation, a F691L mutation, or both D835Y and F691L mutations.

[0235] Embodiment 33 of this disclosure relates to a method for treating a subject with a disease or condition mediated by a (TGF-β) receptor type 2, said method comprising administering to the subject an effective amount of a compound according to any one of Embodiments 1-23, or a pharmaceutically acceptable salt, deuterated analog, a tautomer or an isomer thereof, or a pharmaceutical composition according to any one of claims 23-26, wherein the disease or condition is fibrosis, cardiovascular disease or cancer. In a sub-embodiment of Embodiment 33, the cancer is breast cancer, pancreatic cancer, hepatocellular carcinoma or bladder cancer. In another sub-embodiment of Embodiment 33, the cancer treatement is cancer immunotherapy by (TGF-β) receptor type 2 inhibition.

III. General

[0236] In another embodiment, the present disclosure relates to compounds of Formula I, all embodiments and sub-embodiments thereof including any one or more of compounds P-0001 to P-0215, and any other compounds as described herein, that are useful as inhibitors of an oncogenic FLT3 or a FLT3 mutant, and the use of the compounds in treating a subject suffering from diseases that are mediated by a mutated FLT3 kinase. In another embodiment, the present disclosure relates to compounds of Formula I, all embodiments and sub-embodiments thereof including any one or more of compounds P-0001 to P-0215, and any other compounds as described herein, that are selective for FLT3 over c-KIT.

[0237] In another embodiment, compounds including a cyano or cyanoalkyl group at particular substituents within any of the formulae described in this disclosure, including any one or more of the compounds listed in Tables 1 or 2, exhibit surprising and unexpected potency against FLT3. In another embodiment, compounds including a cyano or cyanoalkyl group at particular substituents within any of the formulae described in this disclosure, including any one or more of the compounds listed in Tables 1 or 2, exhibit surprising and unexpected potency against FLT3 ITD. In another embodiment, compounds having a cyano or cyanoalkyl group as part of the Z^5 variable, as described within any of the formulae in this disclosure, including any one or more of the compounds listed in Tables 1 or 2, exhibit surprising and unexpected-potency against FLT3. In another embodiment, compounds having a cyano or cyanoalkyl group as part of the Z^5 variable, as described within any of the formulae in this disclosure, including any one or more of the compounds listed in Tables 1 or 2, exhibit surprising and unexpected potency against FLT3 ITD.

[0238] FLT3 kinase is a tyrosine kinase receptor involved in the regulation and stimulation of cellular proliferation. See e.g., Gilliland et al., Blood 100: 1532-42 (2002). The FLT3 kinase is a member of the class III receptor tyrosine kinase (RTKIII) receptor family and belongs to the

same subfamily of tyrosine kinases as c-kit, c-fms, and the platelet-derived growth factor α and β receptors. See e.g., Lyman et al., FLT3 Ligand in THE CYTOKINE HANDBOOK 989 (Thomson et al., eds. 4th Ed.) (2003). The FLT3 kinase has five immunoglobulin-like domains in its extracellular region as well as an insert region of 75-100 amino acids in the middle of its cytoplasmic domain. FLT3 kinase is activated upon the binding of the FLT3 ligand, which causes receptor dimerization. Dimerization of the FLT3 kinase by FLT3 ligand activates the intracellular kinase activity as well as a cascade of downstream substrates including Stat5, Ras, phosphatidylinositol-3-kinase (PI3K), PLCγ , Erk2, Akt, MAPK, SHC, SHP2, and SHIP. See e.g., Rosnet et al., Acta Haematol. 95: 218 (1996); Hayakawa et al., Oncogene 19: 624 (2000); Mizuki et al., Blood 96: 3907 (2000); and Gilliand et al., Curr. Opin. Hematol. 9: 274-81 (2002). Both membrane-bound and soluble FLT3 ligand bind, dimerize, and subsequently activate the FLT3 kinase.

[0239] In normal cells, immature hematopoietic cells, typically CD34+ cells, placenta, gonads, and brain express FLT3 kinase. See, e.g., Rosnet, et al., Blood 82: 1110-19 (1993); Small et al., Proc. Natl. Acad. Sci. U.S.A. 91: 459-63 (1994); and Rosnet et al., Leukemia 10: 238-48 (1996). However, efficient stimulation of proliferation via FLT3 kinase typically requires other hematopoietic growth factors or interleukins. FLT3 kinase also plays a critical role in immune function through its regulation of dendritic cell proliferation and differentiation. See e.g., McKenna et al., Blood 95: 3489-97 (2000).

[0240] Numerous hematologic malignancies express FLT3 kinase, the most prominent of which is AML. See e.g., Yokota et al., Leukemia 11: 1605-09 (1997). Other FLT3 expressing malignancies include B-precursor cell acute lymphoblastic leukemias, myelodysplastic leukemias, T-cell acute lymphoblastic leukemias, and chronic myelogenous leukemias. See e.g., Rasko et al., Leukemia 9: 2058-66 (1995).

[0241] FLT3 kinase mutations associated with hematologic malignancies are activating mutations. In other words, the FLT3 kinase is constitutively activated without the need for binding and dimerization by FLT3 ligand, and therefore stimulates the cell to grow continuously.

[0242] Several studies have identified inhibitors of FLT3 kinase activity that also inhibit the kinase activity of related receptors, e.g., VEGF receptor (VEGFR), PDGF receptor (PDGFR), and kit receptor kinases. See e.g., Mendel et al., Clin. Cancer Res. 9: 327-37 (2003); O'Farrell et al., Blood 101: 3597-605 (2003); and Sun et al., J. Med. Chem. 46: 1116-19 (2003). Such compounds effectively inhibit FLT3 kinase-mediated phosphorylation, cytokine production, cellular proliferation, resulting in the induction of apoptosis. See e.g., Spiekermann et al., Blood

101: 1494-1504 (2003). Moreover, such compounds have potent antitumor activity in vitro and in vivo.

[0243] In some embodiments, the oncogenic FLT3 or FLT3 mutant is encoded by a FLT3 gene with an internal tandem duplication (ITD) mutation in the juxtamembrane as described in U.S. Patent No. 6,846,630, which is herein incorporated by reference. In certain embodiments, the oncogenic FLT3 or FLT3 mutant encoded by FLT3 with ITD mutations has one or more mutations at residues F691, D835, Y842 or combinations thereof. In some embodiments, the oncogenic FLT3 or FLT3 mutant has one or more mutations selected from F691L, D835V/Y, Y842C/H or combinations thereof.

[0244] In some embodiments, the subject has a FLT3 gene mutation encoding an FLT3 mutant having an amino acid substitution at residues F691, D835, Y842 or combinations thereof. In certain instances, the amino acid substitution is selected from F691L, D835V/Y, Y842C/H or combinations thereof.

[0245] In some embodiments, the disclosure provides a method of inhibiting an oncogenic FLT3 or a mutant FLT3. The method includes contacting the FLT3 kinase with a compound as described herein. In some embodiments, the oncogenic FLT3 or FLT3 mutant is encoded by a FLT3 gene having an ITD mutation. In some embodiments, the oncogenic FLT3 or FLT3 mutant encoded by an FLT3 gene with an ITD mutation has one or more mutations at residues F691, D835, Y842 or combinations thereof. In some embodiments, the oncogenic FLT3 or FLT3 mutant has one or more mutations are selected from F691L, D835V/Y, Y842C/H or combinations thereof. In another embodiment, the oncogenic FLT3 mutant is encoded by a FLT3 gene having an ITD mutation. In another embodiment, the oncogenic FLT3 mutant is encoded by a FLT3 gene having an ITD mutation and a F691L mutation. In another embodiment, the oncogenic FLT3 mutant is encoded by a FLT3 gene having an ITD mutation and a D835Y mutation. In another embodiment, the oncogenic FLT3 mutant is encoded by a FLT3 gene having an ITD mutation, a F691L mutation, and a D835Y mutation.

[0246] Hematologic cancers, also known as hematologic or hematopoietic malignancies, are cancers of the blood or bone marrow; including leukemia and lymphoma. Acute myelogenous leukemia (AML) is a clonal hematopoietic stem cell leukemia that represents about 90% of all acute leukemias in adults with an incidence of 3.9 per 100,000 (See e.g., Lowenberg et al., N. Eng. J. Med. 341: 1051-62 (1999) and Lopesde Menezes, et al, Clin. Cancer Res. (2005), 11(14):5281-5291). While chemotherapy can result in complete remissions, the long term disease-free survival rate for AML is about 14% with about 7,400 deaths from AML each year in the United States. Approximately 70% of AML blasts express wild type FLT3 and about 25%

to about 35% express FLT3 kinase receptor mutations which result in constitutively active FLT3. Two types of activating mutations have been identified, in AML patients: internal tandem duplications (ITDs) and point mutation in the activating loop of the kinase domain. FLT3-ITD mutations in AML patients is indicative of a poor prognosis for survival, and in patients who are in remission, FLT3-ITD mutations are the most significant factor adversely affecting relapse rate with 64% of patients having the mutation relapsing within 5 years (see Current Pharmaceutical Design (2005), 11:3449-3457. The prognostic significance of FLT3 mutations in clinical studies suggests that FLT3 plays a driving role in AML and may be necessary for the development and maintenance of the disease. Mixed Lineage Leukemia (MLL) involve translocations of chromosome 11 band q23 (11q23) and occur in approximately 80% of infant hematological malignancies and 10% of adult acute leukemias. Although certain 11q23 translocation have been shown to be essential to immortalization of hematopoietic progenitors in vitro, a secondary genotoxic event is required to develop leukemia. There is a strong concordance between FLT3 and MLL fusion gene expression, and the most consistently overexpressed gene in MLL is FLT3. Moreover, it has been shown that activated FLT3 together with MLL fusion gene expression induces acute leukemia with a short latency period (see Ono, et al., J. of Clinical Investigation (2005), 115:919-929). Therefore, it is believed that FLT3 signally is involved in the development and maintenance of MLL (see Armstrong, et al., Cancer Cell (2003), 3:173-183).

[0247] The FLT3-ITD mutation is also present in about 3% of cases of adult myelodysplastic syndrome and some cases of acute lymphocytic leukemia (ALL) (Current Pharmaceutical Design (2005), 11:3449-3457).

[0248] FLT3 has been shown to be a client protein of Hsp90, and 17AAG, a benzoquinone ansamycin antibiotic that inhibits Hsp90 activity, has been shown to disrupts the association of FLT3 with Hsp90. The growth of leukemia cell that express either wild type FLT3 or FLT3-ITD mutations was found to be inhibited by treatment with 17"AAG (Yao, et al., Clinical Cancer Research (2003), 9:4483-4493).

[0249] It has been found that TGFBR2 inhbitors, such as ITD-1, may be valuable for treating diseases associated with pathological processes such as cancer, fibrosis, or cardiovascular disease (including adult cardiovascular disease). (Willems et al., *Cell Stem Cell* (August 3, 2012); 11(2): 242-252). It has also been found that neutralizing TGFBR2 has potent antimetastatic activity and inhibits pancreatic cancer. (Ostapoff et al., *Cancer Res*; 74(18); 1-12). It has been further found that inhibition of TGFBR2 can inhibit hepatocellular carcinoma (HCC) progression. (Dituri et al., PLOS ONE, (June, 2013), Vol. 8, Issue 6, e67109). TGFBR2

is also highly expressed in breast cancer cells, thus TGFBR2 inhibitors may inhibit breast cancer cell proliferation. Gao et al., PLOS ONE (Nov. 9, 2015), http://dx.doi.org/10.1371/journal.pone.0141412.It has been further found that ablation of TGF-β signaling can suppress bladder cancer progression. Liang et al., Scientific Reports (6:29479) DOI: 10.1038/srep29479. TGF-β ligands and receptors have potent immunosuppressive activity on T-cells and NK cells, and TGF-β antagonists can significantly suppress tumorigenesis and greatly improves the efficacy of immunodulatory chemotheraphy in preclinical models. (Isarna Therapeutics CIMT Satellite Sympossium, May 07, 2014).

[0250] The compounds as described herein are useful for the treatment or prevention of haematological malignancies, including, but not limiting to, acute myeloic leukemia (AML); mixed lineage leukemia (MLL); acute promyelocytic leukemia; acute lymphocytic leukemia, acute lymphoblastic leukemia, myeloid sarcoma; T-cell type acute lymphocytic leukemia (T-ALL); B-cell type acute lymphocytic leukemia (B-ALL); chronic myelomonocytic leukemia (CMML); myelodysplastic syndrome; myeloproliferative disorders; other proliferative disorders, including, but not limiting to, cancer; autoimmune disorders; and skin disorders, such as psoriasis and atopic dermatitis.

[0251] In another embodiment, the present disclosure also provides a method for modulating FLT3 activity by contacting a FLT3 or a mutant FLT3 with administering an effective amount of a compound having any of the Formulae described in this disclosure, including any one of the compounds listed in Table I or Table II, or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer or a deuterated analog of any of these compounds. The compound is, in some embodiments, provided at a level sufficient to modulate the activity of the FLT3 by at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90%, or greater than 90%. In many embodiments, the compound will be at a concentration of about 1 μM, 100 μM, or 1 mM, or in a range of 1-100 nM, 100-500 nM, 500-1000 nM, 1-100 μM, 100-500 μM, or 500-1000 μM. In some embodiments, the contacting is carried out *in vitro*. In other embodiments, the contacting is carried out *in vivo*.

[0252] As used herein, the term "FLT3 mediated disease or condition" refers to a disease or condition in which the biological function of FLT3 affects the development and/or course of the disease or condition, and/or in which modulation of FLT3 alters the development, course, and/or symptoms. These mutations attenuate the intrinsic tyrosine kinase activity of the receptor to different degrees and are models for the effect of modulation of FLT3 activity. A FLT3 mediated disease or condition includes a disease or condition for which FLT3 inhibition provides a therapeutic benefit, e.g. wherein treatment with FLT3 inhibitors, including

compounds described herein, provides a therapeutic benefit to the subject suffering from or at risk of the disease or condition.

[0253] Reference to particular amino acid residues in human FLT3 polypeptide is defined by the numbering corresponding to the FLT3 sequence in GenBank NP004110.2 (SEQ ID NO:1). Reference to particular nucleotide positions in a nucleotide sequence encoding all or a portion of FLT3 is defined by the numbering corresponding to the sequence provided in GenBank NM_44119 (SEQ ID NO:2).

[0254] The terms "FLT3" (also referred to herein as Flt3) or "FLT3 kinase" or "FLT3 protein kinase" mean an enzymatically active kinase that contains a portion with greater than 90% amino acid sequence identity to amino acid residues including the ATP binding site of full-length FLT3 (e.g., human FLT3, e.g., the sequence NP_004110.2 , SEQ ID NO:1), for a maximal alignment over an equal length segment; or that contains a portion with greater than 90% amino acid sequence identity to at least 200 contiguous amino acids of native FLT3 and retains kinase activity. In some embodiments, the sequence identity is at least 95, 97, 98, 99, or even 100%. In some embodiments, the specified level of sequence identity is over a sequence at least 100-500, at least 200-400, or at least 300 contiguous amino acid residues in length. Unless indicated to the contrary, the term includes reference to wild-type c- FLT3, allelic variants, and mutated forms (e.g., having activating mutations).

[0255] The terms "FLT3-mediated diseases or disorders" shall include diseases associated with or implicating FLT3 activity, for example, the overactivity of FLT3, and conditions that accompany with these diseases. The term "overactivity of FLT3 " refers to either 1) FLT3 expression in cells which normally do not express FLT3; 2) FLT3 expression by cells which normally do not express v; 3) increased FLT3 expression leading to unwanted cell proliferation; or 4) mutations leading to constitutive activation of FLT3. Examples of "FLT3-mediated diseases or disorders" include disorders resulting from over stimulation of FLT3 or from abnormally high amount of FLT3 activity, due to abnormally high amount of FLT3 or mutations in FLT3. It is known that overactivity of FLT3 has been implicated in the pathogenesis of a number of diseases, including inflammatory and autoimmune diseases, cell proliferative disorders, neoplastic disorders and cancers as described herein.

[0256] The term " FLT3-ITD allelic ratio" refers to the percentage of tumor DNA alleles harboring the FLT3-ITD mutation normalized to the percent blast cells in a patient sample. In one embodiment, a low FLT3-ITD allelic ratio is where less than 25% of normalized tumor DNA alleles is a FLT3-ITD allele. In certain embodiments, an intermediate FLT3-ITD allelic ratio is where between 25% and 50% of normalized tumor DNA alleles is a FLT3-ITD allele. In

certain embodiments, a high FLT3-ITD allelic ratio is where greater than 50% of normalized tumor DNA alleles is a FLT3-ITD allele.

[0257] The "FLT3/ITD mutation-containing cells" include any of cells having tandem duplication mutation absent in healthy humans in a region of exons 14 to 15 in a juxtamembrane region of FLT3, that is, cells highly expressing mRNA derived from the mutation, cells having increased FLT3-derived growth signals caused by the mutation, cells highly expressing the mutant FLT3 protein, etc. The "FLT3/ITD mutation-containing cancerous cells" include any of cancerous cells having tandem duplication mutation absent in healthy humans in a region of exons 14 to 15 in a juxtamembrane region of FLT3, that is, cancerous cells highly expressing mRNA derived from the mutation, cancerous cells having increased FLT3-derived growth signals caused by the mutation, cancerous cells highly expressing the mutant FLT3 protein, etc. The "FLT3/ITD mutation-containing leukemic cells" include any of leukemic cells having tandem duplication mutation absent in healthy humans in a region of exons 14 to 15 in a juxtamembrane region of FLT3, that is, leukemic cells highly expressing mRNA derived from the mutation, leukemic cells having increased FLT3-derived growth signals caused by the mutation, leukemic cells highly expressing the mutant FLT3 protein, etc.

[0258] The terms "modulate," "modulation," and the like refer to the ability of a compound to increase or decrease the function and/or expression of a protein kinase such as FLT3, where such function may include transcription regulatory activity and/or protein-binding. Modulation may occur *in vitro* or *in vivo*. Such activity is typically indicated in terms of an inhibitory concentration (IC_{50}) or excitation concentration (EC_{50}) of the compound for an inhibitor or activator, respectively, with respect to, for example, the protein kinase. Modulation, as described herein, includes the inhibition, antagonism, partial antagonism, activation, agonism or partial agonism of a function or characteristic associated with FLT3, either directly or indirectly, and/or the upregulation or downregulation of the expression of FLT3, either directly or indirectly. In another 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.

[0259] The ability of a compound to inhibit the function of FLT3 can be demonstrated in a biochemical assay, e.g., binding assay, or a cell-based assay.

[0260] Also in the context of compounds binding to a biomolecular target, the term "greater specificity" indicates that a compound binds to a specified target to a greater extent than to

another biomolecule or biomolecules that may be present under relevant binding conditions, where binding to such other biomolecules produces a different biological activity than binding to the specified target. Typically, the specificity is with reference to a limited set of other biomolecules, *e.g.*, in the case of FLT3, other tyrosine kinases or even other type of enzymes. In particular embodiments, the greater specificity is at least 2, 3, 4, 5, 8, 10, 50, 100, 200, 400, 500, or 1000-fold greater specificity.

[0261] As used herein in connection with binding compounds or ligands, the term "specific for FLT3 kinase", "specific for FLT3", and terms of like import mean that a particular compound binds to FLT3 to a statistically greater extent than to other kinases that may be present in a particular sample. Also, where biological activity other than binding is indicated, the term "specific for FLT3" indicates that a particular compound has greater biological effect associated with binding FLT3 than to other tyrosine kinases, e.g., kinase activity inhibition. The specificity is also with respect to other biomolecules (not limited to tyrosine kinases) that may be present in a particular sample. The term "specific for FLT3kinase", "specific for FLT3", and terms of like import mean that a particular compound binds to FLT3 to a statistically greater extent than to other kinases that may be present in a particular sample. Also, where biological activity other than binding is indicated, the term "specific for FLT3" indicates that a particular compound has greater biological effect associated with binding FLT3 than to other tyrosine kinases, e.g., kinase activity inhibition. The specificity is also with respect to other biomolecules (not limited to tyrosine kinases) that may be present in a particular sample.

[0262] The term "first line cancer therapy" refers to therapy administered to a subject as an initial regimen to reduce the number of cancer cells. First line therapy is also referred to as induction therapy, primary therapy and primary treatment. Commonly administered first-line therapy for AML is cytarabine-based therapy in which cytarabine is administered often in combination with one or more agents selected from daunorubicin, idarubicin, doxorubicin, mitoxantrone, tipifarnib, thioguanine or gemtuzumab ozogamicin. Common regimens used in cytarabine-based therapy include the "7 + 3" or "5 + 2" therapy comprising administration of cytarabine with an anthracycline such as daunorubicin or idarubicin. Another first-line therapy is clofarabine-based therapy in which clofarabine is administered, often in combination with an anthracycline such as daunorubicin, idarubicin or doxorubicin. Other first-line therapy for AML are etoposide-based therapy in which etoposide is administered, often in combination with mitoxantrone, and optionally, with cytarabine. Another first- line therapy for AML (for subtype M3, also called acute promyelocytic leukemia) is all-trans-retinoic acid (ATRA). It is recognized that what is considered "first line therapy" by those of ordinary skill in the art will continue to

evolve as new anti-cancer agents are developed and tested in the clinics. A summary of the currently accepted approaches to first line treatment is described in NCCN Clinical Practice Guidelines in Oncology for acute myeloid leukemia and the NCI guidelines on acute myeloid leukemia treatment (see, e.g., http://www.cancer.gov/cancertopics/pdq/treatment/adultAML/HealthProfessional/page7).

[0263] The term "second line cancer therapy" refers to a cancer treatment that is administered to a subject who does not respond to first line therapy, that is, often first line therapy is administered or who has a recurrence of cancer after being in remission. In certain embodiments, second line therapy that may be administered includes a repeat of the initial successful cancer therapy, which may be any of the treatments described under "first line cancer therapy". In certain embodiments, second line therapy is the administration of gemtuzumab ozogamicin. In certain embodiments, investigational drugs may also be administered as second line therapy in a clinical trial setting. A summary of the currently accepted approaches to second line treatment is described in the NCCN Clinical Practice Guidelines in Oncology for acute myeloid leukemia and the NCI guidelines on acute myeloid leukemia treatment (see, e.g., http://www.cancer.gov/cancertopics/pdq/treatment/adultAML/HealthProfessional/page5).

[0264] The term "refractory" refers to wherein a subject fails to respond or is otherwise resistant to cancer therapy or treatment. The cancer therapy may be first-line, second-line or any subsequently administered treatment. In certain embodiments, refractory refers to a condition where a subject fails to achieve complete remission after two induction attempts. A subject may be refractory due to a cancer cell's intrinsic resistance to a particular therapy, or the subject may be refractory due to an acquired resistance that develops during the course of a particular therapy.

IV. Binding Assays

[0265] The methods of the present disclosure can involve assays that are able to detect the binding of compounds to a target molecule. Such binding is at a statistically significant level, with a confidence level of at least 90%, or at least 95, 97, 98, 99% or greater confidence level that the assay signal represents binding to the target molecule, *i.e.*, is distinguished from background. In some embodiments, controls are used to distinguish target binding from non-specific binding. A large variety of assays indicative of binding are known for different target types and can be used for this disclosure.

[0266] Binding compounds can be characterized by their effect on the activity of the target molecule. Thus, a "low activity" compound has an inhibitory concentration (IC_{50}) or effective

concentration (EC_{50}) of greater than 1 μM under standard conditions. By "very low activity" is meant an IC_{50} or EC_{50} of above 100 μM under standard conditions. By "extremely low activity" is meant an IC_{50} or EC_{50} of above 1 mM under standard conditions. By "moderate activity" is meant an IC_{50} or EC_{50} of 200 nM to 1 μM under standard conditions. By "moderately high activity" is meant an IC_{50} or EC_{50} of 1 nM to 200 nM. By "high activity" is meant an IC_{50} or EC_{50} of below 1 nM under standard conditions. The IC_{50} or EC_{50} is defined as the concentration of compound at which 50% of the activity of the target molecule (e.g. enzyme or other protein) activity being measured is lost or gained relative to the range of activity observed when no compound is present. Activity can be measured using methods known to those of ordinary skill in the art, *e.g.*, by measuring any detectable product or signal produced by occurrence of an enzymatic reaction, or other activity by a protein being measured.

[0267] By "background signal" in reference to a binding assay is meant the signal that is recorded under standard conditions for the particular assay in the absence of a test compound, molecular scaffold, or ligand that binds to the target molecule. Persons of ordinary skill in the art will realize that accepted methods exist and are widely available for determining background signal.

[0268] By "standard deviation" is meant the square root of the variance. The variance is a measure of how spread out a distribution is. It is computed as the average squared deviation of each number from its mean. For example, for the numbers 1, 2, and 3, the mean is 2 and the variance is:

$$\sigma^2 = \frac{(1-2)^2 + (2-2)^2 + (3-2)^2}{3} = 0.667 .$$

Surface Plasmon Resonance

[0269] Binding parameters can be measured using surface plasmon resonance, for example, with a BIAcore® chip (Biacore, Japan) coated with immobilized binding components. Surface plasmon resonance is used to characterize the microscopic association and dissociation constants of reaction between an sFv or other ligand directed against target molecules. Such methods are generally described in the following references which are incorporated herein by reference. Vely F. et al., (2000) BIAcore® analysis to test phosphopeptide-SH2 domain interactions, Methods in Molecular Biology. 121:313-21; Liparoto et al., (1999) Biosensor analysis of the interleukin-2 receptor complex, Journal of Molecular Recognition. 12:316-21; Lipschultz et al., (2000) Experimental design for analysis of complex kinetics using surface plasmon resonance, Methods. 20(3):310-8; Malmqvist., (1999) BIACORE: an affinity biosensor system for

characterization of biomolecular interactions, Biochemical Society Transactions 27:335-40; Alfthan, (1998) Surface plasmon resonance biosensors as a tool in antibody engineering, Biosensors & Bioelectronics. 13:653-63; Fivash et al., (1998) BIAcore for macromolecular interaction, Current Opinion in Biotechnology. 9:97-101; Price et al.; (1998) Summary report on the ISOBM TD-4 Workshop: analysis of 56 monoclonal antibodies against the MUC1 mucin. Tumour Biology 19 Suppl 1:1-20; Malmqvist et al, (1997) Biomolecular interaction analysis: affinity biosensor technologies for functional analysis of proteins, Current Opinion in Chemical Biology. 1:378-83; O'Shannessy et al., (1996) Interpretation of deviations from pseudo-first-order kinetic behavior in the characterization of ligand binding by biosensor technology, Analytical Biochemistry. 236:275-83; Malmborg et al., (1995) BIAcore as a tool in antibody engineering, Journal of Immunological Methods. 183:7-13; Van Regenmortel, (1994) Use of biosensors to characterize recombinant proteins, Developments in Biological Standardization. 83:143-51; and O'Shannessy, (1994) Determination of kinetic rate and equilibrium binding constants for macromolecular interactions: a critique of the surface plasmon resonance literature, Current Opinions in Biotechnology. 5:65-71.

[0270] BIAcore® uses the optical properties of surface plasmon resonance (SPR) to detect alterations in protein concentration bound to a dextran matrix lying on the surface of a gold/glass sensor chip interface, a dextran biosensor matrix. In brief, proteins are covalently bound to the dextran matrix at a known concentration and a ligand for the protein is injected through the dextran matrix. Near infrared light, directed onto the opposite side of the sensor chip surface is reflected and also induces an evanescent wave in the gold film, which in turn, causes an intensity dip in the reflected light at a particular angle known as the resonance angle. If the refractive index of the sensor chip surface is altered (e.g. by ligand binding to the bound protein) a shift occurs in the resonance angle. This angle shift can be measured and is expressed as resonance units (RUs) such that 1000 RUs is equivalent to a change in surface protein concentration of 1 ng/mm^2. These changes are displayed with respect to time along the y-axis of a sensorgram, which depicts the association and dissociation of any biological reaction.

High Throughput Screening (HTS) Assays

[0271] HTS typically uses automated assays to search through large numbers of compounds for a desired activity. Typically HTS assays are used to find new drugs by screening for chemicals that act on a particular enzyme or molecule. For example, if a chemical inactivates an enzyme it might prove to be effective in preventing a process in a cell which causes a disease. High throughput methods enable researchers to assay thousands of different chemicals against

each target molecule very quickly using robotic handling systems and automated analysis of results.

[0272] As used herein, "high throughput screening" or "HTS" refers to the rapid in vitro screening of large numbers of compounds (libraries); generally tens to hundreds of thousands of compounds, using robotic screening assays. Ultra high-throughput Screening (uHTS) generally refers to the high-throughput screening accelerated to greater than 100,000 tests per day.

[0273] To achieve high-throughput screening, it is advantageous to house samples on a multicontainer carrier or platform. A multicontainer carrier facilitates measuring reactions of a plurality of candidate compounds simultaneously. Multi-well microplates may be used as the carrier. Such multi-well microplates, and methods for their use in numerous assays, are both known in the art and commercially available.

[0274] Screening assays may include controls for purposes of calibration and confirmation of proper manipulation of the components of the assay. Blank wells that contain all of the reactants but no member of the chemical library are usually included. As another example, a known inhibitor (or activator) of an enzyme for which modulators are sought, can be incubated with one sample of the assay, and the resulting decrease (or increase) in the enzyme activity used as a comparator or control. It will be appreciated that modulators can also be combined with the enzyme activators or inhibitors to find modulators which inhibit the enzyme activation or repression that is otherwise caused by the presence of the known the enzyme modulator.

Measuring Enzymatic and Binding Reactions During Screening Assays

[0275] Techniques for measuring the progression of enzymatic and binding reactions, e.g., in multicontainer carriers, are known in the art and include, but are not limited to, the following.

[0276] Spectrophotometric and spectrofluorometric assays are well known in the art. Examples of such assays include the use of colorimetric assays for the detection of peroxides, as described in Gordon, A. J. and Ford, R. A., (1972) The Chemist's Companion: A Handbook Of Practical Data, Techniques, And References, John Wiley and Sons, N.Y., Page 437.

[0277] Fluorescence spectrometry may be used to monitor the generation of reaction products. Fluorescence methodology is generally more sensitive than the absorption methodology. The use of fluorescent probes is well known to those skilled in the art. For reviews, see Bashford et al., (1987) Spectrophotometry and Spectrofluorometry: A Practical Approach, pp. 91-114, IRL Press Ltd.; and Bell, (1981) Spectroscopy In Biochemistry, Vol. I, pp. 155-194, CRC Press.

[0278] In spectrofluorometric methods, enzymes are exposed to substrates that change their intrinsic fluorescence when processed by the target enzyme. Typically, the substrate is

nonfluorescent and is converted to a fluorophore through one or more reactions. As a non-limiting example, SMase activity can be detected using the Amplex® Red reagent (Molecular Probes, Eugene, OR). In order to measure sphingomyelinase activity using Amplex® Red, the following reactions occur. First, SMase hydrolyzes sphingomyelin to yield ceramide and phosphorylcholine. Second, alkaline phosphatase hydrolyzes phosphorylcholine to yield choline. Third, choline is oxidized by choline oxidase to betaine. Finally, H_2O_2, in the presence of horseradish peroxidase, reacts with Amplex® Red to produce the fluorescent product, Resorufin, and the signal therefrom is detected using spectrofluorometry.

[0279] Fluorescence polarization (FP) is based on a decrease in the speed of molecular rotation of a fluorophore that occurs upon binding to a larger molecule, such as a receptor protein, allowing for polarized fluorescent emission by the bound ligand. FP is empirically determined by measuring the vertical and horizontal components of fluorophore emission following excitation with plane polarized light. Polarized emission is increased when the molecular rotation of a fluorophore is reduced. A fluorophore produces a larger polarized signal when it is bound to a larger molecule (i.e. a receptor), slowing molecular rotation of the fluorophore. The magnitude of the polarized signal relates quantitatively to the extent of fluorescent ligand binding. Accordingly, polarization of the "bound" signal depends on maintenance of high affinity binding.

[0280] FP is a homogeneous technology and reactions are very rapid, taking seconds to minutes to reach equilibrium. The reagents are stable, and large batches may be prepared, resulting in high reproducibility. Because of these properties, FP has proven to be highly automatable, often performed with a single incubation with a single, premixed, tracer-receptor reagent. For a review, see Owickiet al., (1997), Application of Fluorescence Polarization Assays in High-Throughput Screening, Genetic Engineering News, 17:27.

[0281] FP is particularly desirable since its readout is independent of the emission intensity (Checovich, W. J., et al., (1995) Nature 375:254-256; Dandliker, W. B., et al., (1981) Methods in Enzymology 74:3-28) and is thus insensitive to the presence of colored compounds that quench fluorescence emission. FP and FRET (see below) are well-suited for identifying compounds that block interactions between sphingolipid receptors and their ligands. See, for example, Parker et al., (2000) Development of high throughput screening assays using fluorescence polarization: nuclear receptor-ligand-binding and kinase/phosphatase assays, J Biomol Screen 5:77-88.

[0282] Fluorophores derived from sphingolipids that may be used in FP assays are commercially available. For example, Molecular Probes (Eugene, OR) currently sells

sphingomyelin and one ceramide flurophores. These are, respectively, N-(4,4-difluoro-5,7-dimethyl-4-bora-3a,4a-diaza-s-indacene- 3-pentanoyl)sphingosyl phosphocholine (BODIPY® FL C5-sphingomyelin); N-(4,4-difluoro-5,7-dimethyl-4-bora-3a,4a-diaza-s-indacene- 3-dodecanoyl)sphingosyl phosphocholine (BODIPY® FL C12-sphingomyelin); and N-(4,4-difluoro-5,7-dimethyl-4-bora-3a,4a-diaza-s-indacene- 3-pentanoyl)sphingosine (BODIPY® FL C5-ceramide). U.S. Patent No. 4,150,949, (Immunoassay for gentamicin), discloses fluorescein-labelled gentamicins, including fluoresceinthiocarbanyl gentamicin. Additional fluorophores may be prepared using methods well known to the skilled artisan.

[0283] Exemplary normal-and-polarized fluorescence readers include the POLARION® fluorescence polarization system (Tecan AG, Hombrechtikon, Switzerland). General multiwell plate readers for other assays are available, such as the VERSAMAX® reader and the SPECTRAMAX® multiwell plate spectrophotometer (both from Molecular Devices).

[0284] Fluorescence resonance energy transfer (FRET) is another useful assay for detecting interaction and has been described. See, e.g., Heim et al., (1996) Curr. Biol. 6:178-182; Mitra et al., (1996) Gene 173:13-17; and Selvin et al., (1995) Meth. Enzymol. 246:300-345. FRET detects the transfer of energy between two fluorescent substances in close proximity, having known excitation and emission wavelengths. As an example, a protein can be expressed as a fusion protein with green fluorescent protein (GFP). When two fluorescent proteins are in proximity, such as when a protein specifically interacts with a target molecule, the resonance energy can be transferred from one excited molecule to the other. As a result, the emission spectrum of the sample shifts, which can be measured by a fluorometer, such as a fMAX multiwell fluorometer (Molecular Devices, Sunnyvale Calif.).

[0285] Scintillation proximity assay (SPA) is a particularly useful assay for detecting an interaction with the target molecule. SPA is widely used in the pharmaceutical industry and has been described (Hanselman et al., (1997) J. Lipid Res. 38:2365-2373; Kahl et al., (1996) Anal. Biochem. 243:282-283; Undenfriend et al., (1987) Anal. Biochem. 161:494-500). See also U.S. Patent Nos. 4,626,513 and 4,568,649, and European Patent No. 0,154,734. One commercially available system uses FLASHPLATE® scintillant-coated plates (NEN Life Science Products, Boston, MA).

[0286] The target molecule can be bound to the scintillator plates by a variety of well known means. Scintillant plates are available that are derivatized to bind to fusion proteins such as GST, His6 or Flag fusion proteins. Where the target molecule is a protein complex or a multimer, one protein or subunit can be attached to the plate first, then the other components of the complex added later under binding conditions, resulting in a bound complex.

[0287] In a typical SPA assay, the gene products in the expression pool will have been radiolabeled and added to the wells, and allowed to interact with the solid phase, which is the immobilized target molecule and scintillant coating in the wells. The assay can be measured immediately or allowed to reach equilibrium. Either way, when a radiolabel becomes sufficiently close to the scintillant coating, it produces a signal detectable by a device such as a TOPCOUNT NXT® microplate scintillation counter (Packard BioScience Co., Meriden Conn.). If a radiolabeled expression product binds to the target molecule, the radiolabel remains in proximity to the scintillant long enough to produce a detectable signal.

[0288] In contrast, the labeled proteins that do not bind to the target molecule, or bind only briefly, will not remain near the scintillant long enough to produce a signal above background. Any time spent near the scintillant caused by random Brownian motion will also not result in a significant amount of signal. Likewise, residual unincorporated radiolabel used during the expression step may be present, but will not generate significant signal because it will be in solution rather than interacting with the target molecule. These non-binding interactions will therefore cause a certain level of background signal that can be mathematically removed. If too many signals are obtained, salt or other modifiers can be added directly to the assay plates until the desired specificity is obtained (Nichols et al., (1998) Anal. Biochem. 257:112-119).

V. Kinase Activity Assays

[0289] A number of different assays for kinase activity can be utilized for assaying for active modulators and/or determining specificity of a modulator for a particular kinase or group or kinases. In addition to the assay mentioned in the Examples below, one of ordinary skill in the art will know of other assays that can be utilized and can modify an assay for a particular application. For example, numerous papers concerning kinases described assays that can be used.

[0290] Additional alternative assays can employ binding determinations. For example, this sort of assay can be formatted either in a fluorescence resonance energy transfer (FRET) format, or using an AlphaScreen (*a*mplified *l*uminescent *p*roximity *h*omogeneous *a*ssay) format by varying the donor and acceptor reagents that are attached to streptavidin or the phospho-specific antibody.

VI. Alternative Compound Forms or Derivatives

(a) Isomers, Prodrugs, and Active Metabolites

[0291] Compounds contemplated herein are described with reference to both generic Formulae and specific compounds. In addition, the compounds described herein may exist in a

number of different forms or derivatives, all within the scope of the present disclosure. These include, for example, tautomers, stereoisomers, racemic mixtures, regioisomers, salts, prodrugs (e.g. carboxylic acid esters), solvated forms, different crystal forms or polymorphs, and active metabolites.

(b) Tautomers, Stereoisomers, Regioisomers, and Solvated Forms

[0292] It is understood that some compounds may exhibit tautomerism. In such cases, the Formulae provided herein expressly depict only one of the possible tautomeric forms. It is therefore to be understood that the Formulae provided herein are intended to represent any tautomeric form of the depicted compounds and are not to be limited merely to the specific tautomeric form depicted by the drawings of the Formulae.

[0293] Likewise, some of the compounds according to the present disclosure may exist as stereoisomers, i.e. having the same atomic connectivity of covalently bonded atoms yet differing in the spatial orientation of the atoms. For example, compounds may be optical stereoisomers, which contain one or more chiral centers, and therefore, may exist in two or more stereoisomeric forms (e.g. enantiomers or diastereomers). Thus, such compounds may be present as single stereoisomers (*i.e.,* essentially free of other stereoisomers), racemates, and/or mixtures of enantiomers and/or diastereomers. As another example, stereoisomers include geometric isomers, such as *cis*- or *trans*- orientation of substituents on adjacent carbons of a double bond. All such single stereoisomers, racemates and mixtures thereof are intended to be within the scope of the present disclosure. Unless specified to the contrary, all such steroisomeric forms are included within the Formulae provided herein.

[0294] In some embodiments, a chiral compound of the present disclosure is in a form that contains at least 80% of a single isomer (60% enantiomeric excess ("e.e.") or diastereomeric excess ("d.e.")), or at least 85% (70% e.e. or d.e.), 90% (80% e.e. or d.e.), 95% (90% e.e. or d.e.), 97.5% (95% e.e. or d.e.), or 99% (98% e.e. or d.e.). As generally understood by those skilled in the art, an optically pure compound having one chiral center is one that consists essentially of one of the two possible enantiomers (*i.e.,* is enantiomerically pure), and an optically pure compound having more than one chiral center is one that is both diastereomerically pure and enantiomerically pure. In some embodiments, the compound is present in optically pure form.

[0295] For compounds in which synthesis involves addition of a single group at a double bond, particularly a carbon-carbon double bond, the addition may occur at either of the double

bond-linked atoms. For such compounds, the present disclosure includes both such regioisomers.

(c) Prodrugs and Metabolites

[0296] In addition to the present Formulae and compounds described herein, the disclosure also includes prodrugs (generally pharmaceutically acceptable prodrugs), active metabolic derivatives (active metabolites), and their pharmaceutically acceptable salts.

[0297] Prodrugs are compounds or pharmaceutically acceptable salts thereof which, when metabolized under physiological conditions or when converted by solvolysis, yield the desired active compound. Prodrugs include, without limitation, esters, amides, carbamates, carbonates, ureides, solvates, or hydrates of the active compound. Typically, the prodrug is inactive, or less active than the active compound, but may provide one or more of advantageous handling, administration, and/or metabolic properties. For example, some prodrugs are esters of the active compound; during metabolysis, the ester group is cleaved to yield the active drug. Also, some prodrugs are activated enzymatically to yield the active compound, or a compound which, upon further chemical reaction, yields the active compound.

[0298] In this context, a common example of a prodrug is an alkyl ester of a carboxylic acid. Relative to compounds o this disclosure, further examples include, without limitation, an amide or carbamate derivative at the pyrrole nitrogen (i.e. N1) of the azaindole core.

[0299] As described in The Practice of Medicinal Chemistry, Ch. 31-32 (Ed. Wermuth, Academic Press, San Diego, CA, 2001), prodrugs can be conceptually divided into two non-exclusive categories, bioprecursor prodrugs and carrier prodrugs. Generally, bioprecursor prodrugs are compounds that are inactive or have low activity compared to the corresponding active drug compound, that contain one or more protective groups and are converted to an active form by metabolism or solvolysis. Both the active drug form and any released metabolic products should have acceptably low toxicity. Typically, the formation of active drug compound involves a metabolic process or reaction that is one of the follow types:

[0300] Oxidative reactions: Oxidative reactions are exemplified without limitation to reactions such as oxidation of alcohol, carbonyl, and acid functionalities, hydroxylation of aliphatic carbons, hydroxylation of alicyclic carbon atoms, oxidation of aromatic carbon atoms, oxidation of carbon-carbon double bonds, oxidation of nitrogen-containing functional groups, oxidation of silicon, phosphorus, arsenic, and sulfur, oxidative N-dealkylation, oxidative O- and S-dealkylation, oxidative deamination, as well as other oxidative reactions.

[0301] Reductive reactions: Reductive reactions are exemplified without limitation to reactions such as reduction of carbonyl functionalities, reduction of alcohol functionalities and carbon-carbon double bonds, reduction of nitrogen-containing functional groups, and other reduction reactions.

[0302] Reactions without change in the oxidation state: Reactions without change in the state of oxidation are exemplified without limitation to reactions such as hydrolysis of esters and ethers, hydrolytic cleavage of carbon-nitrogen single bonds, hydrolytic cleavage of non-aromatic heterocycles, hydration and dehydration at multiple bonds, new atomic linkages resulting from dehydration reactions, hydrolytic dehalogenation, removal of hydrogen halide molecule, and other such reactions.

[0303] Carrier prodrugs are drug compounds that contain a transport moiety, e.g., that improves uptake and/or localized delivery to a site(s) of action. Desirably for such a carrier prodrug, the linkage between the drug moiety and the transport moiety is a covalent bond, the prodrug is inactive or less active than the drug compound, the prodrug and any release transport moiety are acceptably non-toxic. For prodrugs where the transport moiety is intended to enhance uptake, typically the release of the transport moiety should be rapid. In other cases, it is desirable to utilize a moiety that provides slow release, e.g., certain polymers or other moieties, such as cyclodextrins. (See, e.g., Cheng et al., U.S. Patent Publ. No. 2004/0077595, incorporated herein by reference.) Such carrier prodrugs are often advantageous for orally administered drugs. Carrier prodrugs can, for example, be used to improve one or more of the following properties: increased lipophilicity, increased duration of pharmacological effects, increased site-specificity, decreased toxicity and adverse reactions, and/or improvement in drug formulation (e.g. stability, water solubility, suppression of an undesirable organoleptic or physiochemical property). For example, lipophilicity can be increased by esterification of hydroxyl groups with lipophilic carboxylic acids, or of carboxylic acid groups with alcohols, e.g., aliphatic alcohols. Wermuth, *supra*.

[0304] Prodrugs may proceed from prodrug form to active form in a single step or may have one or more intermediate forms which may themselves have activity or may be inactive.

[0305] Metabolites, e.g., active metabolites, overlap with prodrugs as described above, e.g., bioprecursor prodrugs. Thus, such metabolites are pharmacologically active compounds or compounds that further metabolize to pharmacologically active compounds that are derivatives resulting from metabolic process in the body of a subject. Of these, active metabolites are such pharmacologically active derivative compounds. For prodrugs, the prodrug compound is

generally inactive or of lower activity than the metabolic product. For active metabolites, the parent compound may be either an active compound or may be an inactive prodrug.

[0306] Prodrugs and active metabolites may be identified using routine techniques known in the art. See, e.g., Bertolini et al., 1997, *J. Med. Chem.*, 40:2011-2016; Shan et al., 1997, *J Pharm Sci* 86(7):756-757; Bagshawe, 1995, *Drug Dev. Res.*, 34:220-230; Wermuth, *supra*.

(d) Pharmaceutically acceptable salts

[0307] Compounds can be formulated as or be in the form of pharmaceutically acceptable salts. Contemplated pharmaceutically acceptable salt forms include, without limitation, mono, bis, tris, tetrakis, and so on. Pharmaceutically acceptable salts are non-toxic in the amounts and concentrations at which they are administered. The preparation of such salts can facilitate the pharmacological use by altering the physical characteristics of a compound without preventing it from exerting its physiological effect. Useful alterations in physical properties include lowering the melting point to facilitate transmucosal administration and increasing the solubility to facilitate administering higher concentrations of the drug.

[0308] Pharmaceutically acceptable salts include acid addition salts such as those containing sulfate, chloride, hydrochloride, fumarate, maleate, phosphate, sulfamate, acetate, citrate, lactate, tartrate, methanesulfonate, ethanesulfonate, benzenesulfonate, *p*-toluenesulfonate, cyclohexylsulfamate and quinate. Pharmaceutically acceptable salts can be obtained from acids such as hydrochloric acid, maleic acid, sulfuric acid, phosphoric acid, sulfamic acid, acetic acid, citric acid, lactic acid, tartaric acid, malonic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, *p*-toluenesulfonic acid, cyclohexylsulfamic acid, fumaric acid, and quinic acid.

[0309] Pharmaceutically acceptable salts also include basic addition salts such as those containing benzathine, chloroprocaine, choline, diethanolamine, ethanolamine, t-butylamine, ethylenediamine, meglumine, procaine, aluminum, calcium, lithium, magnesium, potassium, sodium, ammonium, alkylamine, and zinc, when acidic functional groups, such as carboxylic acid or phenol are present. For example, see Remington's Pharmaceutical Sciences, 19th ed., Mack Publishing Co., Easton, PA, Vol. 2, p. 1457, 1995. Such salts can be prepared using the appropriate corresponding bases.

[0310] Pharmaceutically acceptable salts can be prepared by standard techniques. For example, the free-base form of a compound can be dissolved in a suitable solvent, such as an aqueous or aqueous-alcohol solution containing the appropriate acid and then isolated by

evaporating the solution. In another example, a salt can be prepared by reacting the free base and acid in an organic solvent.

[0311] Thus, for example, if the particular compound is a base, the desired pharmaceutically acceptable salt may be prepared by any suitable method available in the art, for example, treatment of the free base with an inorganic acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like, or with an organic acid, such as acetic acid, maleic acid, succinic acid, mandelic acid, fumaric acid, malonic acid, pyruvic acid, oxalic acid, glycolic acid, salicylic acid, a pyranosidyl acid, such as glucuronic acid or galacturonic acid, an alpha-hydroxy acid, such as citric acid or tartaric acid, an amino acid, such as aspartic acid or glutamic acid, an aromatic acid, such as benzoic acid or cinnamic acid, a sulfonic acid, such as p-toluenesulfonic acid or ethanesulfonic acid, or the like.

[0312] Similarly, if the particular compound is an acid, the desired pharmaceutically acceptable salt may be prepared by any suitable method, for example, treatment of the free acid with an inorganic or organic base, such as an amine (primary, secondary or tertiary), an alkali metal hydroxide or alkaline earth metal hydroxide, or the like. Illustrative examples of suitable salts include organic salts derived from amino acids, such as L-glycine, L-lysine, and L-arginine, ammonia, primary, secondary, and tertiary amines, and cyclic amines, such as hydroxyethylpyrrolidine, piperidine, morpholine or piperazine, and inorganic salts derived from sodium, calcium, potassium, magnesium, manganese, iron, copper, zinc, aluminum and lithium.

[0313] The pharmaceutically acceptable salt of the different compounds may be present as a complex. Examples of complexes include 8-chlorotheophylline complex (analogous to, *e.g.*, dimenhydrinate: diphenhydramine 8-chlorotheophylline (1:1) complex; Dramamine) and various cyclodextrin inclusion complexes.

[0314] Unless specified to the contrary, specification of a compound herein includes pharmaceutically acceptable salts of such compound.

(e) Other Compound Forms

[0315] In the case of agents that are solids, it is understood by those skilled in the art that the compounds and salts may exist in different crystal or polymorphic forms, or may be formulated as co-crystals, or may be in an amorphous form, or may be any combination thereof (e.g. partially crystalline, partially amorphous, or mixtures of polymorphs) all of which are intended to be within the scope of the present disclosure and specified Formulae. Whereas salts are formed by acid/base addition, i.e. a free base or free acid of the compound of interest forms an acid/base reaction with a corresponding addition base or addition acid, respectively, resulting in

an ionic charge interaction, co-crystals are a new chemical species that is formed between neutral compounds, resulting in the compound and an additional molecular species in the same crystal structure.

[0316] In some instances, compounds of the disclosure are complexed with an acid or a base, including base addition salts such as ammonium, diethylamine, ethanolamine, ethylenediamine, diethanolamine, t-butylamine, piperazine, meglumine; acid addition salts, such as acetate, acetylsalicylate, besylate, camsylate, citrate, formate, fumarate, glutarate, hydrochlorate, maleate, mesylate, nitrate, oxalate, phosphate, succinate, sulfate, tartrate, thiocyanate and tosylate; and amino acids such as alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine or valine. In combining the compound of the disclosure with the acid or base, an amorphous complex is formed rather than a crystalline material such as a typical salt or co-crystal. In some instances, the amorphous form of the complex is facilitated by additional processing, such as by spray-drying, mechanochemical methods such as roller compaction, or microwave irradiation of the parent compound mixed with the acid or base. Such methods may also include addition of ionic and/or non-ionic polymer systems, including, but not limited to, hydroxypropyl methyl cellulose acetate succinate (HPMCAS) and methacrylic acid copolymer (e.g. Eudragit® L100-55), that further stabilize the amorphous nature of the complex. Such amorphous complexes provide several advantages. For example, lowering of the melting temperature relative to the free base facilitates additional processing, such as hot melt extrusion, to further improve the biopharmaceutical properties of the compound. Also, the amorphous complex is readily friable, which provides improved compression for loading of the solid into capsule or tablet form.

[0317] Additionally, the Formulae are intended to cover hydrated or solvated as well as unhydrated or unsolvated forms of the identified structures. For example, the indicated compounds include both hydrated and non-hydrated forms. Other examples of solvates include the structures in combination with a suitable solvent, such as isopropanol, ethanol, methanol, dimethyl sulfoxide, ethyl acetate, acetic acid, or ethanolamine.

VII. Formulations and Administration

[0318] The methods and compounds will typically be used in therapy for human subjects. However, they may also be used to treat similar or identical indications in other animal subjects. In this context, the terms "subject," "animal subject," and the like refer to human and non-human vertebrates, e.g. mammals, such as non-human primates, sports and commercial animals, e.g., equines, bovines, porcines, ovines, rodents, and pets, e.g., canines and felines.

[0319] Suitable dosage forms, in part, depend upon the use or the route of administration, for example, oral, transdermal, transmucosal, inhalant, or by injection (parenteral). Such dosage forms should allow the compound to reach target cells. Other factors are well known in the art, and include considerations such as toxicity and dosage forms that retard the compound or composition from exerting its effects. Techniques and formulations generally may be found in The Science and Practice of Pharmacy, 21st edition, Lippincott, Williams and Wilkins, Philadelphia, PA, 2005 (hereby incorporated by reference herein).

[0320] Carriers or excipients can be used to produce compositions. The carriers or excipients can be chosen to facilitate administration of the compound. Examples of carriers include calcium carbonate, calcium phosphate, various sugars such as lactose, glucose, or sucrose, or types of starch, cellulose derivatives, gelatin, vegetable oils, polyethylene glycols and physiologically compatible solvents. Examples of physiologically compatible solvents include sterile solutions of water for injection (WFI), saline solution, and dextrose.

[0321] The compounds can be administered by different routes including intravenous, intraperitoneal, subcutaneous, intramuscular, oral, transmucosal, rectal, transdermal, or inhalant. In some embodiments, the compounds can be administered by oral administration. For oral administration, for example, the compounds can be formulated into conventional oral dosage forms such as capsules, tablets, and liquid preparations such as syrups, elixirs, and concentrated drops.

[0322] For inhalants, compounds of the disclosure may be formulated as dry powder or a suitable solution, suspension, or aerosol. Powders and solutions may be formulated with suitable additives known in the art. For example, powders may include a suitable powder base such as lactose or starch, and solutions may comprise propylene glycol, sterile water, ethanol, sodium chloride and other additives, such as acid, alkali and buffer salts. Such solutions or suspensions may be administered by inhaling via spray, pump, atomizer, or nebulizer, and the like. The compounds of the disclosure may also be used in combination with other inhaled therapies, for example corticosteroids such as fluticasone propionate, beclomethasone dipropionate, triamcinolone acetonide, budesonide, and mometasone furoate; beta agonists such as albuterol, salmeterol, and formoterol; anticholinergic agents such as ipratropium bromide or tiotropium; vasodilators such as treprostinal and iloprost; enzymes such as DNAase; therapeutic proteins; immunoglobulin antibodies; an oligonucleotide, such as single or double stranded DNA or RNA, siRNA; antibiotics such as tobramycin; muscarinic receptor antagonists; leukotriene antagonists; cytokine antagonists; protease inhibitors; cromolyn sodium; nedocril sodium; and sodium cromoglycate.

[0323] Pharmaceutical preparations for oral use can be obtained, for example, by combining the active compounds with solid excipients, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose (CMC), and/or polyvinylpyrrolidone (PVP: povidone). If desired, disintegrating agents may be added, such as the cross-linked polyvinylpyrrolidone, agar, or alginic acid, or a salt thereof such as sodium alginate.

[0324] Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain, for example, gum arabic, talc, poly-vinylpyrrolidone, carbopol gel, polyethylene glycol (PEG), and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dye-stuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

[0325] Pharmaceutical preparations that can be used orally include push-fit capsules made of gelatin ("gelcaps"), as well as soft, sealed capsules made of gelatin, and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols (PEGs). In addition, stabilizers may be added.

[0326] Alternatively, injection (parenteral administration) may be used, *e.g.*, intramuscular, intravenous, intraperitoneal, and/or subcutaneous. For injection, the compounds of the disclosure are formulated in sterile liquid solutions, such as in physiologically compatible buffers or solutions, such as saline solution, Hank's solution, or Ringer's solution. In addition, the compounds may be formulated in solid form and redissolved or suspended immediately prior to use. Lyophilized forms can also be produced.

[0327] Administration can also be by transmucosal, topical, transdermal, or inhalant means. For transmucosal, topical or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, bile salts and fusidic acid derivatives. In addition, detergents may be used to facilitate permeation. Transmucosal administration, for example, may be through nasal sprays or suppositories (rectal or vaginal).

[0328] The topical compositions of this disclosure are formulated as oils, creams, lotions, ointments, and the like by choice of appropriate carriers known in the art. Suitable carriers include vegetable or mineral oils, white petrolatum (white soft paraffin), branched chain fats or oils, animal fats and high molecular weight alcohol (greater than C_{12}). In another embodiment, the carriers are those in which the active ingredient is soluble. Emulsifiers, stabilizers, humectants and antioxidants may also be included as well as agents imparting color or fragrance, if desired. Creams for topical application are formulated from a mixture of mineral oil, self-emulsifying beeswax and water in which mixture the active ingredient, dissolved in a small amount solvent (e.g. an oil), is admixed. Additionally, administration by transdermal means may comprise a transdermal patch or dressing such as a bandage impregnated with an active ingredient and optionally one or more carriers or diluents known in the art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

[0329] The amounts of various compounds to be administered can be determined by standard procedures taking into account factors such as the compound IC_{50}, the biological half-life of the compound, the age, size, and weight of the subject, and the indication being treated. The importance of these and other factors are well known to those of ordinary skill in the art. Generally, a dose will be between about 0.01 and 50 mg/kg, or 0.1 and 20 mg/kg of the subject being treated. Multiple doses may be used.

[0330] The compounds of the disclosure may also be used in combination with other therapies for treating the same disease. Such combination use includes administration of the compounds and one or more other therapeutics at different times, or co-administration of the compound and one or more other therapies. In some embodiments, dosage may be modified for one or more of the compounds of the disclosure or other therapeutics used in combination, e.g., reduction in the amount dosed relative to a compound or therapy used alone, by methods well known to those of ordinary skill in the art.

[0331] It is understood that use in combination includes use with other therapies, drugs, medical procedures etc., where the other therapy or procedure may be administered at different times (e.g. within a short time, such as within hours (e.g. 1, 2, 3, 4-24 hours), or within a longer time (e.g. 1-2 days, 2-4 days, 4-7 days, 1-4 weeks)) than a compound of the present disclosure, or at the same time as a compound of the disclosure. Use in combination also includes use with a therapy or medical procedure that is administered once or infrequently, such as surgery, along with a compound of the disclosure administered within a short time or longer time before or after the other therapy or procedure. In some embodiments, the present disclosure provides for

delivery of compounds of the disclosure and one or more other drug therapeutics delivered by a different route of administration or by the same route of administration. The use in combination for any route of administration includes delivery of compounds of the disclosure and one or more other drug therapeutics delivered by the same route of administration together in any formulation, including formulations where the two compounds are chemically linked in such a way that they maintain their therapeutic activity when administered. In one embodiment, the other drug therapy may be co-administered with one or more compounds of the disclosure. Use in combination by co-administration includes administration of co-formulations or formulations of chemically joined compounds, or administration of two or more compounds in separate formulations within a short time of each other (e.g. within an hour, 2 hours, 3 hours, up to 24 hours), administered by the same or different routes. Co-administration of separate formulations includes co-administration by delivery via one device, for example the same inhalant device, the same syringe, etc., or administration from separate devices within a short time of each other. Co-formulations of compounds of the disclosure and one or more additional drug therapies delivered by the same route includes preparation of the materials together such that they can be administered by one device, including the separate compounds combined in one formulation, or compounds that are modified such that they are chemically joined, yet still maintain their biological activity. Such chemically joined compounds may have a linkage that is substantially maintained *in vivo*, or the linkage may break down *in vivo*, separating the two active components.

[0332] In certain embodiments, the patient is 60 years or older and relapsed after a first line cancer therapy. In certain embodiments, the patient is 18 years or older and is relapsed or refractory after a second line cancer therapy. In certain embodiments, the patient is 60 years or older and is primary refractory to a first line cancer therapy. In certain embodiments, the patient is 70 years or older and is previously untreated. In certain embodiments, the patient is 70 years or older and is ineligible and/or unlikely to benefit from cancer therapy.

[0333] In certain embodiments, the therapeutically effective amount used in the methods provided herein is at least 10 mg per day of a compound of having any of the Formulae described in this disclosure, including any one of the compounds listed in Table I or Table II, or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer or a deuterated analog of any of these compounds. In certain embodiments, the therapeutically effective amount is 10, 50, 90, 100, 135, 150, 200, 250, 300, 350, 400, 450, 500, 600, 700, 800, 900, 1000, 1200, 1300, 1400, 1500, 1600, 1700, 1800, 1900, 2000, 2200, 2500 mg per dosage. In other embodiments, the therapeutically effective amount is 10, 50, 90, 100, 135, 150, 200, 250, 300, 350, 400, 450, 500,

600, 700, 800, 900, 1000, 1200, 1300, 1400, 1500, 1600, 1700, 1800, 1900, 2000, 2200, 2500, 3000, 3500, 4000, 4500, 5000 mg per day or more. In certain embodiments, the compound is administered continuously. In certain embodiments, the compound is administered in one or more dosages daily (such as once daily, twice daily, three times daily, four times daily, and the like) or weekly (such as once weekly, twice weekly, three times weekly, four times weekly, and the like).

[0334] In certain embodiments, provided herein is a method for treating a diseases or condition mediated by FLT3 or oncogenic FLT3 by administering to a mammal having a disease or condition at least 10, 50, 90, 100, 135, 150, 200, 250, 300, 350, 400, 450, 500, 600, 700, 800, 900, 1000, 1200, 1300, 1400, 1500, 1600, 1700, 1800, 1900, 2000, 2200, 2500, 3000, 3500, 4000, 4500, 5000 mg per day of a compound of having any of the Formulae described in this disclosure, including any one of the compounds listed in Table I or Table II, or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer or a deuterated analog of any of these compounds, and wherein the compound is administered on an empty stomach.

VIII. Methods for Treating Conditions Mediated by FLT3 or c-Kit Kinases

[0335] In another embodiment, the present disclosure provides a method for treating a subject suffering from or at risk of FLT3 or c-Kit protein kinase mediated diseases or conditions. The method includes administering to the subject an effective amount of one or more compound having any of the Formulae described in this disclosure, including any one of the compounds listed in Table I or Table II, or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer or a deuterated analog of any of these compounds, or a pharmaceutical composition thereof. In certain embodiments, the method involves administering to the subject an effective amount of any one or more compound(s) as described herein in combination with one or more other therapies for the disease or condition. Non-limiting examples of a disease or condition mediated by a FLT3 protein kinase include acute myeloid leukemia, stem cell ablation and myelopreparation for stem cell transplant, primary progressive multiple sclerosis, complex regional pain syndrome, reflex sympathetic dystrophy, muscular dystrophy, duchenne muscular dystrophy, causalgia, neuro-inflammation, neuroinflammatory disorders, benign forgetfulness, HIV, binswager type dementia, dementia with lewy bodie, prosencephaly, microencepahy, cerebral palsy, congenital hydrocephalus, abdominal dropsy, progressive supranuclear palsy, glaucoma, addiction disorders, dependencies, alcoholism, tremors, Wilson's disease, vascular dementias, multi infarct dementia, fronto temporal dementia, pseudo-dementia, bladder cancer, basal cell carcinoma, cholangiocarcinoma, colon cancer, endometrial cancer, esophageal cancer, Ewing's sarcoma, gastric cancer, glioma, hepatocellular carcinoma, Hodgkin lymphoma,

laryngeal carcinoma, leukemia, liver cancer, lung cancer, melanoma, mesothelioma, pancreatic cancer, rectal cancer, renal cancer, squamous cell carcinoma, t cell lymphoma, thyroid cancer, monocytic leukemia, pheochromocytoma, malignant peripheral nerve cell tumors, malignant peripheral nerve sheath tumors (MPNST), cutaneous and plexiform neurofibromas, leiomyoadenomatoid tumor, fibroids, uterine fibroids, leiomyosarcoma, papillary thyroid cancer, anaplastic thyroid cancer, medullary thyroid cancer, follicular thyroid cancer, hurthle cell carcinoma, thyroid cancer, ascites, malignant ascites, mesothelioma, salivary gland tumors, mucoepidermoid carcinoma of the salivary gland, acinic cell carcinoma of the salivary gland, gastrointestinal stromal tumors (GIST), tumors that cause effusions in potential spaces of the body, pleural effusions, pericardial effusions, peritoneal effusions aka ascites, giant cell tumors (GCT), GCT of bone other sarcomas, tumor angiogenesis, or paracrine tumor growth .

[0336] In one aspect, the disclosure provides a method for treating a disease or condition in a subject in need thereof, by administering to the subject a therapeutically effective amount of any one or more compound(s) as described herein, a prodrug of such compound, a pharmaceutically acceptable salt of such compound or prodrug, or a pharmaceutically acceptable formulation of such compound or prodrug. The compound can be alone or can be part of a composition. In one embodiment, the disclosure provides a method of treating a disease or condition in a subject in need thereof, by administering to the subject a therapeutically effective amount of any one or more compound(s) as described herein, a prodrug of such compound, a pharmaceutically acceptable salt of such compound or prodrug, or a pharmaceutically acceptable formulation of such compound or prodrug in combination with one or more other suitable therapies for the disease or condition.

[0337] In another embodiment of this disclosure, the disease or condition that can be treated by one or more a compounds having any of the Formulae described in this disclosure, including any one of the compounds listed in Table I or Table II, or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer or a deuterated analog of any of these compounds, is a lysosomal storage disorder. Non-limiting examples of lysosomal storage disorders include mucolipodosis, alpha-mannosidosis; aspartylglucosaminuria; Batten disease; beta-mannosidosis; cystinosis; Danon disease; Fabry disease; Farber disease; fucosidosis; galactosialidosis; Gaucher disease; gangliosidosis (e.g., GM1 gangliosidosis and GM2-gangliosidosis AB variant); Krabbe disease; metachromatic leukodystrophy; mucopolysaccharidoses disorders (e.g., MPS 1 – Hurler syndrome, MPS II – Hunter syndrome, MPS III – Sanfilippo (A,B,C,D), MPS IVA – Morquio, MPS IX – hyaluronidase, deficiency, MPS VI – Maroteaux-Lamy, or MPS VII – Sly syndrome); mucolipidosis type I (Sialidosis); Mucolipidosis type II (I-Cell disease);

Mucolipidosis type III (Pseudo-Hurler polydystrophy); Mucolipidosis type IV; multiple sulfatase deficiency; Niemann–Pick types A, B, C; Pompe disease (glycogen storage disease); pycnodysostosis; Sandhoff disease; Schindler disease; Salla disease/sialic acid storage disease; Tay–Sachs; and Wolman disease.

[0338] In aspects and embodiments involving treatment of a disease or condition with one or more of the compounds described herein, the disclosure provides methods for treating a disease or condition mediated by and FLT3 in a subject in need thereof (e.g. a mammal such as a human, other primates, sports animals, animals of commercial interest such as cattle, farm animals such as horses, or pets such as dogs and cats), e.g., a disease or condition characterized by abnormal FLT3 activity (e.g. kinase activity). In some embodiments, the methods may involve administering to the subject suffering from or at risk of a disease or condition mediated by FLT3 an effective amount of one or more compound(s) as described herein. **[0339]** In another embodiment, the FLT3 kinase is a mutated form. In another embodiment, the FLT3 Kinase mutation is FLT3 internal tandem duplication (ITD) mutation. In another embodiment, the FLT3 mutation further includes D835Y, F691L or both D835Y and F691L. In another embodiment, the disease or condition is selected from acute myeloid leukemia, acute lymphocytic leukemia or chronic myelogenous leukemia.

[0339] In some embodiments, the present disclosure provides a method for inhibiting mutant FLT3 kinase, such as FLT3 ITD and drug resistant FLT3 mutants such as D835Y and F691L. The method includes contacting one or more a compound having any of the Formulae described in this disclosure, including any one of the compounds listed in Table I or Table II, or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer or a deuterated analog of any of these compounds, or a pharmaceutical composition thereof, with a cell or a FLT3 mutant protein kinase either in vitro or in vivo.

[0340] In certain embodiments, the present disclosure provides use of one or more compounds having any of the Formulae described in this disclosure, including any one of the compounds listed in Table I or Table II, or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer or a deuterated analog of any of these compounds, or a pharmaceutical composition thereof, in the manufacture of a medicament for the treatment of a disease or condition as described herein. In other embodiments, the present disclosure provides a compound having any of the Formulae described in this disclosure, including any one of the compounds listed in Table I or Table II, or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer or a deuterated analog of any of these compounds, or a composition comprising a compound having any of the Formulae described in this disclosure, including any

one of the compounds listed in Table I or Table II, or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer or a deuterated analog of any of these compoundsfor use in treating a disease or condition as described herein.

[0341] In certain embodiments, the disease or condition in the methods provided herein is cancer. In certain embodiments, the disease or condition in the methods provided herein is a solid tumor. In yet another embodiment, the disease or condition in the methods provided herein is a blood-borne tumor. In yet another embodiment, the disease or condition is leukemia. In certain embodiments, the leukemia is acute myeloid leukemia. In certain embodiments, the leukemia is acute lymphocytic leukemia. In still another embodiment, the leukemia is a refractory or drug resistant leukemia.

[0342] In certain embodiments, the drug resistant leukemia is drug resistant acute myeloid leukemia. In certain embodiments, the mammal having the drug resistant acute myeloid leukemia has an activating FLT3 mutation. In still another embodiment, the drug resistant acute myeloid leukemia has a FLT3 internal tandem duplication (ITD) mutation. In still another embodiment, the drug resistant acute myeloid leukemia has a FLT3 internal tandem duplication (ITD) mutation and a drug resistant D835Y mutation. In still another embodiment, the drug resistant acute myeloid leukemia has a FLT3 internal tandem duplication (ITD) mutation and a drug resistant F691L mutation. In still another embodiment, the drug resistant acute myeloid leukemia has a FLT3 internal tandem duplication (ITD) mutation and drug resistant D835Y and F691L mutations.

VII. Combination Therapy

[0343] Protein kinase modulators may be usefully combined with another pharmacologically active compound, or with two or more other pharmacologically active compounds, particularly in the treatment of cancer. In one embodiment, the composition includes any one or more compound(s) as described herein along with one or more compounds that are therapeutically effective for the same disease indication, wherein the compounds have a synergistic effect on the disease indication. In one embodiment, the composition includes any one or more compound(s) as described herein effective in treating a cancer and one or more other compounds that are effective in treating the same cancer, further wherein the compounds are synergistically effective in treating the cancer.

[0344] In some embodiments, the present disclosure provides a composition comprising one or more a compounds having any of the Formulae described in this disclosure, including any one of the compounds listed in Table I or Table II, or a pharmaceutically acceptable salt, a

solvate, a tautomer, an isomer or a deuterated analog of any of these compounds, or a pharmaceutical composition thereof, and one or more agents. In some embodiments, the one or more agents are selected from an alkylating agent, including, but not limited to, adozelesin, altretamine, bendamustine, bizelesin, busulfan, carboplatin, carboquone, carmofur, carmustine, chlorambucil, cisplatin, cyclophosphamide, dacarbazine, estramustine, etoglucid, fotemustine, hepsulfam, ifosfamide, improsulfan, irofulven, lomustine, mannosulfan, mechlorethamine, melphalan, mitobronitol, nedaplatin, nimustine, oxaliplatin, piposulfan, prednimustine, procarbazine, ranimustinc, satraplatin, semustine, streptozocin, temozolomide, thiotepa, treosulfan, triaziquone, triethylenemelamine, triplatin tetranitrate, trofosphamide, and uramustine; an antibiotic, including, but not limited to, aclarubicin, amrubicin, bleomycin, dactinomycin, daunorubicin, doxorubicin, elsamitrucin, epirubicin, idarubicin, menogaril, mitomycin, neocarzinostatin, pentostatin, pirarubicin, plicamycin, valrubicin, and zorubicin; an antimetabolite, including, but not limited to, aminopterin, azacitidine, azathioprine, capecitabine, cladribine, clofarabine, cytarabine, decitabine, floxuridine, fludarabine, 5-fluorouracil, gemcitabine, hydroxyurea, mercaptopurine, methotrexate, nelarabine, pemetrexed, azathioprine, raltitrexed, tegafur-uracil, thioguanine, trimethoprim, trimetrexate, and vidarabine; an immunotherapy, including, but not limited to, alemtuzumab, bevacizumab, cetuximab, galiximab, gemtuzumab, panitumumab, pertuzumab, rituximab, tositumomab, trastuzumab, 90 Y ibritumomab tiuxetan, ipilimumab, and tremelimumab; a hormone or hormone antagonist, including, but not limited to, anastrozole, androgens, buserelin, diethylstilbestrol, exemestane, flutamide, fulvestrant, goserelin, idoxifene, letrozole, leuprolide, magestrol, raloxifene, tamoxifen, and toremifene; a taxane, including, but not limited to, DJ-927, docetaxel, TPI 287, larotaxel, ortataxel, paclitaxel, DHA-paclitaxel, and tesetaxel; a retinoid, including, but not limited to, alitretinoin, bexarotene, fenretinide, isotretinoin, and tretinoin; an alkaloid, including, but not limited to, demecolcine, homoharringtonine, vinblastine, vincristine, vindesine, vinflunine, and vinorelbine; an antiangiogenic agent, including, but not limited to, AE-941 (GW786034, Neovastat), ABT-510, 2-methoxyestradiol, lenalidomide, and thalidomide; a topoisomerase inhibitor, including, but not limited to, amsacrine, belotecan, edotecarin, etoposide, etoposide phosphate, exatecan, irinotecan (also active metabolite SN-38 (7-ethyl-10-hydroxy-camptothecin)), lucanthone, mitoxantrone, pixantrone, rubitecan, teniposide, topotecan, and 9-aminocamptothecin; a kinase inhibitor, including, but not limited to, axitinib (AG 013736), dasatinib (BMS 354825), erlotinib, gefitinib, flavopiridol, imatinib mesylate, lapatinib, motesanib diphosphate (AMG 706), nilotinib (AMN107), seliciclib, sorafenib, sunitinib malate, AEE-788, BMS-599626, UCN-01 (7-hydroxystaurosporine), and vatalanib; a targeted signal transduction inhibitor including, but not limited to bortezomib, geldanamycin, and rapamycin; a

biological response modifier, including, but not limited to, imiquimod, interferon-.alpha., and interleukin-2; and other chemotherapeutics, including, but not limited to 3-AP (3-amino-2-carboxyaldehyde thiosemicarbazone), altrasentan, aminoglutethimide, anagrelide, asparaginase, bryostatin-1, cilengitide, elesclomol, eribulin mesylate (E7389), ixabepilone, lonidamine, masoprocol, mitoguanazone, oblimersen, sulindac, testolactone, tiazofurin, mTOR inhibitors (e.g. temsirolimus, everolimus, deforolimus), PI3K inhibitors (e.g. BEZ235, GDC-0941, XL147, XL765), Cdk4 inhibitors (e.g. PD-332991), Akt inhibitors, Hsp90 inhibitors (e.g. tanespimycin) and farnesyltransferase inhibitors (e.g. tipifarnib); MEK inhibitors (e.g., AS703026, AZD6244 (selumetinib), AZD8330, BIX02188, C11040 (PD184352), D-87503, GSK1120212 (JTP-74057), PD0325901, PD318088, PD98059, PDEA119 (BAY 869766), TAK-733).

[0345] In another embodiment, each method provided herein may further comprise administering a second therapeutic agent. In certain embodiments, the second therapeutic agent is an anticancer agent. In certain embodiments, the second therapeutic agent is a protein kinase inhibitor; In certain embodiments, a tyrosine kinase inhibitor; and in yet another embodiment, a second FLT3 kinase inhibitor, including, but not limiting to, Sunitinib, Cediranib, XL-184 free base (Cabozantinib, Ponatinib (AP24534), PHA-665752, Dovitinib (TKI258, CHIR-258), AC220 (Quizartinib), TG101209 , KW-2449, AEE788 (NVP-AEE788), MP-470 (Amuvatinib), TSU-68 (SU6668, Orantinib, ENMD-2076, Vatalanib dihydrochloride (PTK787) and Tandutinib (MLN518).

[0346] In one embodiment, the present disclosure provides methods for treating a disease or condition mediated by FLT3 kinase, including mutant FLT3 kinase (such as FLT3 ITD and drug resistant FLT3 mutants such as D835Y and F691L), by administering to the subject an effective amount of a composition including any one or more compound(s) as described herein in combination with one or more other suitable therapies for treating the disease.

[0347] In another embodiment, the present disclosure provides a method of treating a cancer in a subject in need thereof by administering to the subject an effective amount of a composition including any one or more compound(s) as described herein in combination with one or more other therapies or medical procedures effective in treating the cancer. Other therapies or medical procedures include suitable anticancer therapy (e.g. drug therapy, vaccine therapy, gene therapy, photodynamic therapy) or medical procedure (e.g. surgery, radiation treatment, hyperthermia heating, bone marrow or stem cell transplant). In one embodiment, the one or more suitable anticancer therapies or medical procedures is selected from treatment with a chemotherapeutic agent (e.g. chemotherapeutic drug), radiation treatment (e.g. x-ray, .gamma.-ray, or electron, proton, neutron, or .alpha. particle beam), hyperthermia heating (e.g. microwave, ultrasound,

radiofrequency ablation), Vaccine therapy (e.g. AFP gene hepatocellular carcinoma vaccine, AFP adenoviral vector vaccine, AG-858, allogeneic GM-CSF-secretion breast cancer vaccine, dendritic cell peptide vaccines), gene therapy (e.g. Ad5CMV-p53 vector, adenovector encoding MDA7, adenovirus 5-tumor necrosis factor alpha), photodynamic therapy (e.g. aminolevulinic acid, motexatin lutetium), surgery, or bone marrow and stem cell transplantation.

IX. Kits

[0348] In another embdiment, the present disclosure provides kits that include one or more compounds having any of the Formulae described in this disclosure, including any one of the compounds listed in Table I or Table II, or a pharmaceutically acceptable salt, a solvate, a tautomer, an isomer or a deuterated analog of any of these compounds, or a pharmaceutical composition thereof. In some embodiments, the compound or composition is packaged, e.g., in a vial, bottle, flask, which may be further packaged, e.g., within a box, envelope, or bag; the compound or composition is approved by the U.S. Food and Drug Administration or similar regulatory agency for administration to a mammal, e.g., a human; the compound or composition is approved for administration to a mammal, e.g., a human, for a protein kinase mediated disease or condition; the kits described herein may include written instructions for use and/or other indication that the compound or composition is suitable or approved for administration to a mammal, e.g., a human, for a protein kinase-mediated disease or condition; and the compound or composition may be packaged in unit dose or single dose form, e.g., single dose pills, capsules, or the like.

X. Companion Diagnostics

[0349] Another embodiment of the disclosure relates to a method of (1) identifying the presence of a tumor in a patient; and (2) treating the patient, identified as needing the treatment, by administering a therapeutically effective amount of one or more compounds having any of the Formulae described in this disclosure, including any one of the compounds listed in Table I or Table II, or a pharmaceutical composition thereof. In one embodiment, the tumor can be identified by employing a tumor biomarker. Tumor biomarkers can also be useful in establishing a specific diagnosis, such as determining whether tumors are of primary or metastatic origin. To make this distinction, chromosomal alterations found on cells located in the primary tumor site can be screened against those found in the secondary site. If the alterations match, the secondary tumor can be identified as metastatic; whereas if the alterations differ, the secondary tumor can be identified as a distinct primary tumor.

[0350] In another embodiment, the tumor can be identified by a biopsy. Non-limiting examples of biopsies that can be employed include fine needle aspiration biopsy, a core needle biopsy, a vacuum-assisted biopsy, an image-guided biopsy, a surgical biopsy, an incisional biopsy, an endoscopic biopsy, and a bone marrow biopsy.

[0351] In another embodiment, the identification of tumor can be by magnetic resonance imaging (MRI), which is a test that uses magnetic fields to produce detailed images of the body.

[0352] In another embodiment, the identification of tumor can be by a bone scan. In another embodiment, the identification of tumor can be a computed tomography (CT) scan, also called a CAT scan.

[0353] In another embodiment, the identification of tumor can be by an integrated PET-CT scan combines images from a positron emission tomography (PET) scan and a computed tomography (CT) scan that have been performed at the same time using the same machine.

[0354] In another embodiment, the identification of tumor can be by an ultrasound, which is an imaging test that uses high-frequency sound waves to locate a tumor inside the body.

[0355] In more specific embodiments, companion diagnostics that can be used to help treat patients, as a form of personalized medicine, can be employed by identifying a patient having a FLT3 mutant that is encoded by a FLT3 gene having an ITD mutation. In another embodiment, the companion diagnostic that can be used to help treat patients, as a form of personalized medicine, can be employed by identifying a patient having an oncogenic FLT3 mutant that is encoded by a FLT3 gene having an ITD mutation and a drug resistant F691L mutation. In another embodiment, the companion diagnostic that can be used to help treat patients, as a form of personalized medicine, can be employed by identifying a patient having an oncogenic FLT3 mutant that is encoded by a FLT3 gene having an ITD mutation and a D835Y drug resistant mutation. In another embodiment, the companion diagnostic that can be used to help treat patients, as a form of personalized medicine, can be employed by identifying a patient having an oncogenic FLT3 mutant that is encoded by a FLT3 gene having an ITD mutation, a drug resistant F691L mutation, and a D835Y drug resistant mutation.

XI. Manipulation of FLT3

[0356] Techniques for the manipulation of nucleic acids, such as, e.g., subcloning, labeling probes (e.g. random-primer labeling using Klenow polymerase, nick translation, amplification), sequencing, hybridization and the like are well described in the scientific and patent literature, see, e.g., Sambrook, ed., Molecular Cloning: a Laboratory Manual (2nd ed.), Vols. 1-3, Cold Spring Harbor Laboratory, (1989); Current Protocols in Molecular Biology, Ausubel, ed. John

Wiley & Sons, Inc., New York (1997); Laboratory Techniques in Biochemistry and Molecular Biology: Hybridization With Nucleic Acid Probes, Part I. Theory and Nucleic Acid Preparation, Tijssen, ed. Elsevier, N.Y. (1993).

[0357] Nucleic acid sequences can be amplified as necessary for further use using amplification methods, such as PCR, isothermal methods, rolling circle methods, etc., are well known to the skilled artisan. See, e.g., Saiki, "Amplification of Genomic DNA" in PCR Protocols, Innis et al., Eds., Academic Press, San Diego, CA 1990, pp 13-20; Wharam et al., Nucleic Acids Res. 2001 Jun 1;29(11):E54-E54; Hafner et al., Biotechniques 2001 Apr;30(4):852-6, 858, 860 passim; Zhong et al., Biotechniques 2001 Apr;30(4):852-6, 858, 860 passim.

[0358] Nucleic acids, vectors, capsids, polypeptides, and the like can be analyzed and quantified by any of a number of general means well known to those of skill in the art. These include, e.g., analytical biochemical methods such as NMR, spectrophotometry, radiography, electrophoresis, capillary electrophoresis, high performance liquid chromatography (HPLC), thin layer chromatography (TLC), and hyperdiffusion chromatography, various immunological methods, e.g. fluid or gel precipitin reactions, immunodiffusion, immuno-electrophoresis, radioimmunoassays (RIAs), enzyme-linked immunosorbent assays (ELISAs), immuno-fluorescent assays, Southern analysis, Northern analysis, dot-blot analysis, gel electrophoresis (e.g. SDS-PAGE), nucleic acid or target or signal amplification methods, radiolabeling, scintillation counting, and affinity chromatography.

[0359] Obtaining and manipulating nucleic acids used to practice the methods of the disclosure can be performed by cloning from genomic samples, and, if desired, screening and re-cloning inserts isolated or amplified from, e.g., genomic clones or cDNA clones. Sources of nucleic acid used in the methods of the present disclosure include genomic or cDNA libraries contained in, e.g., mammalian artificial chromosomes (MACs), see, e.g., U.S. Patent Nos. 5,721,118; 6,025,155; human artificial chromosomes, see, e.g., Rosenfeld (1997) Nat. Genet. 15:333-335; yeast artificial chromosomes (YAC); bacterial artificial chromosomes (BAC); P1 artificial chromosomes, see, e.g., Woon (1998) Genomics 50:306-316; P1-derived vectors (PACs), see, e.g., Kern (1997) Biotechniques 23:120-124; cosmids, recombinant viruses, phages or plasmids.

[0360] The nucleic acids used to practice the methods of the present disclosure can be operatively linked to a promoter. A promoter can be one motif or an array of nucleic acid control sequences which direct transcription of a nucleic acid. A promoter can include necessary nucleic acid sequences near the start site of transcription, such as, in the case of a

polymerase II type promoter, a TATA element. A promoter also optionally includes distal enhancer or repressor elements which can be located as much as several thousand base pairs from the start site of transcription. A "constitutive" promoter is a promoter which is active under most environmental and developmental conditions. An "inducible" promoter is a promoter which is under environmental or developmental regulation. A "tissue specific" promoter is active in certain tissue types of an organism, but not in other tissue types from the same organism. The term "operably linked" refers to a functional linkage between a nucleic acid expression control sequence (such as a promoter, or array of transcription factor binding sites) and a second nucleic acid sequence, wherein the expression control sequence directs transcription of the nucleic acid corresponding to the second sequence.

[0361] The nucleic acids used to practice the methods of the present disclosure can also be provided in expression vectors and cloning vehicles, e.g., sequences encoding the polypeptides used to practice the methods of the present disclosure. Expression vectors and cloning vehicles used to practice the methods of the present disclosure can comprise viral particles, baculovirus, phage, plasmids, phagemids, cosmids, fosmids, bacterial artificial chromosomes, viral DNA (e.g. vaccinia, adenovirus, foul pox virus, pseudorabies and derivatives of SV40), P1-based artificial chromosomes, yeast plasmids, yeast artificial chromosomes, and any other vectors specific for specific hosts of interest (such as bacillus, *Aspergillus* and yeast). Vectors used to practice the methods of the present disclosure can include chromosomal, non-chromosomal and synthetic DNA sequences. Large numbers of suitable vectors are known to those of skill in the art, and are commercially available.

[0362] The nucleic acids used to practice the methods of the present disclosure can be cloned, if desired, into any of a variety of vectors using routine molecular biological methods; methods for cloning *in vitro* amplified nucleic acids are described, *e.g.*, U.S. Pat. No. 5,426,039. To facilitate cloning of amplified sequences, restriction enzyme sites can be "built into" a PCR primer pair. Vectors may be introduced into a genome or into the cytoplasm or a nucleus of a cell and expressed by a variety of conventional techniques, well described in the scientific and patent literature. See, e.g., Roberts (1987) Nature 328:731; Schneider (1995) Protein Expr. Purif. 6435:10; Sambrook, Tijssen or Ausubel. The vectors can be isolated from natural sources, obtained from such sources as ATCC or GenBank libraries, or prepared by synthetic or recombinant methods. For example, the nucleic acids used to practice the methods of the present disclosure can be expressed in expression cassettes, vectors or viruses which are stably or transiently expressed in cells (e.g. episomal expression systems). Selection markers can be incorporated into expression cassettes and vectors to confer a selectable phenotype on

transformed cells and sequences. For example, selection markers can code for episomal maintenance and replication such that integration into the host genome is not required.

[0363] In one embodiment, the nucleic acids used to practice the methods of the present disclosure are administered *in vivo* for *in situ* expression of the peptides or polypeptides used to practice the methods of the disclosure. The nucleic acids can be administered as "naked DNA" (see, e.g., U.S. Patent No. 5,580,859) or in the form of an expression vector, e.g., a recombinant virus. The nucleic acids can be administered by any route, including peri- or intra-tumorally, as described below. Vectors administered *in vivo* can be derived from viral genomes, including recombinantly modified enveloped or non-enveloped DNA and RNA viruses, selected from baculoviridiae, parvoviridiae, picornoviridiae, herpesveridiae, poxviridae, adenoviridiae, or picornnaviridiae. Chimeric vectors may also be employed which exploit advantageous merits of each of the parent vector properties (See e.g., Feng (1997) Nature Biotechnology 15:866-870). Such viral genomes may be modified by recombinant DNA techniques to include the nucleic acids used to practice the methods of the present disclosure; and may be further engineered to be replication deficient, conditionally replicating or replication competent. In alternative embodiments, vectors are derived from the adenoviral (e.g. replication incompetent vectors derived from the human adenovirus genome, see, e.g., U.S. Patent Nos. 6,096,718**;** 6,110,458**;** 6,113,913; 5,631,236); adeno-associated viral and retroviral genomes. Retroviral vectors can include those based upon murine leukemia virus (MuLV), gibbon ape leukemia virus (GaLV), Simian Immuno deficiency virus (SIV), human immuno deficiency virus (HIV), and combinations thereof; see, e.g., U.S. Patent Nos. 6,117,681; 6,107,478; 5,658,775; 5,449,614; Buchscher (1992) J. Virol. 66:2731-2739; Johann (1992) *J. Virol.* 66:1635-1640). Adeno-associated virus (AAV)-based vectors can be used to transduce cells with target nucleic acids, e.g., in the *in vitro* production of nucleic acids and peptides, and in *in vivo* and *ex vivo* gene therapy procedures; see, e.g., U.S. Patent Nos. 6,110,456; 5,474,935; Okada (1996) *Gene Ther.* 3:957-964.

[0364] The present disclosure also relates to use of fusion proteins, and nucleic acids encoding them. A polypeptide used to practice the methods of the present disclosure can be fused to a heterologous peptide or polypeptide, such as N-terminal identification peptides which impart desired characteristics, such as increased stability or simplified purification. Peptides and polypeptides used to practice the methods of the present disclosure can also be synthesized and expressed as fusion proteins with one or more additional domains linked thereto for, e.g., producing a more immunogenic peptide, to more readily isolate a recombinantly synthesized peptide, to identify and isolate antibodies and antibody-expressing B cells, and the like.

Detection and purification facilitating domains include, e.g., metal chelating peptides such as polyhistidine tracts and histidine-tryptophan modules that allow purification on immobilized metals, protein A domains that allow purification on immobilized immunoglobulin, and the domain utilized in the FLAGS extension/affinity purification system (Immunex Corp, Seattle WA). The inclusion of a cleavable linker sequences such as Factor Xa or enterokinase (Invitrogen, San Diego CA) between a purification domain and the motif-comprising peptide or polypeptide to facilitate purification. For example, an expression vector can include an epitope-encoding nucleic acid sequence linked to six histidine residues followed by a thioredoxin and an enterokinase cleavage site (see e.g., Williams (1995) Biochemistry 34:1787-1797; Dobeli (1998) Protein Expr. Purif. 12:404-414). The histidine residues facilitate detection and purification while the enterokinase cleavage site provides a means for purifying the epitope from the remainder of the fusion protein. In one embodiment, a nucleic acid encoding a polypeptide used to practice the methods of the present disclosure is assembled in appropriate phase with a leader sequence capable of directing secretion of the translated polypeptide or fragment thereof. Technology pertaining to vectors encoding fusion proteins and application of fusion proteins are well described in the scientific and patent literature, see e.g., Kroll (1993) DNA Cell. Biol. 12:441-53.

[0365] The nucleic acids and polypeptides used to practice the methods of the present disclosure can be bound to a solid support, e.g., for use in screening and diagnostic methods. Solid supports can include, e.g., membranes (e.g. nitrocellulose or nylon), a microtiter dish (e.g. PVC, polypropylene, or polystyrene), a test tube (glass or plastic), a dip stick (e.g. glass, PVC, polypropylene, polystyrene, latex and the like), a microfuge tube, or a glass, silica, plastic, metallic or polymer bead or other substrate such as paper. One solid support uses a metal (e.g. cobalt or nickel)-comprising column which binds with specificity to a histidine tag engineered onto a peptide.

[0366] Adhesion of molecules to a solid support can be direct (*i.e.,* the molecule contacts the solid support) or indirect (a "linker" is bound to the support and the molecule of interest binds to this linker). Molecules can be immobilized either covalently (e.g. utilizing single reactive thiol groups of cysteine residues (see, e.g., Colliuod (1993) Bioconjugate Chem. 4:528-536) or non-covalently but specifically (e.g. via immobilized antibodies (see, e.g., Schuhmann (1991) Adv. Mater. 3:388-391; Lu (1995) Anal. Chem. 67:83-87; the biotin/strepavidin system (see, e.g., Iwane (1997) Biophys. Biochem. Res. Comm. 230:76-80); metal chelating, e.g., Langmuir-Blodgett films (see, e.g., Ng (1995) Langmuir 11:4048-55); metal-chelating self-assembled

monolayers (see, e.g., Sigal (1996) Anal. Chem. 68:490-497) for binding of polyhistidine fusions.

[0367] Indirect binding can be achieved using a variety of linkers which are commercially available. The reactive ends can be any of a variety of functionalities including, but not limited to: amino reacting ends such as N-hydroxysuccinimide (NHS) active esters, imidoesters, aldehydes, epoxides, sulfonyl halides, isocyanate, isothiocyanate, and nitroaryl halides; and thiol reacting ends such as pyridyl disulfides, maleimides, thiophthalimides, and active halogens. The heterobifunctional crosslinking reagents have two different reactive ends, e.g., an amino-reactive end and a thiol-reactive end, while homobifunctional reagents have two similar reactive ends, e.g., bismaleimidohexane (BMH) which permits the cross-linking of sulfhydryl-containing compounds. The spacer can be of varying length and be aliphatic or aromatic. Examples of commercially available homobifunctional cross-linking reagents include, but are not limited to, the imidoesters such as dimethyl adipimidate dihydrochloride (DMA); dimethyl pimelimidate dihydrochloride (DMP); and dimethyl suberimidate dihydrochloride (DMS). Heterobifunctional reagents include commercially available active halogen-NHS active esters coupling agents such as N-succinimidyl bromoacetate and N-succinimidyl (4-iodoacetyl)aminobenzoate (SIAB) and the sulfosuccinimidyl derivatives such as sulfosuccinimidyl(4-iodoacetyl)aminobenzoate (sulfo-SIAB) (Pierce). Another group of coupling agents is the heterobifunctional and thiol cleavable agents such as N-succinimidyl 3-(2-pyridyidithio)propionate (SPDP) (Pierce Chemicals, Rockford, IL).

[0368] Antibodies can also be used for binding polypeptides and peptides used to practice the methods of the present disclosure to a solid support. This can be done directly by binding peptide-specific antibodies to the column or it can be done by creating fusion protein chimeras comprising motif-containing peptides linked to, e.g., a known epitope (e.g. a tag (e.g. FLAG, myc) or an appropriate immunoglobulin constant domain sequence (an "immunoadhesin," see, e.g., Capon (1989) *Nature* 377:525-531 (1989).

[0369] Nucleic acids or polypeptides used to practice the methods of the present disclosure can be immobilized to or applied to an array. Arrays can be used to screen for or monitor libraries of compositions (e.g. small molecules, antibodies, nucleic acids, etc.) for their ability to bind to or modulate the activity of a nucleic acid or a polypeptide used to practice the methods of the present disclosure. For example, in one embodiment of the disclosure, a monitored parameter is transcript expression of a gene comprising a nucleic acid used to practice the methods of the present disclosure. One or more, or all the transcripts of a cell can be measured by hybridization of a sample comprising transcripts of the cell, or nucleic acids representative of

or complementary to transcripts of a cell, by hybridization to immobilized nucleic acids on an array, or "biochip." By using an "array" of nucleic acids on a microchip, some or all of the transcripts of a cell can be simultaneously quantified. Alternatively, arrays comprising genomic nucleic acid can also be used to determine the genotype of a newly engineered strain made by the methods of the present disclosure. Polypeptide arrays" can also be used to simultaneously quantify a plurality of proteins.

[0370] The terms "array" or "microarray" or "biochip" or "chip" as used herein is a plurality of target elements, each target element comprising a defined amount of one or more polypeptides (including antibodies) or nucleic acids immobilized onto a defined area of a substrate surface. In practicing the methods of the present disclosure, any known array and/or method of making and using arrays can be incorporated in whole or in part, or variations thereof, as described, for example, in U.S. Patent Nos. 6,277,628; 6,277,489; 6,261,776; 6,258,606; 6,054,270; 6,048,695; 6,045,996; 6,022,963; 6,013,440; 5,965,452; 5,959,098; 5,856,174; 5,830,645; 5,770,456; 5,632,957; 5,556,752; 5,143,854; 5,807,522; 5,800,992; 5,744,305; 5,700,637; 5,556,752; 5,434,049; see also, e.g., WO 99/51773; WO 99/09217; WO 97/46313; WO 96/17958; see also, e.g., Johnston (1998) Curr. Biol. 8:R171-R174; Schummer (1997) Biotechniques 23:1087-1092; Kern (1997) Biotechniques 23:120-124; Solinas-Toldo (1997) Genes, Chromosomes & Cancer 20:399-407; Bowtell (1999) Nature Genetics Supp. 21:25-32. See also published U.S. patent application Nos. 20010018642; 20010019827; 20010016322; 20010014449; 20010014448; 20010012537; 20010008765.

Host Cells and Transformed Cells

[0371] The present disclosure also provides a transformed cell comprising a nucleic acid sequence used to practice the methods of the present disclosure, *e.g.*, a sequence encoding a polypeptide used to practice the methods of the present disclosure, or a vector used to practice the methods of the present disclosure. The host cell may be any of the host cells familiar to those skilled in the art, including prokaryotic cells, eukaryotic cells, such as bacterial cells, fungal cells, yeast cells, mammalian cells, insect cells, or plant cells. Exemplary bacterial cells include *E. coli*, *Streptomyces*, *Bacillus subtilis*, *Salmonella typhimurium* and various species within the genera *Pseudomonas*, *Streptomyces*, and *Staphylococcus*. Exemplary insect cells include *Drosophila* S2 and *Spodoptera* Sf9. Exemplary animal cells include CHO, COS or Bowes melanoma or any mouse or human cell line. The selection of an appropriate host is within the abilities of those skilled in the art.

[0372] Vectors may be introduced into the host cells using any of a variety of techniques, including transformation, transfection, transduction, viral infection, gene guns, or Ti-mediated

gene transfer. Particular methods include calcium phosphate transfection, DEAE-Dextran mediated transfection, lipofection, or electroporation.

[0373] Engineered host cells can be cultured in conventional nutrient media modified as appropriate for activating promoters, selecting transformants or amplifying the genes used to practice the methods of the present disclosure. Following transformation of a suitable host strain and growth of the host strain to an appropriate cell density, the selected promoter may be induced by appropriate means (e.g. temperature shift or chemical induction) and the cells may be cultured for an additional period to allow them to produce the desired polypeptide or fragment thereof.

[0374] Cells can be harvested by centrifugation, disrupted by physical or chemical means, and the resulting crude extract is retained for further purification. Microbial cells employed for expression of proteins can be disrupted by any convenient method, including freeze-thaw cycling, sonication, mechanical disruption, or use of cell lysing agents. Such methods are well known to those skilled in the art. The expressed polypeptide or fragment can be recovered and purified from recombinant cell cultures by methods including ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. Protein refolding steps can be used, as necessary, in completing configuration of the polypeptide. If desired, high performance liquid chromatography (HPLC) can be employed for final purification steps.

[0375] Various mammalian cell culture systems can also be employed to express recombinant protein. Examples of mammalian expression systems include the COS-7 lines of monkey kidney fibroblasts and other cell lines capable of expressing proteins from a compatible vector, such as the C127, 3T3, CHO, HeLa and BHK cell lines.

[0376] The constructs in host cells can be used in a conventional manner to produce the gene product encoded by the recombinant sequence. Depending upon the host employed in a recombinant production procedure, the polypeptides produced by host cells containing the vector may be glycosylated or may be non-glycosylated. Polypeptides used to practice the methods of the present disclosure may or may not also include an initial methionine amino acid residue.

[0377] Cell-free translation systems can also be employed to produce a polypeptide used to practice the methods of the present disclosure. Cell-free translation systems can use mRNAs transcribed from a DNA construct comprising a promoter operably linked to a nucleic acid

encoding the polypeptide or fragment thereof. In some embodiments, the DNA construct may be linearized prior to conducting an *in vitro* transcription reaction. The transcribed mRNA is then incubated with an appropriate cell-free translation extract, such as a rabbit reticulocyte extract, to produce the desired polypeptide or fragment thereof.

[0378] The expression vectors can contain one or more selectable marker genes to provide a phenotypic trait for selection of transformed host cells such as dihydrofolate reductase or neomycin resistance for eukaryotic cell culture, or such as tetracycline or ampicillin resistance in *E. coli*.

[0379] For transient expression in mammalian cells, cDNA encoding a polypeptide of interest may be incorporated into a mammalian expression vector, e.g. pcDNA1, which is available commercially from Invitrogen Corporation (San Diego, Calif., U.S.A.; catalogue number V490-20). This is a multifunctional 4.2 kb plasmid vector designed for cDNA expression in eukaryotic systems, and cDNA analysis in prokaryotes, incorporated on the vector are the CMV promoter and enhancer, splice segment and polyadenylation signal, an SV40 and Polyoma virus origin of replication, and M13 origin to rescue single strand DNA for sequencing and mutagenesis, Sp6 and T7 RNA promoters for the production of sense and anti-sense RNA transcripts and a Col E1-like high copy plasmid origin. A polylinker is located appropriately downstream of the CMV promoter (and 3' of the T7 promoter).

[0380] The cDNA insert may be first released from the above phagemid incorporated at appropriate restriction sites in the pcDNAI polylinker. Sequencing across the junctions may be performed to confirm proper insert orientation in pcDNAI. The resulting plasmid may then be introduced for transient expression into a selected mammalian cell host, for example, the monkey-derived, fibroblast like cells of the COS-1 lineage (available from the American Type Culture Collection, Rockville, Md. as ATCC CRL 1650).

[0381] For transient expression of the protein-encoding DNA, for example, COS-1 cells may be transfected with approximately 8 μg DNA per 10^6 COS cells, by DEAE-mediated DNA transfection and treated with chloroquine according to the procedures described by Sambrook et al, Molecular Cloning: A Laboratory Manual, 1989, Cold Spring Harbor Laboratory Press, Cold Spring Harbor N.Y, pp. 16.30-16.37. An exemplary method is as follows. Briefly, COS-1 cells are plated at a density of 5 x 10^6 cells/dish and then grown for 24 hours in FBS-supplemented DMEM/F12 medium. Medium is then removed and cells are washed in PBS and then in medium. A transfection solution containing DEAE dextran (0.4 mg/mL), 100 μM chloroquine, 10% NuSerum, DNA (0.4 mg/mL) in DMEM/F12 medium is then applied on the cells 10 mL volume. After incubation for 3 hours at 37 °C, cells are washed in PBS and medium as just

described and then shocked for 1 minute with 10% DMSO in DMEM/F12 medium. Cells are allowed to grow for 2-3 days in 10% FBS-supplemented medium, and at the end of incubation dishes are placed on ice, washed with ice cold PBS and then removed by scraping. Cells are then harvested by centrifugation at 1000 rpm for 10 minutes and the cellular pellet is frozen in liquid nitrogen, for subsequent use in protein expression. Northern blot analysis of a thawed aliquot of frozen cells may be used to confirm expression of receptor-encoding cDNA in cells under storage.

[0382] In a like manner, stably transfected cell lines can also prepared, for example, using two different cell types as host: CHO K1 and CHO Pro5. To construct these cell lines, cDNA coding for the relevant protein may be incorporated into the mammalian expression vector pRC/CMV (Invitrogen), which enables stable expression. Insertion at this site places the cDNA under the expression control of the cytomegalovirus promoter and upstream of the polyadenylation site and terminator of the bovine growth hormone gene, and into a vector background comprising the neomycin resistance gene (driven by the SV40 early promoter) as selectable marker.

[0383] An exemplary protocol to introduce plasmids constructed as described above is as follows. The host CHO cells are first seeded at a density of $5x10^5$ in 10% FBS-supplemented MEM medium. After growth for 24 hours, fresh medium is added to the plates and three hours later, the cells are transfected using the calcium phosphate-DNA co-precipitation procedure (Sambrook et al, supra). Briefly, 3 μg of DNA is mixed and incubated with buffered calcium solution for 10 minutes at room temperature. An equal volume of buffered phosphate solution is added and the suspension is incubated for 15 minutes at room temperature. Next, the incubated suspension is applied to the cells for 4 hours, removed and cells were shocked with medium containing 15% glycerol. Three minutes later, cells are washed with medium and incubated for 24 hours at normal growth conditions. Cells resistant to neomycin are selected in 10% FBS-supplemented alpha-MEM medium containing G418 (1 mg/mL). Individual colonies of G418-resistant cells are isolated about 2-3 weeks later, clonally selected and then propagated for assay purposes.

EXAMPLES

[0384] The examples below depict the general synthetic procedure for the compounds described herein. Synthesis of the compounds described herein is not limited by these examples and schemes. One skilled in the art will know that other procedures can be used to synthesize the compounds described herein, and that the procedures described in the examples and schemes is only one such procedure. In the descriptions below, one of ordinary skill in the art would recognize that specific reaction conditions, added reagents, solvents, and reaction temperatures

can be modified for the synthesis of specific compounds that fall within the scope of this disclosure. Unless otherwise specified, intermediate compounds in the examples below, that do not contain a description of how they are made, are either commercially available to one skilled in the art, or can otherwise be synthesized by the skilled artisan using commercially available precursor molecules and synthetic methods known in the art.

[0385] Unless otherwise specified, intermediate compounds in the examples below, that do not contain a description of how they are made, are either commercially available to one skilled in the art, or can otherwise be synthesized by the skilled artisan using knowledge and techniques known in the art. In most cases, alternative techniques can be used. The examples are intended to be illustrative and are not limiting or restrictive to the scope of the disclosure.

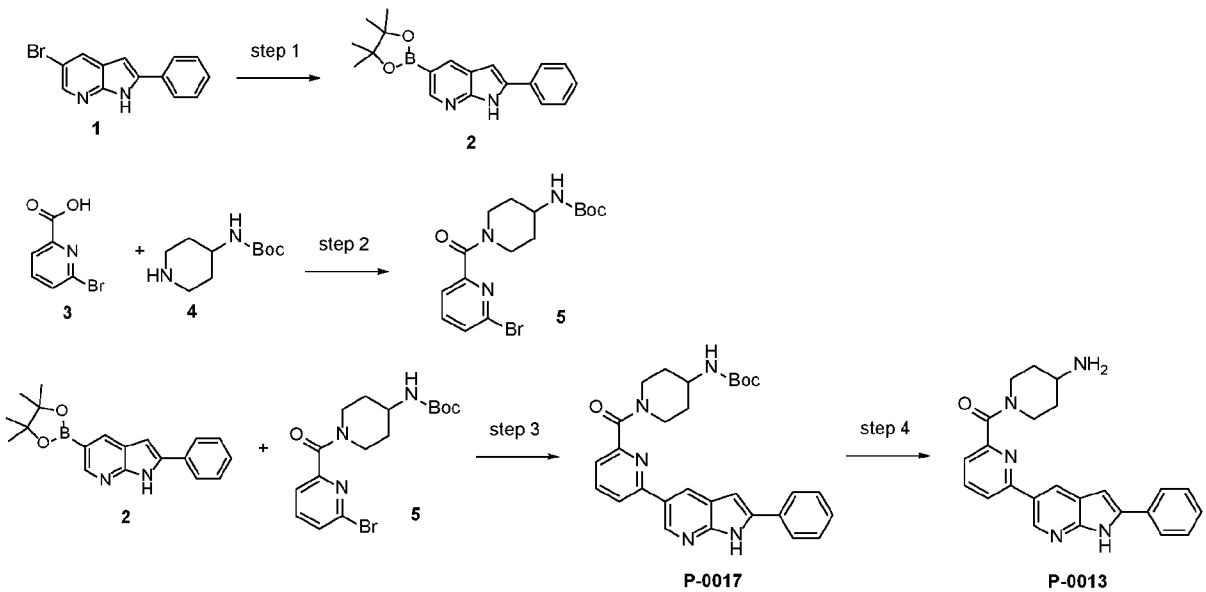
Synthetic Examples

[0386] Standard abbreviations and acronyms as defined in *J. Org. Chem.* 2007 72(1): 23A-24A are used herein. Other abbreviations and acronyms used herein are described above.

Example 1

[0387] Compound **P-0013** is prepared in four steps from 5-bromo-2-phenyl-1H-pyrrolo[2,3-b]pyridine **1**, 6-bromopicolinic acid **3** and *tert*-butyl piperidin-4-ylcarbamate **4** as shown in Scheme 1.

Scheme 1



[0388] Step 1 – Preparation of 2-phenyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridine, 2: To 5-bromo-2-phenyl-1H-pyrrolo[2,3-b]pyridine **1** (21 g, 77 mmol) and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (23.43 g, 92 mmol) in DMF (308 mL) was added potassium acetate (22.64 g, 231 mmol) and [1,1'-Bis(diphenylphosphino) ferrocene]dichloropalladium(II) dichloromethane complex (6.28 g, 7.69 mmol) and the mixture was heated at 110 °C overnight. After cooling, the reaction was poured into water (10 volumes), diluted with ethyl acetate and filtered through Celite washing the cake with ethyl acetate. The organic layer was separated and concentrated under reduced pressure. The crude residue was triturated with MTBE and the solid was collected by filtration giving compound **2** (12 g, 49% yield) as a brown solid.

[0389] Step 2 – Preparation of tert-butyl N-[1-(6-bromopyridine-2-carbonyl)-4-piperidyl]carbamate, 5: To 6-bromopicolinic acid (0.3 g, 1.49 mmol) **3** in tetrahydrofuran (5 mL) was added HBTU (0.2 g, 0.53 mmol), followed by triethylamine (0.2 ml, 1.43 mmol). The suspension was allowed to stir at room temperature for 30 minutes. To this suspension was added tert-butyl piperidin-4-ylcarbamate (0.35 g, 1.75 mmol) **4** in N,N-dimethylformamide (1 mL). The reaction mixture was allowed to stir at room temperature overnight. The reaction mixture was poured into water. The precipitate was collected, washed with ethyl acetate, and purified by silica gel column chromatography to provide compound **5** as off-white solid (0.2 g, 35%). MS ESI $[M(-BOC)+H^+]^+$ = 284.85/286.55.

[0390] Step 3 – Preparation of tert-butyl N-[1-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carbonyl]-4-piperidyl]carbamate, P-0017: To a mixture of 2-phenyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridine (0.10 g, 0.31 mmol) **2**, tert-butyl N-[1-(6-aminopyridine-2-carbonyl)-4-piperidyl]carbamate (0.099 mg, 0.31 mmol) **5**, and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) dichloromethane complex (24 mg, 0.031 mmol) in dioxane (3 ml) was added aqueous potassium hydroxide (1 mL, 1 M). The reaction mixture was irradiated in a microwave reactor at 130 °C for 20 minutes. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was collected, washed with brine and dried over anhydrous sodium sulfate. After filtration of the drying agent and evaporation of the solvent, the residue was purified by silica gel column chromatography to provide compound **P-0017** as off-white solid (0.07 g, 45%). MS (ESI) $[M+H^+]^+$ = 498.00.

[0391] Step 4 – Preparation of (4-amino-1-piperidyl)-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]methanone. P-0013: To a solution of tert-butyl N-[1-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carbonyl]-4-piperidyl]carbamate (0.06 g, 0.12 mmol) **P-0017** in tetrahydrofuran (3 ml) was added hydrochloric acid (2 mL, 4 M). The reaction

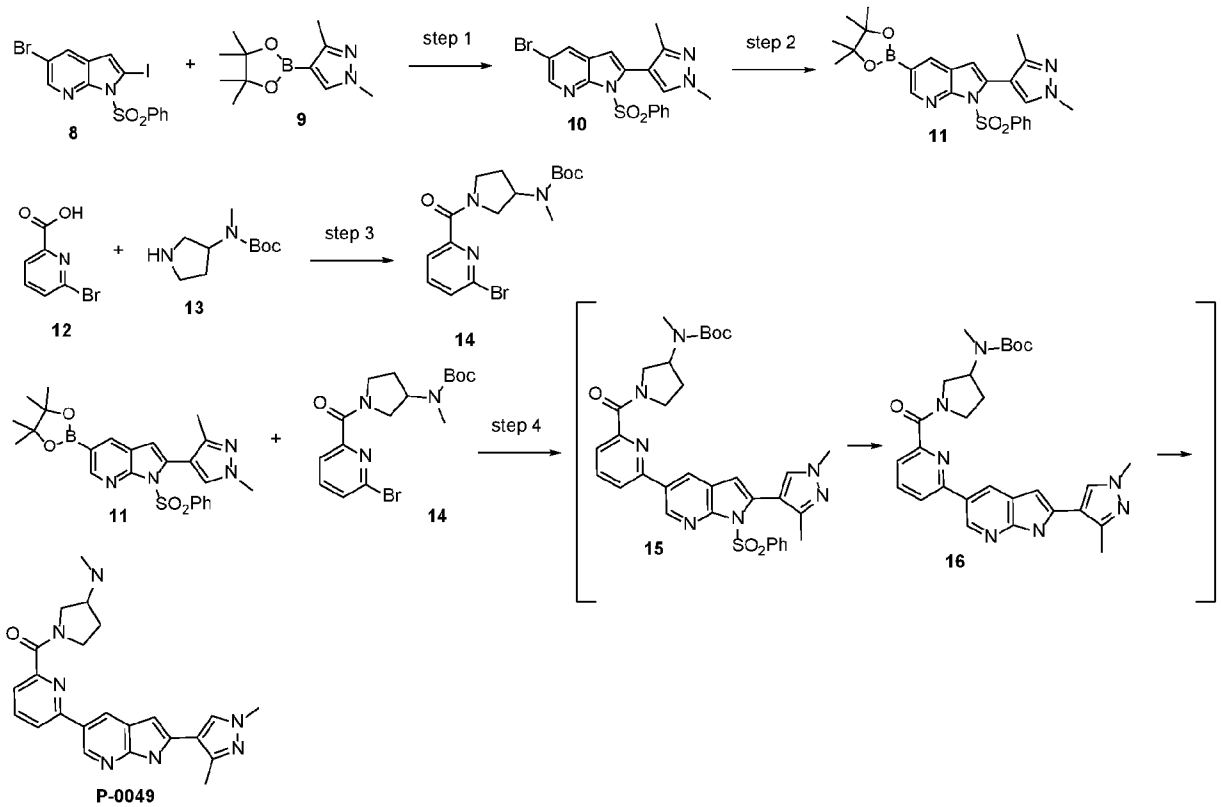
mixture was allowed to stir at room temperature overnight. The reaction mixture was concentrated and the residue was purified by preparative reverse phase HPLC to provide compound **P-0013** as a white solid (19 mg, 39%). MS ESI $[M+H^+]^+$ = 397.90.

[0392] The following compounds may be prepared via the synthetic route depicted in Scheme 1: P-0003, P-0002, P-0005, P-0006, P-0030, P-0032, P-0034, P-0035, P-0046, P-0047, P-0048, P-0050, P-0098 and P-0140.

Example 2

[0393] Compound **P-0049** is prepared in four steps from 1-(benzenesulfonyl)-5-bromo-2-iodo-pyrrolo[2,3-b]pyridine **8**, 1,3-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole **9**, 6-bromopyridine-2-carboxylic acid **12** and tert-butyl N-methyl-N-pyrrolidin-3-yl-carbamate **13** as shown in Scheme 2.

Scheme 2



[0394] **Step 1 – Preparation of 1-(benzenesulfonyl)-5-bromo-2-(1,3-dimethylpyrazol-4-yl)pyrrolo[2,3-b]pyridine, 10:** A mixture of 1-(benzenesulfonyl)-5-bromo-2-iodo-pyrrolo[2,3-b]pyridine **8** (0.5 g, 1.08 mmol), 1,3-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole **9** (0.31 g, 1.4 mmol), aqueous potassium carbonate (1.08 ml, 2.5 M),

tetrakis(triphenylphosphine)palladium(0) (0.06 g, 0.05 mmol) in dioxane was stirred at 80 °C for 18 h. The reaction mixture was filtered through a pad of Celite. The filtrate was partitioned between ethyl acetate and ammonium chloride solution (saturated aqueous). The organic layer was collected and washed with brine, then dried over magnesium sulfate. After removal of the drying agent by filtration and evaporation of the solvent, the residue was purified by silica gel column chromatography to provide compound **10** as a colorless oil (0.11 g, 24%).

[0395] Step 2 – Preparation of 1-(benzenesulfonyl)-2-(1,3-dimethylpyrazol-4-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolo[2,3-b]pyridine, 11: A mixture of 1-(benzenesulfonyl)-5-bromo-2-(1,3-dimethylpyrazol-4-yl)pyrrolo[2,3-b]pyridine **10** (110 mg, 0.26 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (80.96 mg, 0.32 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) dichloromethane complex (0.04 g, 0.05 mmol), and potassium acetate (0.05 ml, 0.77 mmol) in DMF was flushed with nitrogen and was allowed to stir at 90 °C for 18 h. The reaction mixture was filtered through Celite. The pH of the filtrate was adjusted with aqueous hydrochloric acid (1 N) and then was extracted with ethyl acetate. The organic layer was collected and washed with brine, then dried over magnesium sulfate. After removal of the drying agent by filtration and evaporation of the solvent, the residue was dried under vacuum to provide compound **11**. This material was used in the next reaction step without further purification (0.1 g, 80%).

[0396] Step 3 – Preparation of tert-butyl N-[1-(6-bromopyridine-2-carbonyl)pyrrolidin-3-yl]-N-methyl-carbamate, 14: A mixture of 6-bromopyridine-2-carboxylic acid **12** (0.6 g, 2.97 mmol), triethylamine (1.45 ml, 10.4 mmol), and HBTU (1.18 g, 3.11 mmol) in THF was allowed to stir at room temperature for 30 minutes. Then, to this mixture, was added tert-butyl N-methyl-N-pyrrolidin-3-yl-carbamate **13** (0.65 g, 3.25 mmol). The reaction mixture was allowed to stir at room temperature for 18 h. The pH of the reaction mixture was adjusted with aqueous hydrochloric acid (1 N) and then was extracted with ethyl acetate. The organic layer was separated and washed with brine, then dried over magnesium sulfate. After removal of drying agent and solvent, the residue was purified by silica gel column chromatography to provide compound **14** (430 mg, 38%).

[0397] Step 4 – Preparation of [6-[2-(1,3-dimethylpyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]-2-pyridyl]-[3-(methylamino)pyrrolidin-1-yl]methanone, P-0049: A mixture of 1-(benzenesulfonyl)-2-(1,3-dimethylpyrazol-4-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolo[2,3-b]pyridine **11** (100 mg, 0.21 mmol), tert-butyl N-[1-(6-bromopyridine-2-carbonyl)pyrrolidin-3-yl]-N-methyl-carbamate **14** (72.3 mg, 0.19 mmol), aqueous potassium

carbonate (0.2 ml, 2.5M) , and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) dichloromethane complex (0.03 g, 0.04 mmol) in DMF was allowed to stir at 115 °C for 30 minutes with microwave irradiation. The reaction mixture was filtered through Celite. The pH of the filtrate was adjusted with aqueous ammonium chloride and then was extracted with ethyl acetate. The organic layer was separated and washed with brine, then dried over magnesium sulfate. After removal of the drying agent and solvent, the residue was dried under vacuum to provide compound **15** which was used without further purification.

[0398] To compound **15** in THF was added potassium hydroxide in methanol (1.5 mL, 1 N). The mixture was allowed to stir at room temperature for two hours. The pH of the reaction mixture was adjusted with aqueous hydrochloric acid (1 N) and then was extracted with dichloromethane. The organic layer was collected and washed with brine and then dried over magnesium sulfate. After removal of the drying agent and solvent, the residue was dried under vacuum to provide compound **16** which was used without further purification.

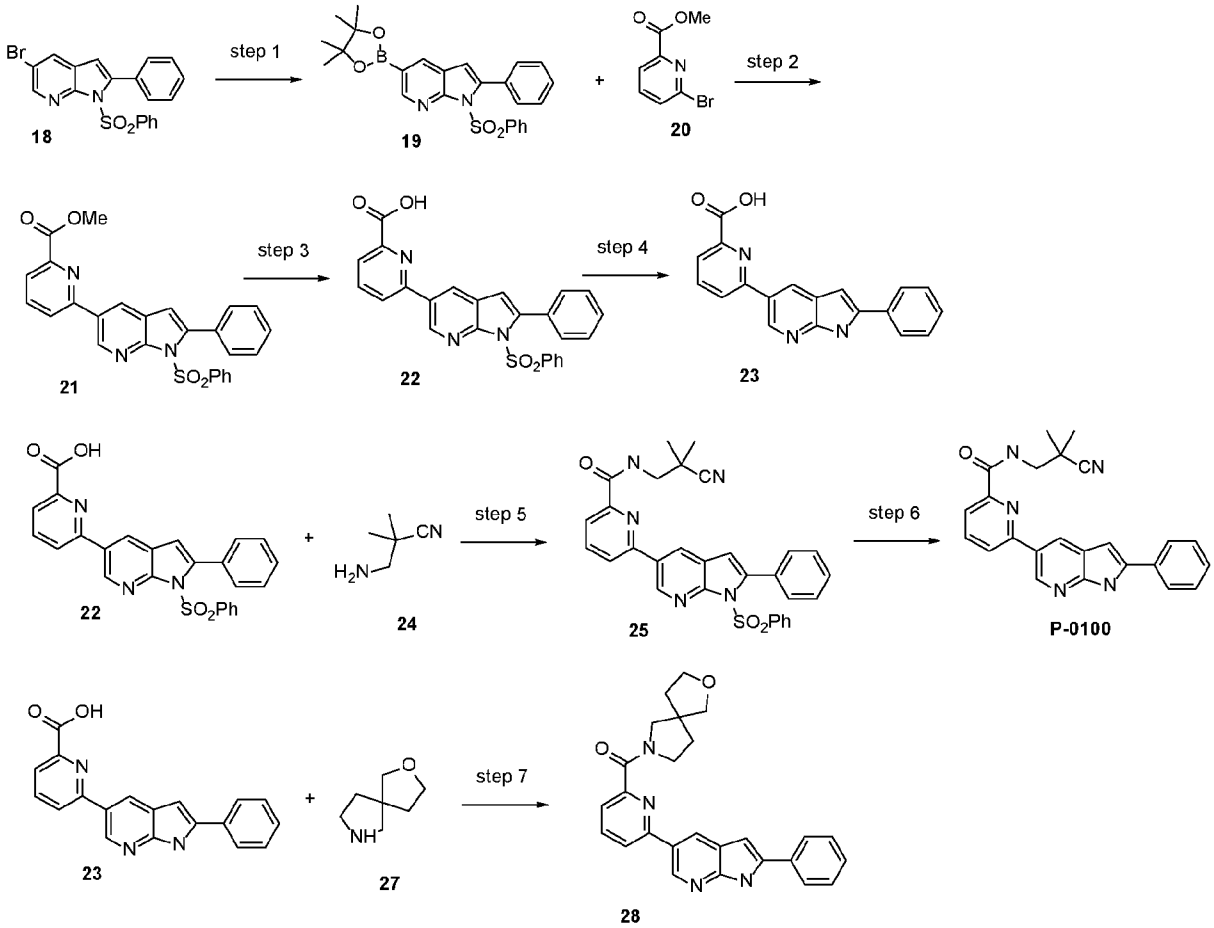
[0399] To compound **16** in DCM was added TFA (0.3 mL). The mixture was allowed to stir at room temperature for two hours. The reaction mixture was dried under vacuum after removal of solvent under reduced pressure. The residue was partitioned between dichloromethane and saturated sodium bicarbonate solution. The organic layer was collected and washed with brine, then dried over magnesium sulfate. After removal of the drying agent and solvent, the residue was purified by reverse phase silica gel chromatography to provide compound **P-0049** (9 mg, 10%). MS ESI $[M+H^+]^+$ = 416.30.

[0400] The following compounds may be prepared via the synthetic route depicted in Scheme 2: P-0001, P-0055, P-0058, P-0060, P-0061, P-0062, P-0112, P-0113, P-0064, P-0065, P-0116, P-0130, P-0133, P-0134, P-0144, P-0145, P-0152, P-0153, P-0154, P-0155, and P-0158.

Example 3

[0401] Compound **P-0100** and Compound **28** are prepared from 1-(benzenesulfonyl)-5-bromo-2-phenyl-pyrrolo[2,3-b]pyridine **18** (prepared in a manner analogous to scheme 2), methyl 6-bromopicolinate **20** as shown in Scheme 3.

Scheme 3



[0402] Step 1 – Preparation of 2-Phenyl-1-(phenylsulfonyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridine, 19: A mixture of 1-(benzenesulfonyl)-5-bromo-2-phenyl-pyrrolo[2,3-b]pyridine **18** (50 g, 121 mmol), bis(pinacolato)diboron (36.9 g, 145 mmol, 1.2 equiv), potassium acetate (35.6 g, 363 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) dichloromethane complex (9.88 g, 12.10 mmol) in DMF (484 mL) was heated at 80 °C for 4 hours. After cooling, the reaction was poured into water (4 L) and diluted with ethyl acetate (1 L). The organic layer was separated, filtered through Celite washing the cake with ethyl acetate (200 mL). The combined filtrates were concentrated under reduced pressure. The crude residue was dissolved in a minimal amount of dichloromethane and purified by silica gel column chromatography eluting with a gradient of 0 to100% ethyl acetate in heptanes. The product was triturated with MTBE (~100 mL) to give compound **19** (26.7 g, 48% yield) as a pink solid.

[0403] Step 2 – Preparation of methyl 6-(2-phenyl-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)picolinate, 21: A suspension of 2-phenyl-1-(phenylsulfonyl)-5-(4,4,5,5-

tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridine **19** (16.7 g, 36.3 mmol), methyl 6-bromopicolinate **20** (9.40 g, 43.5 mmol), potassium carbonate (15.04 g, 109 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) dichloromethane complex (1.48 g, 1.81 mmol) in dioxane (150 mL) and water (30 mL) was heated at 90 °C for 2 hours. The reaction was diluted with ethyl acetate (500 mL) and water (500 mL). The organic layer was separated and concentrated under reduced pressure to give the crude product which was dissolved in a minimal amount of dichloromethane and purified by silica gel column chromatography, eluting with a gradient of 0 to 100% ethyl acetate in heptanes to give compound **21** (15 g, 88% yield) as a tan foam.

[0404] Step 3 – Preparation of 6-(2-Phenyl-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)picolinic acid, 22: 2 M lithium hydroxide (160 mL, 319 mmol) was added to a solution of methyl 6-(2-phenyl-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)picolinate **21** (15 g, 31.9 mmol) in THF (320 mL). The reaction mixture was allowed to stir overnight at room temperature. The reaction was poured into 1 N aqueous HCl (0.5 L) and extracted with ethyl acetate (500 mL). The organic layer was separated, washed with brine and concentrated under reduced pressure. The crude product was dissolved in a minimal amount of dichloromethane and purified by silica gel chromatography, eluting with a gradient of 0 to 10% methanol in dichloromethane. The foam like solid was triturated with a 1 to 1 mixture of heptanes and MTBE (~100 mL) to give compound **22** (12.5 g, 86% yield) as an off white solid.

[0405] Step 4 – Preparation of 6-(2-Phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)picolinic acid, 23: Tetrabutylammonium fluoride trihydrate (20.78 g, 65.9 mmol) was added to a solution of 6-(2-phenyl-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)picolinic acid **22** (7.5 g, 16.47 mmol) in THF (165 mL). The reaction was allowed to stir at room temperature over the weekend, at which point LC/MS indicated the reaction was mostly complete. The reaction mixture was concentrated under reduced pressure and the residue was triturated with dichloromethane (~50 mL) and filtered to give the tetrabutylammonium salt of the product which was slurried in water (200 mL) and acidified with 1 N aqueous HCl (~10 mL). The resulting fine precipitate was filtered, washed with water (~100 mL) and dried under vacuum at 50 °C overnight to give compound **23** (1.9 g, 37% yield) as a white solid.

[0406] Step 5 – Preparation of 6-[1-(benzenesulfonyl)-2-phenyl-pyrrolo[2,3-b]pyridin-5-yl]-N-(2-cyano-2-methyl-propyl)pyridine-2-carboxamide, 25: To 6-[1-(benzenesulfonyl)-2-phenyl-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxylic acid **22** (0.4 g, 0.88 mmol) in tetrahydrofuran (10 mL) was added HBTU (0.4 g, 1.1 mmol), followed by triethylamine (0.5 ml, 3.6 mmol). The suspension was allowed to stir at room temperature for 30 minutes. To this

suspension was added 3-amino-2,2-dimethylpropanenitrile **24** (0.1 g, 1.43 mmol) in tetrahydrofuran (3 mL). The reaction mixture was allowed to stir at room temperature overnight. The reaction was poured into water, and extracted with ethyl acetate. The organic layer was separated, washed with brine, and dried over anhydrous sodium sulfate. After removal of drying agent and solvent, the residue was purified by silica gel column chromatography to provide compound **25** as white solid.

[0407] Step 6 – Preparation of N-(2-cyano-2-methyl-propyl)-6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carboxamide, P-0100: 6-[1-(benzenesulfonyl)-2-phenyl-pyrrolo[2,3-b]pyridin-5-yl]-N-(2-cyano-2-methyl-propyl)pyridine-2-carboxamide **25** was dissolved in THF (20 mL), and to this solution was added tetrabutylammonium fluoride in THF (1 N, 2 mL, 2 mmol). The reaction mixture was allowed to stir at room temperature overnight. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was separated, washed with water (4x100 mL), brine, and dried over sodium sulfate. After removal of the drying agent and solvent, the residue was purified by silica gel column chromatography to provide N-(2-cyano-2-methyl-propyl)-6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carboxamide **P-0100** as an off-white solid (0.23 g, 66%). MS (ESI) $[M+H^+]^+$ =395.90.

[0408] Step 7 – Preparation of 2-oxa-7-azaspiro[4.4]nonan-7-yl-[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]methanone, 28: To 6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carboxylic acid **23** (21 mg, 0.07 mmol) in tetrahydrofuran (3 mL) was added HBTU (25 mg, 0.066 mmol), followed by triethylamine (0.1 ml, 0.72 mmol). The suspension was allowed to stir at room temperature for 30 minutes. To this suspension was added 8-oxa-3-azaspiro[4.4]nonane **27** (10 mg, 0.08 mmol). The reaction mixture was allowed to stir at room temperature overnight. The reaction was poured into water, and extracted with ethyl acetate. The organic layer was separated, washed with brine, and dried over anhydrous sodium sulfate. After removal of drying agent and solvent, the residue was purified by silica gel column chromatography to provide compound **28** as pale yellow solid (10 mg, 34%). MS (ESI) $[M+H^+]^+$ = 424.90.

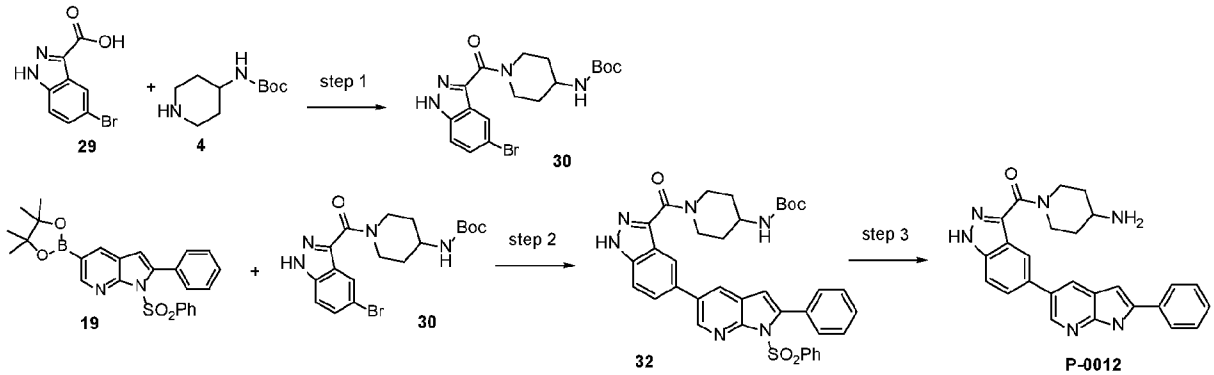
[0409] The following compounds may be prepared via the synthetic route depicted in Scheme 3: P-0015, P-0013, P-0017, P-0018, P-0020, P-0023, P-0024, P-0025, P-0026, P-0031, P-0033, P-0036, P-0037, P-0038, P-0040, P-0041, P-0045, P-0046, P-0043, P-0057, P-0051, P-0052, P-0054, P-0066, P-0067, P-0068, P-0069, P-0075, P-0076, P-0077, P-0078, P-0079, P-0080, P-0081, P-0082, P-0083, P-0084, P-0085, P-0087, P-0089, P-0090, P-0091, P-0092, P-0093, P-0094, P-0095, P-0096, P-0097, P-0098, P-0099, P-0100, P-0101, P-0102, P-0103, P-0104, P-

0105, P-0106, P-0110, P-0111, P-0114, P-0115, P-0117, P-0118, P-0119, P-0120, P-0122, P-0124, P-0128, P-0129, P-0137, P-0146, P-0149, P-0150, P-0156 and P-0151.

Example 4

[0410] Compound **P-0012** is prepared from 5-bromo-1H-indazole-3-carboxylic acid **29**, *tert*-butyl piperidin-4-ylcarbamate **4** and 2-phenyl-1-(phenylsulfonyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridine **19** as shown in Scheme 4.

Scheme 4



[0411] **Step 1 – Preparation of tert-butyl N-[1-(5-bromo-1H-indazole-3-carbonyl)-4-piperidyl]carbamate, 30:** A solution of 5-bromo-1H-indazole-3-carboxylic acid **29** (1 g, 4.15 mmol) and HBTU (2.36 g, 6.22 mmol) were allowed to stir in dimethylformamide (20 ml) at room temperature for 40 minutes. Tert-butyl N-(4-piperidyl)carbamate (1.08 g, 5.39 mmol) and N,N-diisopropylethylamine (1.08 ml, 6.22 mmol) were added and the reaction was allowed to stir at room temperature for 18 h. The reaction was poured into water and extracted with ethyl acetate. The organic layer was separated, washed with brine, dried over sodium sulfate, filtered, and concentrated. The residue was purified by silica gel column chromatography to afford tert-butyl N-[1-(5-bromo-1H-indazole-3-carbonyl)-4-piperidyl]carbamate **30** (0.80g, 46%).

[0412] **Step 2 – Preparation of tert-butyl (1-(5-(2-phenyl-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-indazole-3-carbonyl)piperidin-4-yl)carbamate, 32:** 1-(benzenesulfonyl)-2-phenyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolo[2,3-b]pyridine **19** (630 mg, 1.37 mmol), tert-butyl N-[1-(5-bromo-1H-indazole-3-carbonyl)-4-piperidyl]carbamate **30** (695 mg, 1.64 mmol), and 1,1'-bis(diphenylphosphino)ferrocene-palladium(ii)dichloride dichloromethane complex (0.11 g, 0.14 mmol) were combined and allowed to stir in 1,4 dioxane (13 ml). Then, 1 M potassium carbonate (4.11 ml) was added via syringe. The reaction was irradiated in a microwave reactor at 120 °C for 30 minutes. The reaction mixture was cooled to room temperature and filtered through Celite. The crude organic

solution was evaporated onto silica gel, purified by silica gel column chromatography (0-15% methanol/dichloromethane) to provide tert-butyl (1-(5-(2-phenyl-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-indazole-3-carbonyl)piperidin-4-yl)carbamate **32**.

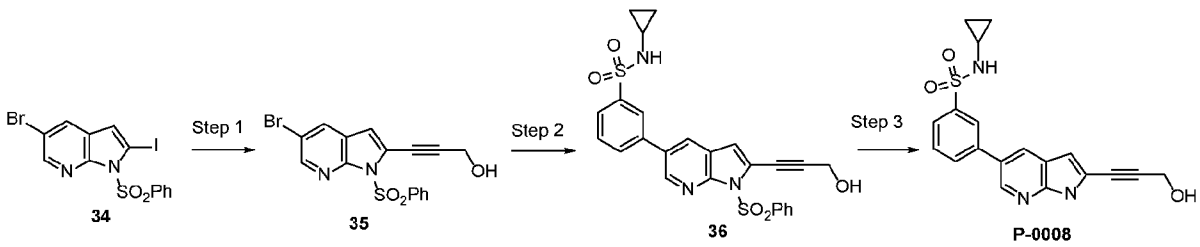
[0413] Step 3 – Preparation of (4-amino-1-piperidyl)-[5-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-indazol-3-yl]methanone, P-0012: To a solution of tert-butyl (1-(5-(2-phenyl-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-indazole-3-carbonyl)piperidin-4-yl)carbamate **32** in tetrahydrofuran (10 ml) was added potassium hydroxide in methanol (1 M solution, 3 mL) and the reaction mixture was allowed to stir for 3 h at room temperature. The reaction mixture was acidified with 1 M aqueous HCl and then extracted with ethyl acetate. The organic layer was separated, washed with brine, dried over sodium sulfate, filtered, and concentrated to dryness. This crude product was dissolved in 25% solution of trifluoroacetic acid in dichloromethane (6 ml) and allowed to stir at room temperature for 1 hour. The reaction mixture was concentrated onto silica gel. Purification by C18 reverse phase column chromatography (0-45% acetonitrile/water) provided the desired product, which was further purified by trituration with methanol to afford (4-amino-1-piperidyl)-[5-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-indazol-3-yl]methanone **P-0012** (89 mg, 15% over steps 2 and 3).

[0414] The following compounds may be prepared via the synthetic route depicted in Scheme 4: P-0011, P-0016, P-0019, P-0021, P-0022, P-0027, P-0028, P-0029, P-0039, P-0044, P-0042, P-0056, P-0053 and P-0059.

Example 5

[0415] Compound **P-0008** is prepared from 5-bromo-2-iodo-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridine **34** as shown in Scheme 5.

Scheme 5



[0416] Step 1 – Preparation of 3-[1-(benzenesulfonyl)-5-bromo-pyrrolo[2,3-b]pyridin-2-yl]prop-2-yn-1-ol, 35: A mixture of 5-bromo-2-iodo-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridine **34** (250 mg, 0.54 mmol), prop-2-yn-1-ol (34 mg, 0.62 mmol), triethylamine (0.75

mL, 5.4 mmol), copper iodide (15 mg, 0.08 mmol) and [1,1'-Bis(diphenylphosphino) ferrocene]dichloropalladium(II) dichloromethane complex (30 mg, 0.038 mmol) in THF was allowed to stir at room temperature for 18 h. The reaction mixture was filtered through a pad of Celite. The filtrate was partitioned between ethyl acetate and aqueous hydrochloric acid (1 N). The organic layer was collected and washed with brine, then dried over magnesium sulfate. After removal of drying agent and solvent, the residue was purified by silica gel column chromatography to provide 3-[1-(benzenesulfonyl)-5-bromo-pyrrolo[2,3-b]pyridin-2-yl]prop-2-yn-1-ol **35** (70 mg, 33%).

[0417] Step 2 – Preparation of 3-[1-(benzenesulfonyl)-2-(3-hydroxyprop-1-ynyl)pyrrolo[2,3-b]pyridin-5-yl]-N-cyclopropyl-benzenesulfonamide, 36: A mixture of 3-[1-(benzenesulfonyl)-5-bromo-pyrrolo[2,3-b]pyridin-2-yl]prop-2-yn-1-ol **35** (70 mg, 0.18 mmol), [3-(cyclopropylsulfamoyl)phenyl]boronic acid (65 mg, 0.27 mmol), aqueous potassium carbonate (0.17 ml, 2.5 M) and [1,1'-Bis(diphenylphosphino) ferrocene]dichloropalladium(II) dichloromethane complex (0.020 g, 0.025 mmol) in acetonitrile was allowed to stir at 130 °C for 30 minutes with microwave irradiation. The reaction mixture was filtered through Celite. The filtrate pH was adjusted with aqueous ammonium chloride and then was extracted with ethyl acetate. The organic layer was collected and washed with brine, then dried over magnesium sulfate. After removal of drying agent and solvent, the residue was dried under vacuum to provide 3-[1-(benzenesulfonyl)-2-(3-hydroxyprop-1-ynyl)pyrrolo[2,3-b]pyridin-5-yl]-N-cyclopropyl-benzenesulfonamide **36**.

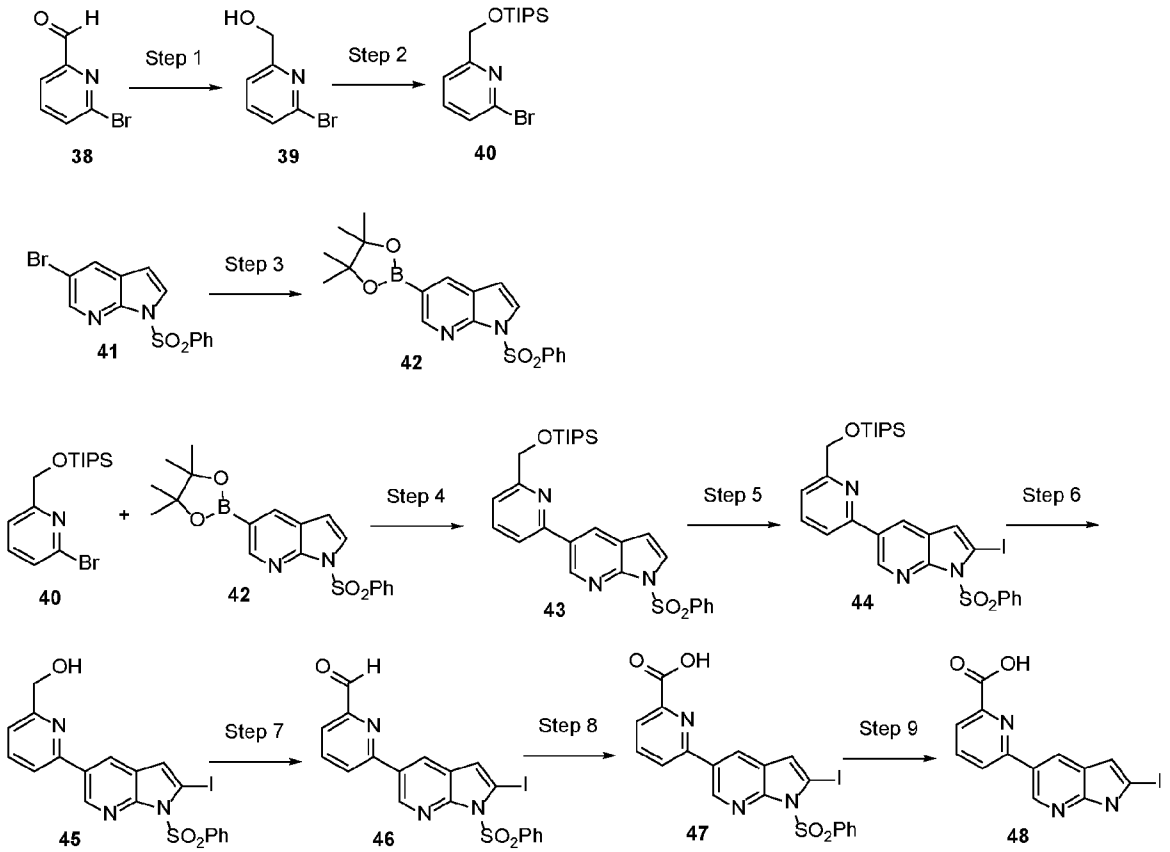
[0418] Step 3 – Preparation of N-cyclopropyl-3-[2-(3-hydroxyprop-1-ynyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]benzenesulfonamide, P-0008: To 3-[1-(benzenesulfonyl)-2-(3-hydroxyprop-1-ynyl)pyrrolo[2,3-b]pyridin-5-yl]-N-cyclopropyl-benzenesulfonamide **36** in THF was added potassium hydroxide in methanol (1.0 mL, 1N). The mixture was allowed to stir at room temperature for two hours. The pH of the reaction mixture was adjusted with aqueous hydrochloric acid (1N) and then was extracted with dichloromethane. The organic layer was separated and washed with brine, then dried over magnesium sulfate. After removal of drying agent and solvent, the residue was dried under vacuum to provide N-cyclopropyl-3-[2-(3-hydroxyprop-1-ynyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]benzenesulfonamide **P-0008** (8 mg, 12% over steps 2 and 3).

[0419] The following compounds may be prepared via the synthetic route depicted in Scheme 5: P-0004, P-0009, P-0010, P-0014, P-0175, P-0176 and P-0177.

Example 6

[0420] Compound **48** is prepared from 6-bromopicolinaldehyde **38** and 5-bromo-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridine **41** as shown in Scheme 6.

Scheme 6



[0421] **Step 1 – Preparation of (6-Bromopyridin-2-yl)methanol, 39:** Sodium borohydride (20.34 g, 538 mmol) was added in portions to a solution of 6-bromopicolinaldehyde **38** (100 g, 538 mmol) in methanol (1.2 L) while maintaining the temperature below 20 °C. After stirring at room temperature for 1 hour, the solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate (2 L) and water (2 L). The organic layer was separated, washed with saturated brine (1 L) and dried over sodium sulfate. The sodium sulfate was removed by filtration and the filtrate was concentrated under reduced pressure to give (6-Bromopyridin-2-yl)methanol **39** (92.8 g, 92% yield) as a yellow oil which slowly solidified to an off-white solid.

[0422] **Step 2 – Preparation of 2-Bromo-6-(((triisopropylsilyl)oxy)methyl)pyridine, 40:** Imidazole (45.0 g, 661 mmol) and triisopropylsilyl chloride (103 mL, 481 mmol) were sequentially added to a solution of (6-Bromopyridin-2-yl)methanol **39** (82.8 g, 440 mmol) in

dichloromethane (1.65 L) at room temperature. After stirring overnight, the reaction mixture was diluted with dichloromethane (2 L) and washed with water (2 L) and saturated brine (1 L). The organic layer was concentrated under reduced pressure. The residue was dissolved in dichloromethane and purified by silica gel column chromatography, eluting with a gradient of 0 to 25% ethyl acetate in heptanes to give 2-Bromo-6-(((triisopropylsilyl)oxy)methyl)pyridine **40** (151 g, 100% yield) as a clear oil.

[0423] Step 3 – Preparation of 1-(Phenylsulfonyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridine, 42: Bis(pinacolato)diboron (111 g, 437 mmol), potassium acetate (107 g, 1090 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) dichloromethane complex (29.8 g, 36.5 mmol) were sequentially added to a solution of 1-(benzenesulfonyl)-5-bromo-pyrrolo[2,3-b]pyridine **41** (123 g, 365 mmol) in DMF (1.46 L). The mixture was allowed to stir at 80 °C for 4 hours. After cooling to room temperature, the reaction was poured into water (15 L) and diluted with ethyl acetate (4 L). The organic layer was separated, dried over sodium sulfate, filtered and concentrated under reduced pressure to give 1-(Phenylsulfonyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridine **42** as a tan solid which was used without further purification.

[0424] Step 4 – Preparation of 1-(Phenylsulfonyl)-5-(6-(((triisopropylsilyl)oxy)methyl)pyridin-2-yl)-1H-pyrrolo[2,3-b]pyridine, 43: A suspension of 1-(Phenylsulfonyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridine **42** (140 g theory, 364 mmol), 2-Bromo-6-(((triisopropylsilyl)oxy)methyl)pyridine **40** (151 g, 438 mmol), potassium carbonate (151 g, 1093 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) dichloromethane complex (14.88 g, 18.22 mmol) in dioxane (1.5 L) and water (304 mL) was allowed to stir at 90 °C for 4 hours. The reaction was diluted with ethyl acetate (1 L) and water (1 L). The organic layer was separated and concentrated under reduced pressure. The residue was dissolved in dichloromethane and purified by silica gel column chromatography, eluting with a gradient of 0 to 50% ethyl acetate in heptanes to give 1-(Phenylsulfonyl)-5-(6-(((triisopropylsilyl)oxy)methyl)pyridin-2-yl)-1H-pyrrolo[2,3-b]pyridine **43** (99 g, 52% yield) as an off-white solid.

[0425] Step 5 – Preparation of 2-iodo-1-(phenylsulfonyl)-5-(6-(((triisopropylsilyl)oxy)methyl)pyridin-2-yl)-1H-pyrrolo[2,3-b]pyridine, 44: 2.5 M *n*-Butyllithium in hexanes (76 mL, 190 mmol) was added dropwise to a solution of 1-(Phenylsulfonyl)-5-(6-(((triisopropylsilyl)oxy)methyl)pyridin-2-yl)-1H-pyrrolo[2,3-b]pyridine

43 (99 g, 189 mmol) in anhydrous THF (1 L) keeping the internal temperature below -70 °C. After stirring the reaction for 1 hour, an aliquot of the mixture was quenched with deuterium oxide and analyzed by ^{1}H NMR in order to confirm full deprotonation. Iodine (96 g, 378 mmol) was added as a solid in one portion at -78 °C. The reaction was allowed to warm to room temperature with stirring for 12 hours. The reaction was quenched with a saturated sodium thiosulfate solution (1 L) and diluted with ethyl acetate (1 L). The layers were separated and the organic layer was washed with saturated brine (1 L) and concentrated under reduced pressure to give 2-iodo-1-(phenylsulfonyl)-5-(6-(((triisopropylsilyl)oxy)methyl)pyridin-2-yl)-1H-pyrrolo[2,3-b]pyridine **44** (123 g, 100% yield) as a yellow foam which was used without further purification.

[0426] Step 6 – Preparation of (6-(2-Iodo-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridin-2-yl)methanol, 45: 4 N HCl in dioxane (562 mL, 2248 mmol) was added to a solution of 2-iodo-1-(phenylsulfonyl)-5-(6-(((triisopropylsilyl)oxy)methyl)pyridin-2-yl)-1H-pyrrolo[2,3-b]pyridine **44** (112 g, 173 mmol) in N,N-dimethylacetamide (1.73 L). The solution was allowed to stir overnight at room temperature. The reaction was slowly poured into saturated sodium bicarbonate (12 L) and diluted with ethyl acetate (4 L). The organic layer was separated and concentrated under reduced pressure to give crude (6-(2-iodo-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridin-2-yl)methanol **45** as a tan oil which was used without further purification.

[0427] Step 7 – Preparation of 6-(2-iodo-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)picolinaldehyde, 46: Dess-Martin periodinane (110 g, 259 mmol) was added to a solution of (6-(2-iodo-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridin-2-yl)methanol **45** (85 g theory, 173 mmol) in THF (1.73 L) at room temperature. The solution was allowed to stir for 2 hours. The reaction was poured into saturated sodium bicarbonate (1.5 L) and diluted with ethyl acetate (1 L). The organic layer was separated and washed with saturated brine (1 L), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was triturated with dichloromethane (500 mL) and filtered to give 6-(2-iodo-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)picolinaldehyde **46** (46.8 g, 55% yield) as an off-white solid.

[0428] Step 8 – Preparation of 6-(2-iodo-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)picolinic acid, 47: Oxone monopersulfate (32.3 g, 105 mmol) was added to a solution of 6-(2-iodo-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)picolinaldehyde **46** (25.7 g, 52.5 mmol) in DMF (263 mL) at room temperature. The suspension was allowed to stir for 2 hours. The reaction was poured into water (2 L) and diluted with ethyl acetate (1 L). The organic layer was separated and washed with saturated brine (1 L), dried over sodium sulfate, filtered, and

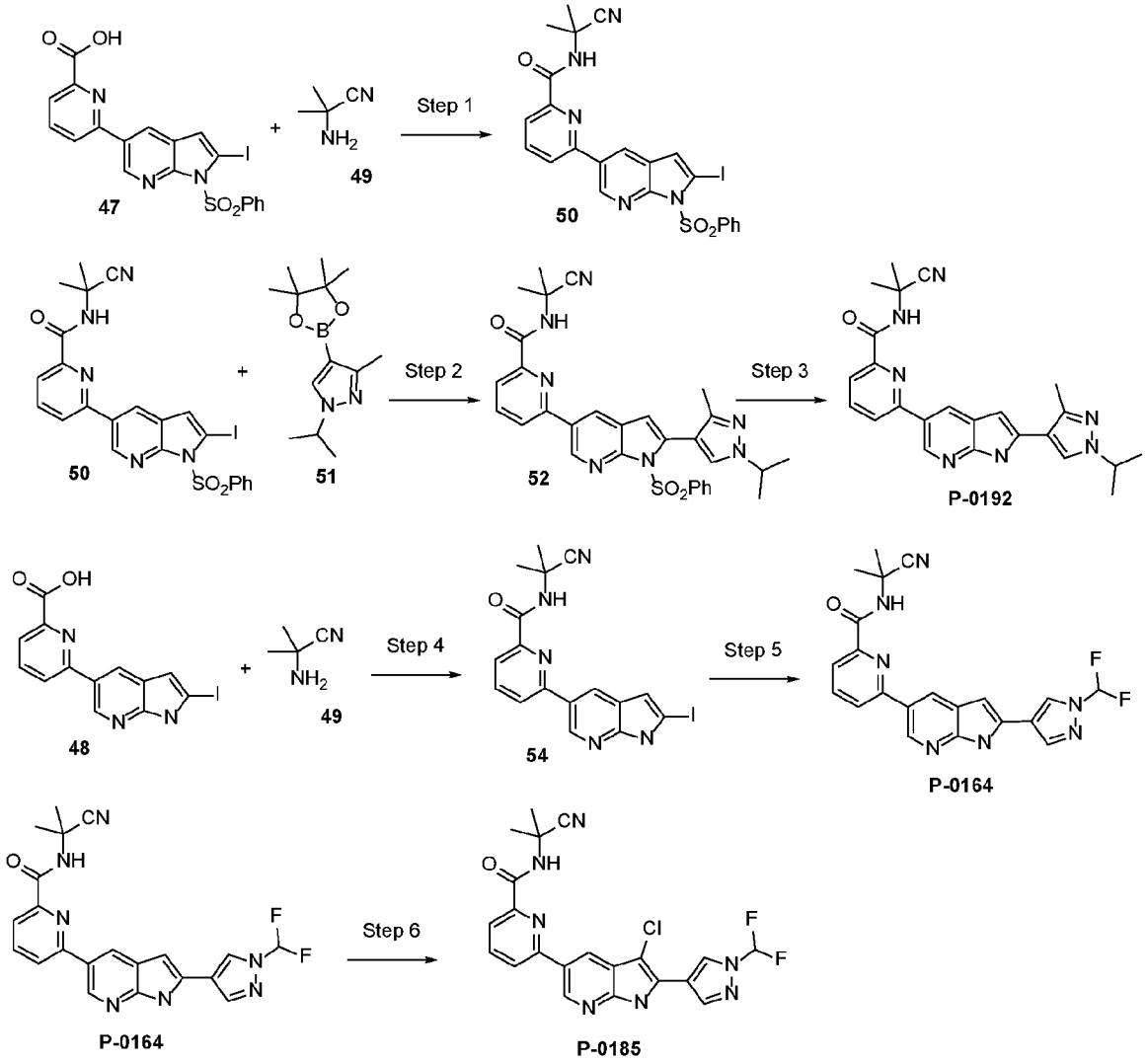
concentrated under reduced pressure. The residue was slurried with dichloromethane (200 mL) and concentrated under reduced pressure. The mixture was diluted with MTBE (200 mL) and filtered to give 6-(2-iodo-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)picolinic acid **47** (23.5 g, 89% yield) as a white solid.

[0429] Step 9 – Preparation of 6-(2-iodo-1H-pyrrolo[2,3-b]pyridin-5-yl)picolinic acid, 48: Tetrabutylammonium fluoride trihydrate (58.7 g, 186 mmol) was added to a solution of 6-(2-iodo-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)picolinic acid **47** (23.5 g, 46.5 mmol) in THF (465 mL). The reaction was allowed to stir at 40 °C for 2 hours. The reaction mixture was concentrated under reduced pressure and the residue was triturated with dichloromethane and filtered to give the tetrabutylammonium salt of the product. This solid was slurried in water (500 mL) and acidified with 1 N aqueous HCl (~50 mL) resulting in a fine precipitate which was filtered, washed with water and dried under vacuum at 50 °C overnight to give 6-(2-iodo-1H-pyrrolo[2,3-b]pyridin-5-yl)picolinic acid **48** (10.3 g, 61% yield) as a white solid.

Example 7

[0430] Compound **P-0192**, compound **P-0164** and compound **P-0185** are prepared from 6-(2-iodo-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)picolinic acid **47** and 6-(2-iodo-1H-pyrrolo[2,3-b]pyridin-5-yl)picolinic acid **48** as shown in Scheme 7.

Scheme 7



[0431] Step 1 – Preparation of N-(2-cyanopropan-2-yl)-6-(2-iodo-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)picolinamide, 50: In a round bottom flask, 6-[1-(benzenesulfonyl)-2-iodo-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxylic acid **47** (3 g, 5.94 mmol) and HBTU (3.04 g, 8.02 mmol) were dissolved in tetrahydrofuran (125 ml). The reaction was allowed to stir for 60 min. Then, 2-amino-2-methyl-propanenitrile **49** (0.75 g, 8.92 mmol) was added as a tetrahydrofuran solution and triethylamine (2.9 ml, 20.79 mmol) was then added dropwise. The reaction was allowed to stir at room temperature for 4 hr. The reaction mixture was diluted with ethyl acetate and washed with aqueous saturated ammonium chloride, then washed with brine and dried over magnesium sulfate. After filtration and concentration under reduced pressure, the residue was triturated initially with dimethylformamide to provide 955 mg, and the filtrate was concentrated to dryness and was triturated with ethyl acetate to provide an additional 800 mg of

6-[1-(benzenesulfonyl)-2-iodo-pyrrolo[2,3-b]pyridin-5-yl]-N-(1-cyano-1-methyl-ethyl)pyridine-2-carboxamide **50** as a white solid.

[0432] Step 2 – Preparation of N-(2-cyanopropan-2-yl)-6-(2-(1-isopropyl-3-methyl-1H-pyrazol-4-yl)-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)picolinamide, 52: A mixture of 6-[1-(benzenesulfonyl)-2-iodo-pyrrolo[2,3-b]pyridin-5-yl]-N-(1-cyano-1-methyl-ethyl)pyridine-2-carboxamide **50** (200 mg, 0.35 mmol), 1-isopropyl-3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole **51** (0.13 g, 0.52 mmol), 2.5 M aqueous potassium carbonate (0.42 ml), and 1,1'-bis(diphenylphosphino)ferrocene-palladium(II) dichloride dichloromethane complex (33 mg, 0.04 mmol) in DMF was flushed with argon, capped in a microwave vial, and heated at 70 °C for 3 h. The reaction was filtered through Celite, then partitioned between ethyl acetate and aqueous ammonium chloride. The organic layer was separated, washed with brine, and dried over magnesium sulfate. After filtration, silica gel column chromatography (0-100% ethyl acetate in hexane) provided N-(2-cyanopropan-2-yl)-6-(2-(1-isopropyl-3-methyl-1H-pyrazol-4-yl)-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)picolinamide **52**.

[0433] Step 3 – Preparation of N-(2-cyanopropan-2-yl)-6-(2-(1-isopropyl-3-methyl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)picolinamide, 53: N-(2-cyanopropan-2-yl)-6-(2-(1-isopropyl-3-methyl-1H-pyrazol-4-yl)-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)picolinamide **52** was added to 1 N KOH (in MeOH, 2 mL) and THF (5 mL) at room temperature. After 2 hours, the reaction was concentrated and then partitioned between dichloromethane and 1 N HCl (aqueous). The organic layer was separated and washed with water, then brine, then dried over magnesium sulfate and filtered. The resulting material was purified by silica gel column chromatography (0-5% methanol in DCM) to provide N-(2-cyanopropan-2-yl)-6-(2-(1-isopropyl-3-methyl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)picolinamide **53** (95 mg, 63% over steps 2 and 3).

[0434] Step 4 – Preparation of N-(2-cyanopropan-2-yl)-6-(2-iodo-1H-pyrrolo[2,3-b]pyridin-5-yl)picolinamide, 54: To 6-(2-iodo-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carboxylic acid **48** (3 g, 8.22 mmol) in DMF (50 mL) was added HBTU (3.2 g, 8.44 mmol) followed by triethylamine (3 ml, 21.5 mmol). The suspension was allowed to stir at room temperature for 30 minutes. To this suspension was added 2-amino-2-methyl-propanenitrile **49** (0.8 g, 9.5 mmol) in DMF (1 mL). The reaction mixture was allowed to stir at room temperature for three days. The mixture was slowly poured into iced water. The precipitate was collected via filtration and washed with ethyl acetate to provide N-(2-cyanopropan-2-yl)-6-(2-iodo-1H-pyrrolo[2,3-b]pyridin-5-yl)picolinamide **54** as a pale yellow solid (2.2 g). The filtrate

was extracted with ethyl acetate. The organic layer was collected, washed with brine, and dried over anhydrous sodium sulfate. After removal of drying agent and solvent, the residue was purified by silica gel column chromatography to provide additional N-(2-cyanopropan-2-yl)-6-(2-iodo-1H-pyrrolo[2,3-b]pyridin-5-yl)picolinamide **54** as an off-white solid (0.5 g).

[0435] Step 5 – Preparation of N-(2-cyanopropan-2-yl)-6-(2-(1-(difluoromethyl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)picolinamide, P-0164: N-(2-cyanopropan-2-yl)-6-(2-iodo-1H-pyrrolo[2,3-b]pyridin-5-yl)picolinamide **54** (0.3 g, 0.7 mmol), 1-(difluoromethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (0.25 g, 1.02 mmol), 2.5 M potassium carbonate (0.97 ml), and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) dichloromethane complex (0.06 g, 0.08 mmol) in DMF was flushed with argon, capped in a microwave vial, and heated at 105 °C for 50 min. The reaction was cooled, filtered with Celite, and partitioned between ethyl acetate and aqueous ammonium chloride. The organic layer was separated and dried over magnesium sulfate, filtered, and concentrated. Purification by silica gel column chromatography (0-5% methanol in dichloromethane) provided N-(2-cyanopropan-2-yl)-6-(2-(1-(difluoromethyl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)picolinamide P-0164 (0.17 g, 58%).

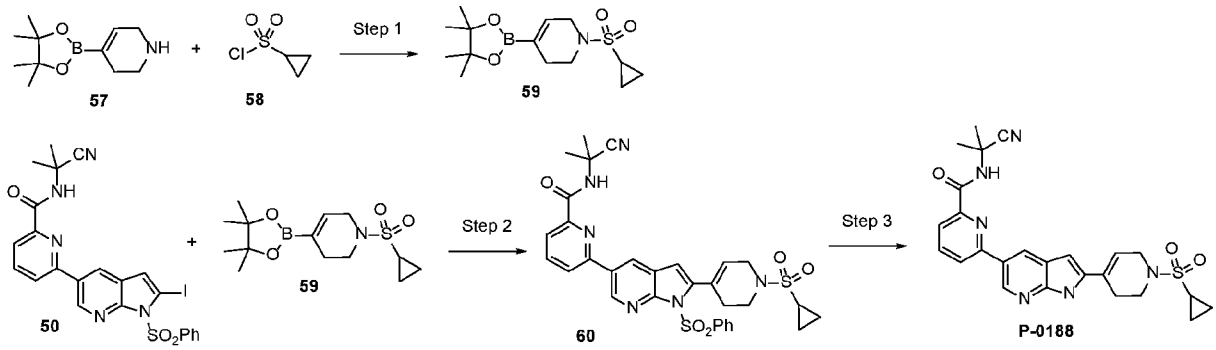
[0436] Step 6 – Preparation of 6-[3-chloro-2-[1-(difluoromethyl)pyrazol-4-yl]-1H-pyrrolo[2,3-b]pyridin-5-yl]-N-(1-cyano-1-methyl-ethyl)pyridine-2-carboxamide, P-0185: A solution of N-(1-cyano-1-methyl-ethyl)-6-[2-[1-(difluoromethyl)pyrazol-4-yl]-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide **P-0164** (50 mg, 0.12 mmol) in THF (3 ml) was stirred in an ice-water bath. To this solution was added 1-chloropyrrolidine-2,5-dione (19 mg, 0.14 mmol). The reaction mixture was allowed to stir and warm to room temperature for five hours. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was separated, washed with brine, and dried over sodium sulfate. After removal of drying agent and solvent, the residue was purified by silica gel column chromatography to provide 6-[3-chloro-2-[1-(difluoromethyl)pyrazol-4-yl]-1H-pyrrolo[2,3-b]pyridin-5-yl]-N-(1-cyano-1-methyl-ethyl)pyridine-2-carboxamide P-0185 as an off-white solid (38 mg, 70%). MS (ESI) $[M+H^+]^+$ = 455.85.

[0437] The following compounds may be prepared via the synthetic route depicted in Scheme 7: P-0125, P-0126, P-0127, P-0138, P-0139, P-0147, P-0148, P-0142, P-0143, P-0163, P-0165, P-0166, P-0167, P-0168, P-0169, P-0170, P-0171, P-0172, P-0173, P-0174, P-0178, P-0183, P-0184, P-0187, P-0193, P-0194, P-0189, P-0190, P-0191, P-0195, P-0196, P-0197, P-0199, P-0200, P-0201, P-0202, P-0199, P-0203, P-0204, P-0205, P-0206, P-0207, P-0208, P-0209, P-0210, and P-0211.

Example 8

[0438] Compound **P-0188** is prepared from 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine **57** and N-(2-cyanopropan-2-yl)-6-(2-iodo-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)picolinamide **50** as shown in Scheme 8.

Scheme 8



[0439] **Step 1 – Preparation of 1-(cyclopropylsulfonyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine, 59:** In round bottom flask was dissolved 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine hydrochloride **57** (300 mg, 1.22 mmol) in tetrahydrofuran (60 ml). To this mixture was added cyclopropanesulfonyl chloride **58** (257 mg, 1.83 mmol), followed by triethylamine (0.17 ml, 1.22 mmol) and a catalytic amount of 4-dimethylaminopyridine. The reaction mixture was allowed to stir at room temperature for two hours. It was quenched with water and partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over sodium sulfate and filtered. The crude mixture was acquired as a solid by concentration of the organic layer to dryness. This provided 1-(cyclopropylsulfonyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine **59** (347 mg, 91%), which was used without further purification.

[0440] **Step 2 – Preparation of N-(2-cyanopropan-2-yl)-6-(2-(1-(cyclopropylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)picolinamide, 60:** In a round bottom flask were dissolved 6-[1-(benzenesulfonyl)-2-iodo-pyrrolo[2,3-b]pyridin-5-yl]-N-(1-cyano-1-methyl-ethyl)pyridine-2-carboxamide **50** (250 mg, 0.44 mmol), 1-cyclopropylsulfonyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine **59** (137.04 mg, 0.44 mmol), tetrakis(triphenylphosphine)palladium(0) (0.04 g, 0.04 mmol) and 1 M potassium carbonate (1.31 ml) in dimethylformamide (80 mL). The reaction was allowed to stir at 60°C for six hours. The reaction was neutralized with 1 N hydrochloric acid, and then partitioned between ethyl acetate and water. The organic layer was separated,

washed with brine, and dried over magnesium sulfate. After filtration, the residue was purified by silica gel column chromatography to provide N-(2-cyanopropan-2-yl)-6-(2-(1-(cyclopropylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)picolinamide **60**.

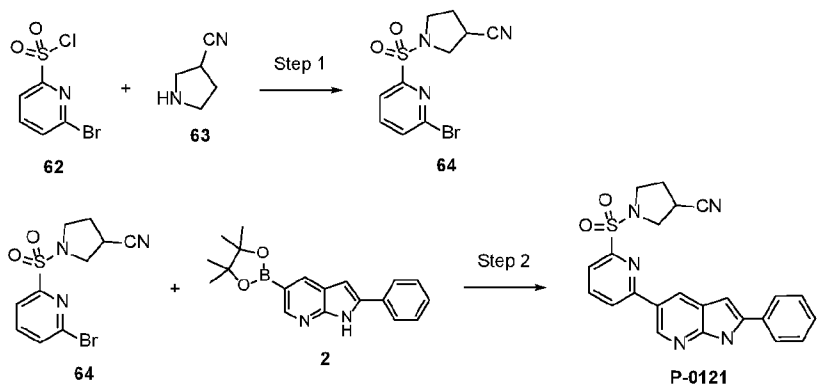
[0441] Step 3 – Preparation of N-(1-cyano-1-methyl-ethyl)-6-[2-(1-cyclopropylsulfonyl-3,6-dihydro-2H-pyridin-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide, P-0188: To N-(2-cyanopropan-2-yl)-6-(2-(1-(cyclopropylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)picolinamide **60** (277 mg, 0.44 mmol theory)in tetrahydrofuran (50 mL) was added tetrabutylammonium fluoride (1.31 ml, 1 M). The mixture was allowed to stir at room temperature for two hours. The reaction was quenched with saturated sodium bicarbonate and partitioned between ethyl acetate and water. The organic layer was washed repeatedly with brine, then dried over magnesium sulfate and filtered. The residue was purified by silica gel column chromatography to provide crude product. The crude product was triturated with methanol to afford N-(1-cyano-1-methyl-ethyl)-6-[2-(1-tetrahydrofuran-3-ylpyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide **P-0188** as a white solid (68 mg, 32% for steps 2 and 3). MS (ESI) $[M+H^+]^+$ = 491.30.

[0442] The following compounds may be prepared via the synthetic route depicted in Scheme 8: P-0070, P-0074, P-0123, P-0131, P-0132, P-0135, P-0136, P-0141, P-0157, P-0159, P-0160, P-0161, P-0162, P-0179, P-0180, P-0181, P-0182 and P-0186.

Example 9

[0443] Compound **P-0121** is prepared from 6-bromopyridine-2-sulfonyl chloride **62** and 2-phenyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridine **2** as shown in Scheme 9.

Scheme 9



[0444] Step 1 – Preparation of 1-((6-bromopyridin-2-yl)sulfonyl)pyrrolidine-3-carbonitrile, 64: To 6-bromopyridine-2-sulfonyl chloride (100 mg, 0.39 mmol) was added pyrrolidine-3-carbonitrile (37.48 mg, 0.39 mmol) and dichloromethane (2 ml). The reaction was allowed to stir at room temperature for 30 minutes. The reaction was quenched with saturated sodium bicarbonate solution and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, filtered and concentrated to dryness to provide 1-((6-bromopyridin-2-yl)sulfonyl)pyrrolidine-3-carbonitrile **64**. This material was used in the next step without further purification.

[0445] Step 2 – Preparation of 1-[[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]sulfonyl]pyrrolidine-3-carbonitrile, P-0121: In microwave vial were dissolved 2-phenyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridine **2** (65 mg, 0.2 mmol), 1-[(6-bromo-2-pyridyl)sulfonyl]pyrrolidine-3-carbonitrile **64** (77.02 mg, 0.24 mmol), 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (17.19 mg, 0.02 mmol) and potassium carbonate solution (0.61 ml, 1 M) in N,N-dimethylformamide (3 ml). The reaction was allowed to stir at 125 ^{o}C for 30 minutes. The reaction mixture was filtered through Celite, and concentrated under reduced pressure. The product was purified by silica gel column chromatography to provide crude product that was triturated with methanol to afford 1-[[6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-pyridyl]sulfonyl]pyrrolidine-3-carbonitrile **P-0121** (16 mg, 18%). MS (ESI) $[M+H^+]^+$ = 430.25.

[0446] The following compounds may be prepared via the synthetic route depicted in Scheme 9: P-0007, P-0063, P-0071, P-0072, P-0073, P-0086, P-0088, P-0107, P-0108 and P-0109.

[0447] Compounds P-0212-P-0215 can be prepared by the appropriate scheme(s) described above.

Biological Examples

Example 10: Cell-based assays of FLT3 kinase activity

[0448] The FLT3 inhibitors may be assessed using the MOLM-14, Acute Myeloid Leukemia cell line that endogenously expresses FLT3 ITD or derivatives of the human FLT3 AML cell line which acquired the D835Y (activation loop) of F691L (gatekeeper) mutation after selection in escalating doses of the FLT3 Inhibitor AC220. FLT3 inhibitors may also be assessed using cells that are engineered to express mutant FLT3. For engineered cells, murine Ba/F3 cells were transfected with full-length FLT3 ITD/D835Y mutations. The parental BA/F3 cells are dependent upon Interleukin-3 (IL-3) for survival, and introduction of the FLT3 constructs rendered these cells dependent upon FLT3 kinase activity when cultured in the absences of IL-3.

Engineered BA/F3 cell growth assays can be performed in either the presence or absence of IL-3, to assess the compound inhibition of FLT3 or to detect the presence of off-target activity, respectively. Inhibitors of FLT3 kinase activity reduce or eliminate the FLT3 oncogenic signaling, resulting in reduced cell proliferation. This inhibition is measured as a function of compound concentration to asses IC_{50} values.

[0449] Cell lines used in proliferation assays are as follows in Table 3:

TABLE 3

Cell line	Cell type	FLT3 expressed	Growth media
MOLM-14	Human AML derived Cells[8]	Endogenous FLT3 ITD	IMDM media[7], and 10% FBS[1]
MOLM-14 D835Y	Human AML derived Cells[8]	Endogenous FLT3 ITD and transfected FLT3 D835Y	IMDM media[7], and 10% FBS[1]
MOLM-14 F691L	Human AML derived Cells[8]	Endogenous FLT3 ITD and transfected FLT3 F691L	IMDM media[7], and 10% FBS[1]
BA/F3-FLT3-ITD+D835Y	Pro B cells[3]	Transfected FLT3-ITD+D835Y	RPMI 1640[2], 10% FBS[1], 1% L-Glutamine[4], 1% NEAA[5], 10% WEHI-3B conditioned medium[6] (i.e. IL-3)

[1] Fetal bovine serum (FBS), Invitrogen catalog #10438026
[2] RPMI 1640, Invitrogen catalog #11875
[3] Parental BA/F3 cells, DSMZ catalog #ACC 300
[4] L-Glutamine, Invitrogen catalog #25030
[5] Non-Essential Amino Acids (NEAA), Invitrogen catalog #11140
[6] WEHI-3B conditioned medium (CM) contains murine IL-3 that supports the growth of parental BA/F3 cells.
[7] IMDM, Invitrogen catalog #12440
[8] MOLM-14 cells obtained from Dr. Neil Shal at University of California, San Francisco.

[0450] Cells were seeded at 1 x 10^4 cells per well of a 96 well cell culture plate in 50 µl of cell culture medium. Compounds were dissolved in DMSO, typically at a concentration of 0.5 mM and were serially diluted 1:3 for a total of eight points and added to the cells to final concentrations of 1, 0.33, 0.11, 0.37, 0.12, 0.0041, 0.0014 and 0.00046 µM in 100 µl cell culture

medium (final concentration 0.2% DMSO). Some of the more potent compounds were run at a 10X lower range. The cells were incubated at 37 °C, 5% CO_2 for three days. CellTiter-Glo Buffer (Promega Cell Viability Assay catalog #G7573) and substrate were equilibrated to room temperature, and enzyme/substrate Recombinant Firefly Luciferase/Beetle Luciferin was reconstituted. The cell plates were equilibrated to room temperature for 30 minutes, then lysed by addition of an equivalent volume of the Celltiter-Glo Reagent. The plate was mixed for 10 minutes on a plate shaker to lyse the cells. The plates were read on a Tecan M1000 using Luminescence protocol modified to read 0.1s per well. The luminescence reading assesses the ATP content, which correlates directly with cell number such that the reading as a function of compound concentration was used to determine the IC_{50} value.

[0451] In order to determine the effect of compounds on FLT3 catalytic activity, kinase assays using recombinant enzymes and AlphaScreen® technology have been established. The catalytic activity of c-kit activity was also measured to determine selectivity of the compounds. When the kinases are catalytically active, they phosphorylate a biotinylated peptide substrate on tyrosine residues. Using AlphaScreen® technology, the ability of the compounds to affect the catalytic activity of the kinases can be measured quantitatively. The peptide substrate is immobilized by the AlphaScreen® Streptavidin Donor beads and, upon phosphorylation by a tyrosine kinase, can bind to AlphaScreen® Anti-Phosphotyrosine (PY20) Acceptor beads. Upon excitation of these beads with laser light at 680 nm, singlet oxygen is produced. This singlet oxygen is rapidly quenched, unless the AlphaScreen® Anti-Phosphotyrosine (PY20) Acceptor beads are in close proximity, in which case a proximity signal can be measured at 580 nm. In the presence of catalytic activity, there is a very strong proximity signal. Selective kinase inhibitors affect a decrease in this proximity signal through a decrease in tyrosine phosphorylation of the peptide substrate. The recombinant enzymes were purchased from the following commercial sources as summarizined in Table 4:

TABLE 4

Enzyme	**Commercial Source**
FLT3-ITD	Invitrogen #PV6190
FLT3-D835Y	Invitrogen #PV3967
c-KIT	Millipore #14-559K

[0452] The assay was performed as summarized below. Buffers used are summarized in Table 5.

TABLE 5

Assay	Assay Buffer	Stop/Detection Buffer
FLT3	25 mM Hepes pH 7.5 5 mM $MnCl_2$ 5 mM $MgCl_2$ 0.01% Tween-20 1 mM DTT 0.01% BSA	25 mM Hepes pH 7.5, 0.01% BSA 100 mM EDTA
c-KIT	25 mM Hepes pH 7.5 2 mM $MnCl_2$ 2 mM $MgCl_2$ 0.01% Tween-20 1 mM DTT 0.01% BSA	25 mM Hepes pH 7.5, 0.01% BSA 100 mM EDTA

Substrate

[0453] Poly (Glu4-Tyr) Peptide, biotin conjugate [Biotin-GG$(EEEEY)_{10}$EE]

[0454] UBI/Millipore #12-440

[0455] Final concentration=30 nM

Adenosine Triphosphate (ATP)

[0456] Sigma #A-3377

[0457] Final concentration for IC50 determination= 10 μM (FLT3-D835Y or FLT3-ITD) or 100 μM (c-KIT)

Detection Reagent

[0458] AlphaScreen® Phosphotyrosine (PY20) Assay Kit

[0459] Perkin-Elmer #6760601M

[0460] Final concentration=10 μg/mL

Protocol IC_{50}

[0461] Dilute compounds in DMSO to 20X final concentration.

[0462] Add 1 μl of compound to each well of 384 well reaction plate (Perkin Elmer #6005359).

[0463] Mix enzyme and Poly (Glu4-Tyr) Peptide substrate at 1.33X final concentration in assay buffer.

[0464] Mix ATP at 5X final concentration in assay buffer.

[0465] Add 15 μL enzyme/substrate mixture to the reaction plate.

[0466] Add 4 μL of ATP to the reaction plate. Centrifuge 1 minute, shake to mix, and incubate as summarized in Table 6:

TABLE 6

Assay	Reaction temperature	Reaction time
FLT3	Room temperature	60 minutes
c-KIT	Room temperature	60 minutes

[0467] Mix Streptavidin Donor beads at 6X final concentration in Stop/Detection buffer.

[0468] Add 5 μL Streptavidin Donor beads to the reaction plate. Centrifuge 1 minute, shake to mix, and incubate at room temperature for 20 minutes.

[0469] Mix Anti-Phosphotyrosine (PY20) Acceptor beads at 6X final concentration in Stop/Detection buffer.

[0470] Add 5 μL Anti-Phosphotyrosine (PY20) beads to the reaction plate.

[0471] Centrifuge 1 minute, shake to mix, and incubate at room temperature for 60 minutes.

[0472] Read plate on Wallac EnVision™ 2103 Multilabel Reader.

Example 11: Biochemical TGFβR2 Assay

[0473] The IC_{50} of certain compounds in this disclosure against TGFβR2 was conducted under contract at Thermo Fisher Scientific, Life Sciences Solutions as part of their SelectScreen™ profiling service. The TGFβR2 assay used the LanthaScreen® Europium Kinase

Binding Assay. Binding of an Alexa Fluor® conjugate Tracer 199 (100 nM) to TGFBR2 (5 nM) was detected by addition of a Eu-labeled anti-tag antibody (5nM) in Kinase Buffer A (50 mM HEPES pH 7.5, 0.01% BRIJ-35, 10 mM MgCl2, 1 mM EGTA) and 1% final DMSO. Binding of the tracer and antibody to a kinase resulted in a high degree of FRET, whereas displacement of the tracer with a kinase inhibitor resulted in a loss of FRET. The percent inhibition was calculated from the emission ratio of Alexa Fluor® and Europium as documented by Thermo Fisher (www.thermofisher.com/kinaseprofiling). The IC_{50} of certain compounds in this disclosure was determined by testing a dilution series of the compound in duplicate at five concentrations (1.0, 0.25, 0.062, 0.015 and 0.0039 μM) by fitting the inhibition data with a sigmoidal curve fit model.

[0474] In another embodiment of this disclosure, compound numbers P-0164, P-0165, P-0166, P-0168, P-0185, P-0201, P-0204 and P-0205 have TGFβR2 IC_{50} values ranging from 0.0001 μM to10 μM.

[0475] The following Table 7 provides data indicating KIT, FLT3 ITD, D835Y and F69L biochemical inhibitory activity for exemplary compounds as described herein. In the table below, activity is provided as follows: +++ = 0.0001 μM $< IC_{50} <$10 μM; ++ = 10 μM $< IC_{50} <$ 50 μM , + = 50 μM $< IC_{50} <$ 100 μM.

TABLE 7

P #	FLT3 D835Y 8pt GMean IC_{50}(uM)	FLT3_ITD 8pt: IC_{50} (μM)	BaF3_FLT3 ITD/D835Y 3d-Growth: IC_{50} (μM)	MOLM-14 D835Y 3d-Growth GMean IC_{50} (μM)	MOLM-14 F691L 3d-Growth GMean IC_{50} (μM)	KIT 100ATP 8pt GMean IC_{50} (μM)
P-0001	++	++	+++			+++
P-0002	+++	+++	+++			+++
P-0003	+++	+++	+++			+++
P-0004	+++		+++		+++	+++
P-0005	++	+++	+++			+++
P-0006	+++	+++	+++			+++
P-0007	+++		+++			++
P-0008	+++		+++			
P-0009	+++		+++		+++	
P-0010	+		+++		+++	

P-0011	+++		+++			
P-0012	+++	+++	+++	+++		+++
P-0013	+++	+++	+++	+++		+++
P-0014	+		+++			
P-0015	+++	+++	+++			+++
P-0016	+++	+++	+++			+++
P-0017	+++	+++	+++			++
P-0018	+++	+++	+++	+++		+++
P-0019	+++	+++				+++
P-0020	+++	+++	+++			+++
P-0021	+++		+++			+
P-0022	+++	+++	+++			+++
P-0023	+++	+++	+++			+
P-0024	+++	+++				++
P-0025	+++	+++	+++			+++
P-0026	+++	+++	+++			+++
P-0027	+++	++	+++			+
P-0028	+++	+++	+++			+++
P-0029	+++	+++	+++			+++
P-0030	+++	+++	+++			+++
P-0031	+++	+++	+++			+++
P-0032	+++	+++	+++			++
P-0033	+++	+++	+++			+++
P-0034	+++	+++	+++			+++
P-0035	+++	+++	+++			+++
P-0036	+++	+++	+++			+++
P-0037	+++	+++	+++			+++

P-0038	+++	+++	+++			+++
P-0039	+++	+++	+++			+++
P-0040	+++	+++	+++	+++		+++
P-0041	+++	+++	+++			+++
P-0042	+++	+++	+++			+++
P-0043	+++	+++	+++			+++
P-0044	+++	+++	+++			+++
P-0045	+++	+++	+++			+++
P-0046	+++	+++	+++			+++
P-0047	+++	+++	+++			+++
P-0048	++	+++	+			
P-0049	+++	+++	+++	+++	+++	+++
P-0050	+++	+++	+++		+++	+++
P-0051	+++	+++				+++
P-0052	+++	+++	+++	+++		+++
P-0053	+++	+++	+++			+++
P-0054	+++	+++	+++		+++	+++
P-0055	+++	+++	+++	+++		+++
P-0056	+++	+++	+++			+++
P-0057	+++	+++	+++			+++
P-0058	+++	+++	+++	+++		+++
P-0059	+++	+++	+++			+++
P-0060	+++	+++	+++	+++		+++
P-0061	+++	+++	+++	+++		++
P-0062	+++	+++	+++	+++		++
P-0063	+++	+++	+++	+++		+++
P-0064	+++	+++	+++	+++		+++
P-0065	+++					++

P-0066	+++	+++				+
P-0067	+++	+++	+++			+++
P-0068	+++	+++	+++			+++
P-0069	+++	+++	+++			++
P-0070	+++	+++	+++	+++		+++
P-0071	+++	+++	+++	+++		++
P-0072	+++	+++	+++	+++		+++
P-0073	+++	+++	+++	+++		+++
P-0074	+++	+++	+++			++
P-0075	+++	+++	+++	+++		
P-0076	+++	+++	+++			
P-0077	+++	+++	+++	+++		
P-0078	+++	+++	+++	+++		
P-0079	+++	+++	+++	+++		
P-0080	+++	+++	+++			
P-0081	+++	+++	+++			
P-0082	+++	+++	+++			
P-0083	+++	+++	+++			
P-0084	+++	+++	+++	+++	+++	+++
P-0085	+++	+++	+++	+++	+++	+++
P-0086	+++	+++	+++	+++	+++	+++
P-0087	+++	+++	+++			+++
P-0088	+++	+++	+++	+++	+++	+++
P-0089	+	+++	+++			+
P-0090	+++	+++	+++	+++		+
P-0091	+++	+++	+++	+++		+
P-0092	+++	+++	+++			+

P-0093	+++	+++	+++	+++		+
P-0094	+++	+++	+++			+
P-0095	+++	+++	+++	+++		++
P-0096	+++	+++	+++	+++		++
P-0097	+++	+++	+++	+++		+++
P-0098	+++	+++	+++			+
P-0099	+++	+++	+++	+++		+
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P-0101	+++	+++	+++			+
P-0102	+++	+++	+++			+
P-0103	+++	+++	+++			+
P-0104	+++	+++	+++			+++
P-0105	+++	+++	+++	+++		++
P-0106	+++	+++	+++	+++	+++	+++
P-0107	+++	+++	+++	+++		+
P-0108			+++	+++		+
P-0109	+++	+++	+++	+++	+++	+
P-0110						++
P-0111	+++	+++	+++	+++	+++	
P-0112	+++	+++	+++	+++	+++	++
P-0113	+++	+++	+++	+++	+++	+++
P-0114	+++	+++	+++	+++	+++	+
P-0115	+++	+++	+++	+++	+++	+
P-0116	+++	+++	+++		+++	+++
P-0117	+++	+++	+++	+++		+++
P-0118	+++	+++	+++	+++	+++	+
P-0119	+++	+++	+++	+++		+

P-0120	+++	+++	+++	+++		+++
P-0121	+++		+++	+++		
P-0122	+++	+++	+++	+++	+++	
P-0123	+++	+++	+++	+++	+++	+++
P-0124	+++	+++	+++	+++		
P-0125	+++	+++	+++	+++		
P-0126	+++	+++	+++	+++		
P-0127	+++	+++	+++	+++		
P-0128	+++			+++	+++	
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P-0146	+++	+++		+++	+++	

P-0147	+++	+++		+++	+++	
P-0148	+++	+++		+++		
P-0149	+++	+++		+++		
P-0150	+++	+++		+++	+++	
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P-0152	+++	+++		+++		
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P-0159	+++	+++		+++		
P-0160	+++	+++		+++	+++	
P-0161	+++	+++		+++	+++	
P-0162	+++	+++		+++	+++	
P-0163	+++	+++		+++		
P-0164	+++	+++		+++	+++	+
P-0165	+++	+++		+++	+++	
P-0166	+++	+++		+++	+++	
P-0167	+++	+++			+++	
P-0168	+++	+++		+++	+++	
P-0169	+++	+++		+++	+++	
P-0170	+++	+++		+++	+++	
P-0171	+++	+++		+++	+++	
P-0172	+++	+++		+++	+++	
P-0173	+++	+++		+++	+++	

P-0174	+++	+++		+++	+++	
P-0175	+++	+++		+++		
P-0176	+++	+++		+++	+++	
P-0177	+++	+++		+++		
P-0178	+++	+++		+++	+++	
P-0179	+++	+++		+++		
P-0180	+++	+++		+++	+++	
P-0181	+++	+++		+++	+++	
P-0182	+++	+++		+++	+++	
P-0183	+++	+++		+++	+++	
P-0184	+++	+++			+++	
P-0185	+++	+++			+++	
P-0186	+++	+++			+++	
P-0187	+++	+++		+++	+++	
P-0188	+++	+++		+++	+++	
P-0189	+++	+++		+++		
P-0190	+++	+++		+++	+++	
P-0191	+++	+++		+++	+++	
P-0192	+++	+++		+++	+++	
P-0193	+++	+++		+++	+++	
P-0194	+++	+++		+++	+++	
P-0195	+++	+++		+++	+++	
P-0196	+++	+++		+++	+++	
P-0197	+++	+++		+++	+++	
P-0198	+++	+++		+++		
P-0199	+++	+++		+++		
P-0200	+++	+++		+++		

P-0201	+++	+++		+++	+++	+
P-0202	+++	+++		+++		
P-0203	+++	+++		+++	+++	
P-0204	+++	+++		+++	+++	+
P-0205	+++	+++		+++	+++	
P-0206	+++	+++		+++	+++	
P-0207	+++			+++	+++	
P-0208	+++	+++		+++	+++	+
P-0209	+++	+++				+
P-0210	+++	+++				+
P-0211	+++	+++		+++	+++	+

[0476] Another aspect of this disclosure relates to one or more compounds of Table 1 or Table 2 that are more than 2 fold as potent for FLT3 than KIT. Another aspect of this disclosure relates to one or more compounds of Table 1 or Table 2 that are more than 3 fold as potent for FLT3 than KIT. Another aspect of this disclosure relates to one or more compounds of Table 1 or Table 2 that are more than 5 fold as potent for FLT3 than KIT. Another aspect of this disclosure relates to one or more compounds of Table 1 or Table 2 that are more than 10 fold as potent for FLT3 than KIT. Another aspect of this disclosure relates to one or more compounds of Table 1 or Table 2 that are more than 100 fold as potent for FLT3 than KIT. Another aspect of this disclosure relates to one or more compounds of Table 1 or Table 2 that are more than 1000 fold as potent for FLT3 than KIT.

[0477] All patents and other references cited herein are indicative of the level of skill of those skilled in the art to which the disclosure pertains, and are incorporated by reference in their entireties, including any tables and figures, to the same extent as if each reference had been incorporated by reference in its entirety individually.

[0478] One skilled in the art would readily appreciate that the present disclosure is well adapted to obtain the ends and advantages mentioned, as well as those inherent therein. The methods, variances, and compositions described herein as presently representative of the embodiments described herein are exemplary and are not intended as limitations on the scope of

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the disclosure. Changes therein and other uses will occur to those skilled in the art, which are encompassed within the spirit of the disclosure, are defined by the scope of the claims.

[0479] It will be readily apparent to one skilled in the art that varying substitutions and modifications may be made to the present disclosure described herein without departing from the scope and spirit of the disclosure. For example, variations can be made to provide additional compounds of Formula I and all sub-embodiments thereof, and/or various methods of administration for the compounds of this disclosure. Thus, such additional embodiments are within the scope of the present disclosure and the following claims.

[0480] The present disclosure illustratively described herein suitably may be practiced in the absence of any element or elements, limitation or limitations which is not specifically described herein. The terms and expressions which have been employed are used as terms of description and not of limitation, and there is no intention that in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the disclosure claimed. Thus, it should be understood that although the present disclosure has been specifically described by the embodiments and optional features, modification and variation of the concepts herein described may be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope of this disclosure as defined by the appended claims.

[0481] In addition, where features or embodiments of the disclosure are described in terms grouping of alternatives, those skilled in the art will recognize that the disclosure is also thereby described in terms of any individual member or subgroup of members of the groups described herein.

[0482] Also, unless indicated to the contrary, where various numerical values are provided for embodiments, additional embodiments are described by taking any 2 different values as the endpoints of a range. Such ranges are also within the scope of the present disclosure.

[0483] Thus, additional embodiments are within the scope of the disclosure and within the following claims.

[0484] Reference to any prior art in the specification is not an acknowledgement or suggestion that this prior art forms part of the common general knowledge in any jurisdiction or that this prior art could reasonably be expected to be combined with any other piece of prior art by a skilled person in the art.

[0485] By way of clarification and for avoidance of doubt, as used herein and except where the context requires otherwise, the term "comprise" and variations of the term, such as "comprising", "comprises" and "comprised", are not intended to exclude further additions, components, integers or steps.

SEQUENCE LISTING

SEQ ID NO:1 Sequence NP_004110.2

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HPSQSALVTIVEKGFINATNSSEDYEIDQYEEFCFSVRFKAYPQIRCTWTFSRKSFPC

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MEFLEFKSCVHRDLAARNVLVTHGKVVKICDFGLARDIMSDSNYVVRGNARLPVKWM

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SEQ ID NO:2 Sequence NM_44119

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301 gacagtgtac gaagctgccg ctgtggaagt ggatgtatct gcttccatca cactgcaagt

361 gctggtcgac gccccaggga acatttcctg tctctgggtc tttaagcaca gctccctgaa

421 ttgccagcca cattttgatt tacaaaacag aggagttgtt tccatggtca ttttgaaaat

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661 cgtggaatgg gtgctttgcg attcacaggg ggaaagctgt aaagaagaaa gtccagctgt

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1141 caattcaagt gaagattatg aaattgacca atatgaagag ttttgttttt ctgtcaggtt

1201 taaagcctac ccacaaatca gatgtacgtg gaccttctct cgaaaatcat ttccttgtga

1261 gcaaaagggt cttgataacg gatacagcat atccaagttt tgcaatcata agcaccagcc

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1381 gaatataaga aggaaacctc aagtgctcgc agaagcatcg gcaagtcagg cgtcctgttt

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3721 aggtgttcta ccataaagag taatacatca cctagacact ttggcggcct tcccagactc

3781 agggccagtc agaagtaaca tggaggatta gtattttcaa taaagttact cttgtcccca

3841 caaaaaaa

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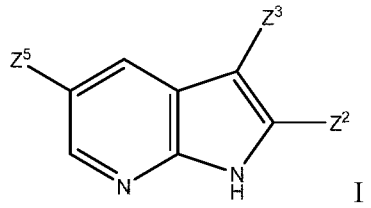
What is claimed is:

1. A compound having Formula I:



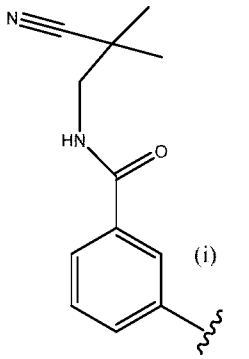
I

or a pharmaceutically acceptable salt, a solvate, a tautomer, a stereoisomer, or a deuterated analog thereof, wherein:

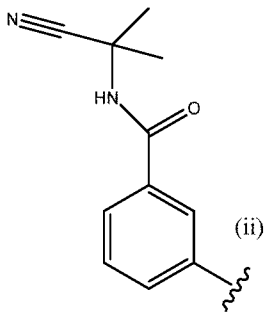
Z^2 is C_{2-10}alkynyl optionally substituted with R^b, C_{6-14}aryl, C_{3-10}cycloalkyl, C_{3-10}cycloalkenyl, 3-12 membered heterocycloalkyl, 3-12 membered heterocycloalkenyl or 5-10 membered heteroaryl, wherein each C_{6-14}aryl, C_{3-10}cycloalkyl, C_{3-10}cycloalkenyl, 3-12 membered heterocycloalkyl, 3-12 membered heterocycloalkenyl, or 5-10 membered heteroaryl is optionally substituted with 1-3 R^1 groups;

Z^3 is hydrogen or halo;

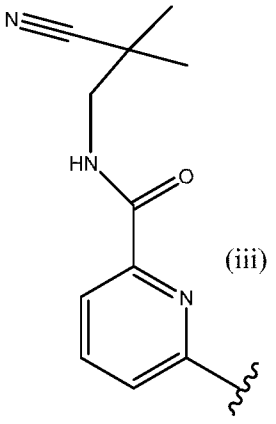
Z^5 is:



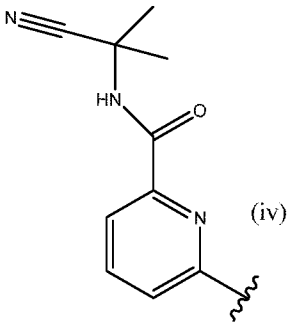
(i),



(ii),



(iii), or



(iv);

each R^1 is independently hydrogen, C_{1-6}alkyl, C_{3-10}cycloalkyl, -C(O)-C_{3-10}cycloalkyl, -C(O)-C_{1-6}alkyl, cyano, C_{1-6}cyanoalkyl, C_{3-10}cyanocycloalkyl, cyanoC_{3-10}cycloalkyl-C_{1-6}alkyl,

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hydroxy, C_{1-6}alkoxy, C_{1-6}alkoxy-C_{1-6}alkyl, C_{1-6}hydroxyalkyl, halo, C_{1-6}haloalkyl, oxo, C_{6-14}aryl, C_{6-14}aryl-C_{1-6}alkyl, C_{3-10}cycloalkylsulfonyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonyl-C_{1-6}alkyl, C_{1-6}alkylcarbonylamino-C_{1-6}alkyl, C_{1-6}alkylsulfonylamino-C_{1-6}alkyl, 3-12 membered heterocycloalkyl optionally substituted with 1-2 R^a, 3-12 membered heterocycloalkyl-C_{1-6}alkyl, -NR^6R^7, -C_{1-6}alkylene-NR^6R^7, -C(O)O-C_{1-6}alkyl, 3-12 membered heterocycloalkyl optionally substituted with 1-2 R^d groups, or 5-10 membered heteroaryl optionally substituted with 1-2 R^e groups;

R^6 is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, C_{1-6}alkylsulfonyl, 5-7 membered cycloalkylamino, or C_{3-10}cycloalkyl, wherein each of the C_{1-6}alkyl, C_{1-6}alkylcarbonyl, C_{1-6}alkylsulfonyl, 5-7 membered cycloalkylamino, and C_{3-10}cycloalkyl are optionally substituted with 1-3 G groups,

R^7 is hydrogen or C_{1-6}alkyl optionally substituted with 1-3 G groups;

or R^6 and R^7, together with the N atom to which they are attached, join to form a 3-12 membered heterocycloalkyl or 5-10 membered heteroaryl moiety, wherein 1-2 carbon atoms of the heterocycloalkyl or heteroaryl moiety is substituted with 1-2 G groups;

each G is independently C_{1-6}alkyl, C_{1-6}haloalkyl, halo, amino, -NH-C_{1-6}alkyl, -N(C_{1-6}alkyl)$_2$, -(C_{1-6}alkylene)-N(H)-C_{1-6}alkyl, -(C_{1-6}alkylene)-amino, -CN, -C(O)-C_{1-6}alkyl, -C(O)-O-C_{1-6}alkyl, -CO_2H, -C(O)-N(H)-C_{1-6}alkyl, oxo, -N(H)-C(O)-C_{1-6}alkyl, -C(=NH)-NH_2, -OH, -N(H)-C(O)-O-C_{1-6}alkyl, -N(H)-C(O)-N(H)-C_{1-6}alkyl, -N(H)-S(O)$_2$-C_{1-6}alkyl, -S(O)$_2$-C_{1-6}alkyl, C_{1-6}hydroxyalkyl, C_{3-10}cycloalkyl, -N(H)-C_{3-6}cycloalkyl , C_{1-6}alkoxy, 3-12 membered heterocycloalkyl or 5-10 membered heteroaryl,

each R^a is independently C_{1-6}alkyl, oxo, halo, or hydroxy;

R^b is halo, C_{3-6}cycloalkyl, C_{6-14}aryl, 5-10 membered heteroaryl, -NR^6R^7, or hydroxy;

each R^d is independently C_{1-6}alkyl, halo, oxo, C_{1-6}alkylaminosulfonyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylcarbonyl, C_{1-6}hydroxyalkyl, or hydroxy; and

each R^e is independently C_{1-6}alkyl, halo, or hydroxy

provided that when G is C_{3-10}cycloalkyl, Z^2 is alkynyl optionally substituted with C_{3-6}cycloalkyl, -NR^6R^7, or hydroxy.

2. The compound according to claim 1, wherein:

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Z^2 is ethynylene optionally substituted with C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-6}cycloalkyl, C_{6-14}aryl, -C_1-C_6alkylene-NR^6R^7, or C_{1-6}hydroxyalkylene; or

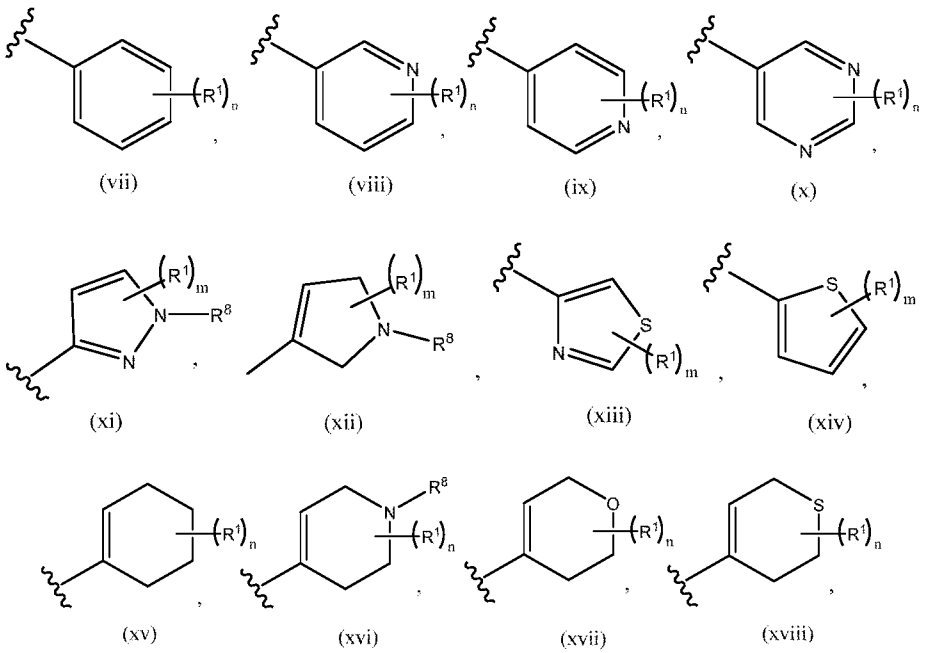
Z^2 is phenyl, cyclohexanyl, cyclohexenyl, pyrazolyl, pyrimidinyl, thiazolyl, pyridyl, pyridazinyl, pyrrolyl, dihydropyrrolyl, dihydropyranyl, dihydropyradinyl, tetrahydropyridyl, dihydrothiopyranyl, dihydrothiopyranyl oxide, or dihydrothiopyranyl dioxide, each of which is optionally substituted with 1-2 R^1 groups;

R^1 is hydrogen, C_{3-10}cycloalkyl, -C(O)-C_{3-10}cycloalkyl, C_{1-6}alkyl, cyano, hydroxy, C_{1-6}alkoxy, halo, C_{1-6}haloalkyl, oxo, phenyl, 3-12 membered heterocycloalkyl, 3-12 membered heterocycloalkyl-C_{1-6}alkyl, -C_{1-6}alkylene-NR^6R^7, -C(O)O-C_{1-6}alkyl, or 5-10 membered heteroaryl optionally substituted with 1-2 R^e groups;

each G is independently C_{1-6}alkyl, halo, amino, -NH-C_{1-6}alkyl, -N(C_{1-6}alkyl)$_2$, -(C_{1-6}alkylene)-N(H)-C_{1-6}alkyl, -CN, -C(O)-C_{1-6}alkyl, -C(O)-N(H)-C_{1-6}alkyl, -N(H)-C(O)-C_{1-6}alkyl, -C(=NH)-NH_2, -N(H)-C(O)-O-C_{1-6}alkyl, -N(H)-C(O)-N(H)-C_{1-6}alkyl, -N(H)-S(O)$_2$-C_{1-6}alkyl, -S(O)$_2$-C_{1-6}alkyl, C_{3-6}cycloalkyl, -N(H)-C_{3-6}cycloalkyl, C_1-C_6alkoxy, 5-6 membered heterocycloalkyl or 5-6 membered heteroaryl, provided that when G is C_{3-6}cycloalkyl, Z^2 is optionally substituted with C_{1-6}alkyl, C_{3-6}cycloalkyl, -C_1-C_6alkylene-NR^6R^7, or C_{1-6}hydroxyalkylene; and

each R^a is independently oxo, halo or hydroxy.

3. The compound according to claim 1, wherein Z^2 is:



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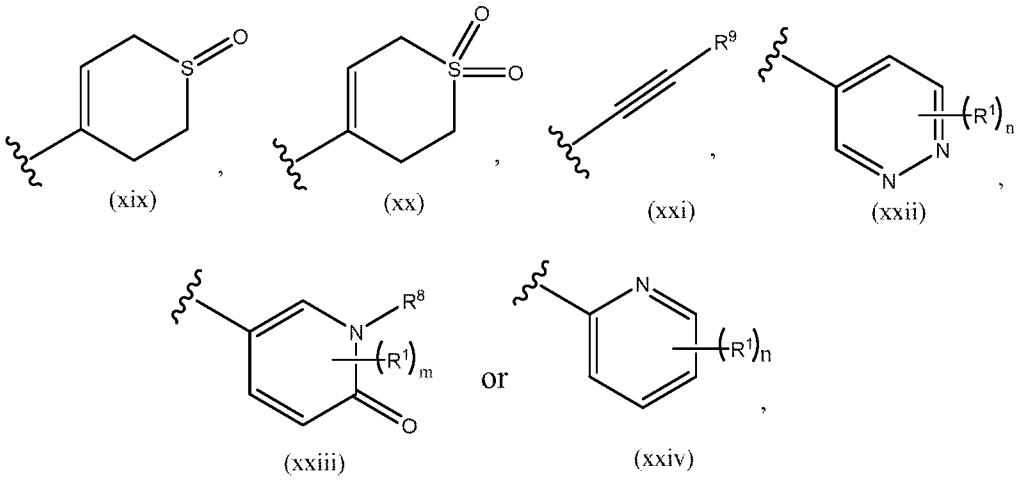

(xix) (xx) (xxi) (xxii)

(xxiii) or (xxiv)

wherein

m is 0-2;

n is 0-3;

R^8 is hydrogen, C_{1-6}alkyl, -C(O)O-C_{1-6}alkyl, C_{3-6}cycloalkyl, -C(O)-C_{3-6}cycloalkyl, C_{6-14}aryl-C_{1-6}alkyl, 5-6 membered heterocycloalkyl-C_{1-6}alkyl or C_{1-6}haloalkyl; and

R^9 is C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-6}cycloalkyl, C_{6-14}aryl, -C_{1-6}alkylene-NR^6R^7, hydroxy-C_{1-6}alkylene or hydroxy.

4. The compound according to claim 1, wherein R^1 is C_{1-3}alkyl, C_{1-3}haloalkyl, C_{3-6}cycloalkyl, -C_{1-3}alkylene-CN, cyano, -(C_{1-3}alkylene)-C_{1-3}alkoxy, 3-12 membered heterocycloalkyl, -C(O)-C_{3-6}cycloalkyl.

5. The compound according to claim 4, wherein R^1 is -CH_3, -CHF_2, -CH_2F, -CF_3, cyclopropyl, -C_{1-3}alkylene-CN, cyano, methoxy-(C_{1-3}alkylene)-, piperidinyl, morpholinyl, tetrahydrofuranyl, or -C(O)-cyclopropyl.

6. The compound according to any one of claims 1-3, having one of the following Formulae:

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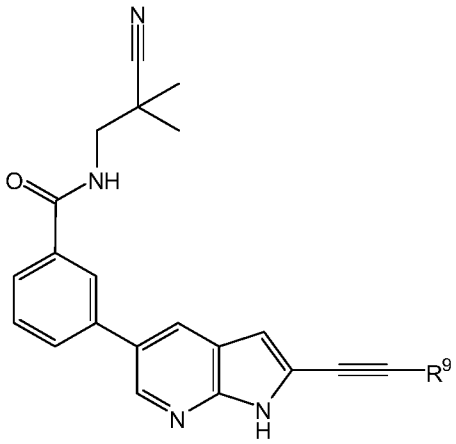
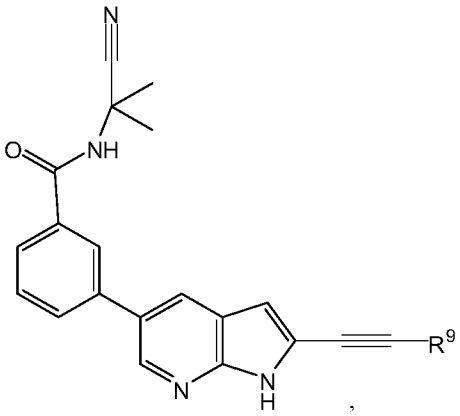
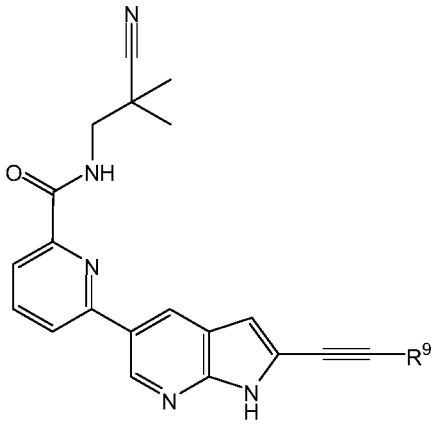


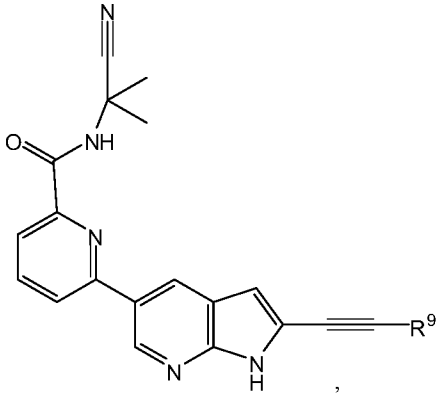
IV(a)



IV(b)



IV(c)



IV(d)

or a pharmaceutically acceptable salt, a solvate, a tautomer, a stereoisomer, or a deuterated analog thereof, wherein R^9 is C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-6}cycloalkyl, phenyl, -(C_{1-6}alkylene)-NR^6R^7, or C_{1-4}hydroxyalkylene.

7. The compound according to claim 1 having one of the following Formulae:

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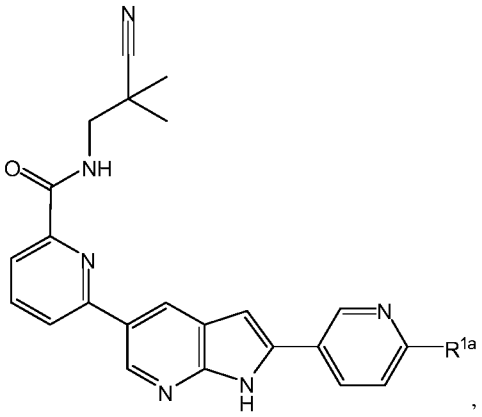
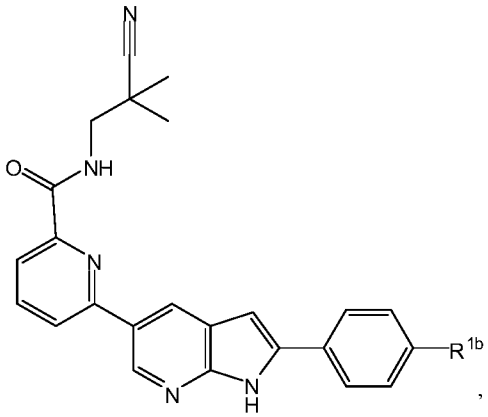
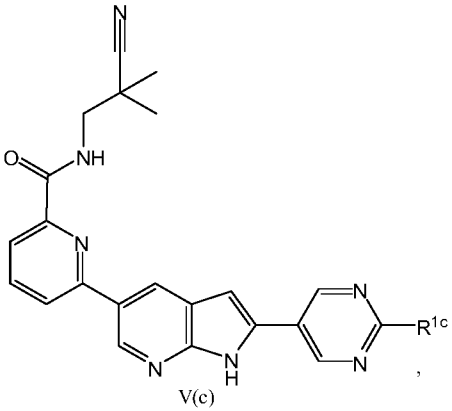


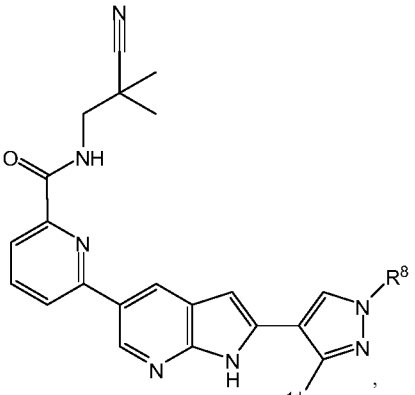
V(a),



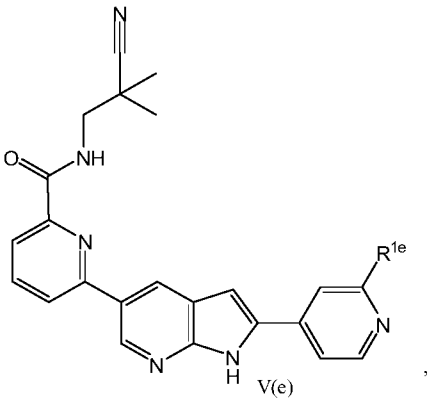
V(b),



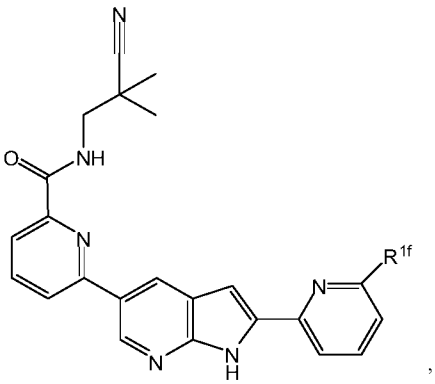
V(c),



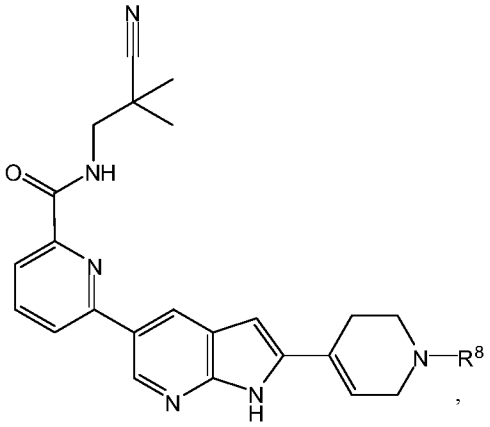
V(d),



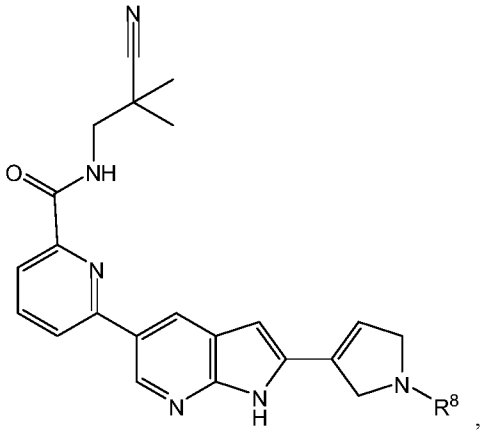
V(e),



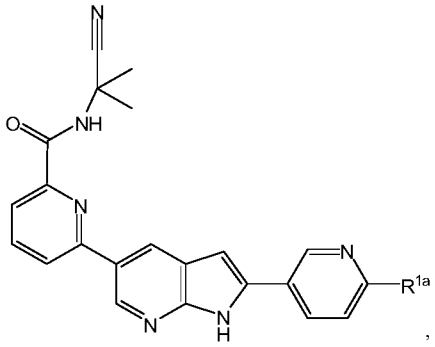
V(f),



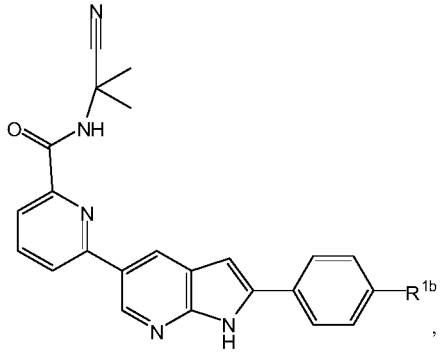
V(g)



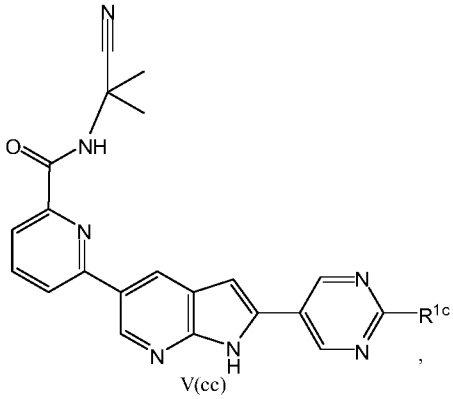
V(h)



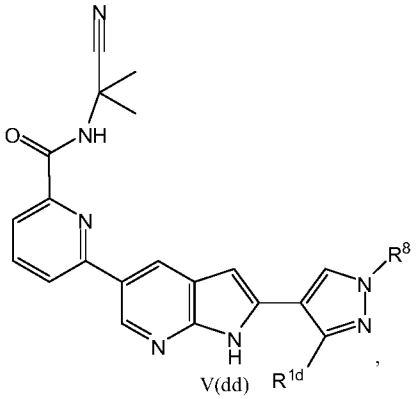
V(aa)



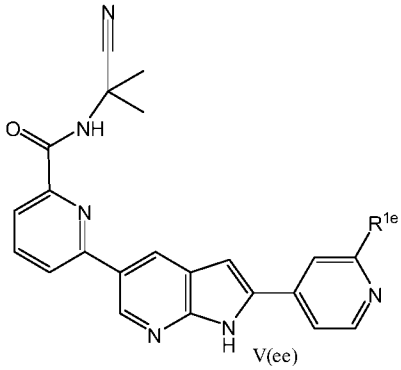
V(bb)



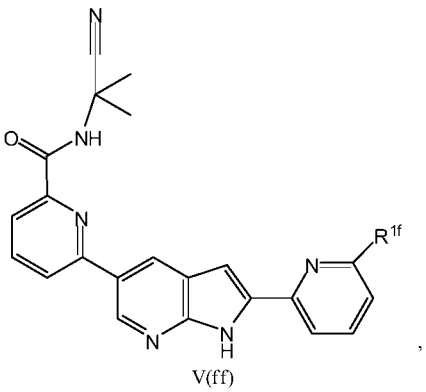
V(cc)



V(dd)



V(ee)



V(ff)

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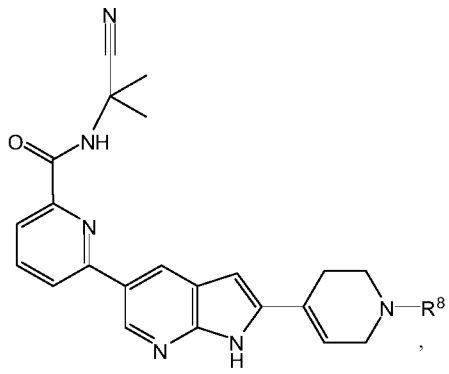
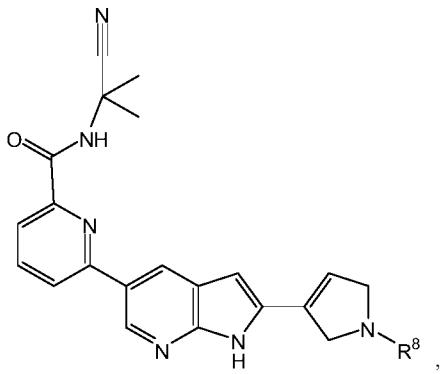


V(gg)



V(hh)

or a pharmaceutically acceptable salt, a solvate, a tautomer, a stereoisomer, or a deuterated analog thereof, wherein:

R^8 is hydrogen, C_{1-6}alkyl, -C(O)O-C_{1-6}alkyl, C_{3-6}cycloalkyl, -C(O)-C_{3-6}cycloalkyl, C_{6-14}aryl-C_{1-6}alkyl, 5-6 membered heterocycloalkyl-C_{1-6}alkyl or C_{1-6}haloalkyl; and

each of R^{1a}, R^{1b}, R^{1c}, R^{1d}, R^{1e}, and R^{1f} are as defined as R^1 in claim 1.

8. The compound according to claim 7, wherein:

R^{1a} is hydrogen, cyclopropyl, -OC(H)(CH_3)$_2$, morpholinyl, -CF_3, -CHF_2 or F;

R^{1b} is hydrogen, F, cyano, cyclopropyl or cyanocyclopropyl;

R^{1c} is hydrogen, cyclopropyl, methoxy, -OC(H)(CH_3)$_2$, pyrrolidinyl, ethoxy, -CH_3,-CF_3 or -CHF_2;

R^{1d} is hydrogen or -CH_3;

R^{1e} is hydrogen, methoxy, cyclopropyl, morpholinyl, -CF_3, -CHF_2, -CH_3, pyrrolidinyl or F;

R^{1f} is hydrogen or cyclopropyl; and

R^8 is hydrogen, -CH(CH_3)$_2$, -C(O)OC(CH_3)$_3$, cyclopropyl, -C(O)cyclopropyl, -(CH_2)$_{1-2}$-phenyl, -(CH_2)$_{1-2}$-morpholinyl, -(CH_2)$_{1-2}$-tetrahydrofuranyl, -(CH_2)$_{1-2}$-piperidinyl, -CH_3, -CF_3 or -CHF_2.

9. The compound according to claim 1, wherein G is amino, -N(H)C(O)-C_{1-6}alkyl, -C(O)-N(H)-C_{1-6}alkyl, -N(H)-C(O)-N(H)-C_{1-6}alkyl, -N(H)-S(O)$_2$-C_{1-6}alkyl, –N(H)-C_{1-6}alkyl, –N(C_{1-6}alkyl)$_2$, -C(=NH)-NH_2, -OH, C_{1-6}alkyl, C_{1-6}haloalkyl, halo, -N(H)-C_{3-6}cycloalkyl, C_{1-6}alkoxy, 4-6 membered heterocycloalkyl, 5-6 membered heteroaryl, -CN, -C(O)-C_{1-6}alkyl, or -C_{1-3}alkylene-N(H)-C_{1-3}alkyl.

10. The compound according to claim 9, wherein G is amino, –N(H)C(O)-C_{1-4}alkyl, -C(O)-N(H)-C_{1-4}alkyl, -N(H)-C(O)-N(H)-C_{1-4}alkyl, -N(H)-S(O)$_2$-C_{1-3}alkyl, –N(H)-CH_3, –N(CH_3)$_2$, -C(=NH)-NH_2, -OH, -C_{1-3}alkyl, -CF_3, fluoro, -N(H)-C_{3-6}cycloalkyl, C_{1-3}alkoxy, morpholinyl, imidazolyl, -CN, -C(O)-C_{1-3}alkyl, or -C_{1-2}alkylene-N(H)-CH_3.

11. The compound according to claim 1, wherein R^a is oxo, fluoro, chloro, or hydroxy.

12. A compound selected from:

N-(2-cyano-2-methyl-propyl)-6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carboxamide;	**P-0100**
N-(2-cyano-2-methyl-propyl)-6-[2-[1-(2,2,2-trifluoroethyl)pyrazol-4-yl]-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0113**
N-(1-cyano-1-methyl-ethyl)-6-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carboxamide;	**P-0118**
N-(2-cyano-2-methyl-propyl)-6-[2-(cyclohexen-1-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0123**
6-(3-bromo-2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-N-(2-cyano-2-methyl-propyl)pyridine-2-carboxamide;	**P-0126**
N-(2-cyano-2-methyl-propyl)-6-(3-iodo-2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carboxamide;	**P-0127**
6-(3-chloro-2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-N-(2-cyano-2-methyl-propyl)pyridine-2-carboxamide;	**P-0138**
N-(2-cyano-2-methyl-propyl)-6-[2-[1-(cyclopropanecarbonyl)-2,5-dihydropyrrol-3-yl]-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0141**
N-(2-cyano-2-methyl-propyl)-6-[2-(4-fluorophenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0144**
N-(1-cyano-1-methyl-ethyl)-6-[2-(4-fluorophenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0145**
N-(2-cyano-2-methyl-propyl)-6-[2-(2-cyclopropyl-4-pyridyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0152**
N-(2-cyano-2-methyl-propyl)-6-[2-[1-(difluoromethyl)pyrazol-4-yl]-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0153**
N-(2-cyano-2-methyl-propyl)-6-[2-(2-methoxy-4-pyridyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0154**
N-(2-cyano-2-methyl-propyl)-6-[2-(1-methyl-6-oxo-3-pyridyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0155**

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N-(2-cyano-2-methyl-propyl)-6-[2-(4,4-difluorocyclohexen-1-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0157**
3-[3-chloro-2-(2-cyclopropyl-4-pyridyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]-N-(2-cyano-2-methyl-propyl)benzamide;	**P-0158**
N-(2-cyano-2-methyl-propyl)-6-[2-(3,6-dihydro-2H-thiopyran-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0159**
N-(2-cyano-2-methyl-propyl)-6-[2-(1,1-dioxo-3,6-dihydro-2H-thiopyran-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0160**
N-(2-cyano-2-methyl-propyl)-6-[2-(1-oxo-3,6-dihydro-2H-thiopyran-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0161**
N-(2-cyano-2-methyl-propyl)-6-[2-[1-(cyclopropanecarbonyl)-3,6-dihydro-2H-pyridin-4-yl]-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0162**
N-(1-cyano-1-methyl-ethyl)-6-[2-(6-methylpyridazin-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0163**
N-(1-cyano-1-methyl-ethyl)-6-[2-[1-(difluoromethyl)pyrazol-4-yl]-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0164**
N-(1-cyano-1-methyl-ethyl)-6-[2-(1-cyclopropylpyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0165**
N-(1-cyano-1-methyl-ethyl)-6-[2-(2-cyclopropylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0166**
N-(1-cyano-1-methyl-ethyl)-6-(2-thiazol-4-yl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carboxamide;	**P-0167**
N-(1-cyano-1-methyl-ethyl)-6-[2-(6-cyclopropyl-3-pyridyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0168**
N-(1-cyano-1-methyl-ethyl)-6-[2-(2-isopropyl-4-methyl-thiazol-5-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0169**
6-[2-[1-(2-cyanoethyl)pyrazol-4-yl]-1H-pyrrolo[2,3-b]pyridin-5-yl]-N-(1-cyano-1-methyl-ethyl)pyridine-2-carboxamide;	**P-0170**
6-[2-(1-benzylpyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]-N-(1-cyano-1-methyl-ethyl)pyridine-2-carboxamide;	**P-0171**
N-(1-cyano-1-methyl-ethyl)-6-[2-[1-(2-methoxyethyl)pyrazol-4-yl]-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0172**
N-(1-cyano-1-methyl-ethyl)-6-[2-(1-tetrahydrofuran-3-ylpyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0173**
N-(1-cyano-1-methyl-ethyl)-6-[2-[1-(2-morpholinoethyl)pyrazol-4-yl]-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0174**
N-(1-cyano-1-methyl-ethyl)-6-(2-ethynyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carboxamide;	**P-0175**
N-(1-cyano-1-methyl-ethyl)-6-[2-(2-phenylethynyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0176**
N-(1-cyano-1-methyl-ethyl)-6-[2-[2-(3-methylimidazol-4-yl)ethynyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0177**
N-(1-cyano-1-methyl-ethyl)-6-[2-(1-isopropyl-3-methyl-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0178**
N-(1-cyano-1-methyl-ethyl)-6-[2-(3,6-dihydro-2H-thiopyran-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0180**
N-(1-cyano-1-methyl-ethyl)-6-[2-[1-(cyclopropanecarbonyl)-3,6-dihydro-2H-pyridin-4-yl]-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0181**

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N-(1-cyano-1-methyl-ethyl)-6-[2-(1,2,3,6-tetrahydropyridin-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0182**
N-(1-cyano-1-methyl-ethyl)-6-[2-(1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0183**
N-(1-cyano-1-methyl-ethyl)-6-[2-[1-(cyclopropanecarbonyl)pyrazol-4-yl]-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0184**
6-[3-chloro-2-[1-(difluoromethyl)pyrazol-4-yl]-1H-pyrrolo[2,3-b]pyridin-5-yl]-N-(1-cyano-1-methyl-ethyl)pyridine-2-carboxamide;	**P-0185**
N-(1-cyano-1-methyl-ethyl)-6-[2-(1,1-dioxo-3,6-dihydro-2H-thiopyran-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0186**
N-(1-cyano-1-methyl-ethyl)-6-[2-[1-(4-piperidyl)pyrazol-4-yl]-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0187**
N-(1-cyano-1-methyl-ethyl)-6-[2-(1-cyclopropylsulfonyl-3,6-dihydro-2H-pyridin-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0188**
N-(1-cyano-1-methyl-ethyl)-6-[2-(4-cyclopropylphenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0189**
N-(1-cyano-1-methyl-ethyl)-6-[2-(6-isopropoxy-3-pyridyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0190**
N-(1-cyano-1-methyl-ethyl)-6-[2-(2-isopropoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0191**
6-[3-chloro-2-(1-isopropyl-3-methyl-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]-N-(1-cyano-1-methyl-ethyl)pyridine-2-carboxamide;	**P-0192**
N-(1-cyano-1-methyl-ethyl)-6-[2-[1-(2,2,2-trifluoroethyl)pyrazol-4-yl]-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0193**
6-[2-[4-(1-cyanocyclopropyl)phenyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]-N-(1-cyano-1-methyl-ethyl)pyridine-2-carboxamide;	**P-0194**
N-(1-cyano-1-methyl-ethyl)-6-(2-pyrimidin-5-yl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-carboxamide;	**P-0195**
N-(1-cyano-1-methyl-ethyl)-6-[2-(2-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0196**
N-(1-cyano-1-methyl-ethyl)-6-[2-(6-morpholino-3-pyridyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0197**
N-(1-cyano-1-methyl-ethyl)-6-[2-(2-morpholinopyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0198**
N-(1-cyano-1-methyl-ethyl)-6-[2-[3-(1,1-dioxo-1,2-thiazolidin-2-yl)phenyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0199**
N-(2-amino-1,1-dimethyl-2-oxo-ethyl)-6-[2-[1-(4-piperidyl)pyrazol-4-yl]-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0200**
N-(1-cyano-1-methyl-ethyl)-6-[2-[6-(trifluoromethyl)-3-pyridyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0201**
N-(1-cyano-1-methyl-ethyl)-6-[2-(2-pyrrolidin-1-ylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0202**
N-(1-cyano-1-methyl-ethyl)-6-[2-(2-ethoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0203**
N-(1-cyano-1-methyl-ethyl)-6-[2-[2-(trifluoromethyl)pyrimidin-5-yl]-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0204**
N-(1-cyano-1-methyl-ethyl)-6-[2-(2-ethylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0205**

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N-(1-cyano-1-methyl-ethyl)-6-[2-(2-propoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0206**
6-[3-chloro-2-[1-(4-piperidyl)pyrazol-4-yl]-1H-pyrrolo[2,3-b]pyridin-5-yl]-N-(1-cyano-1-methyl-ethyl)pyridine-2-carboxamide;	**P-0207**
N-(1-cyano-1-methyl-ethyl)-6-[2-(6-fluoro-3-pyridyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0208**
N-(1-cyano-1-methyl-ethyl)-6-[2-(2-fluoro-4-pyridyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0209**
N-(1-cyano-1-methyl-ethyl)-6-[2-(2-methyl-4-pyridyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0210**
N-(1-cyano-1-methyl-ethyl)-6-[2-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-1H-pyrrolo[2,3-b]pyridin-5-yl]pyridine-2-carboxamide;	**P-0211**
N-(2-cyanopropan-2-yl)-6-(2-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)picolinamide;	**P-0212**
N-(2-cyanopropan-2-yl)-6-(2-(1-(2,2-difluoroethyl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)picolinamide;	**P-0213**
N-(2-cyanopropan-2-yl)-6-(2-(1-(oxetan-3-ylmethyl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)picolinamide;	**P-0214**
N-(2-cyanopropan-2-yl)-6-(2-(1-((methylsulfonyl)methyl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)picolinamide;	**P-0215**

or a pharmaceutically acceptable salt, a solvate, a tautomer, a stereoisomer, or a deuterated analog of any one of the above compounds.

13. A pharmaceutical composition comprising a compound according to any one of the preceding claims and a pharmaceutically acceptable carrier.

14. The pharmaceutical composition according to claim 13 further comprising a second pharmaceutical agent selected from the group consisting of an anti-proliferative agent, an anti-inflammatory agent, an immunomodulatory agent and an immunosuppressive agent.

15. The pharmaceutical composition according to claim 13, further comprising a second pharmaceutical agent selected from: i) an alkylating agent selected from adozelesin, altretamine, bizelesin, busulfan, carboplatin, carboquone, carmustine, chlorambucil, cisplatin, cyclophosphamide, dacarbazine, estramustine, fotemustine, hepsulfam, ifosfamide, improsulfan, irofulven, lomustine, mechlorethamine, melphalan, oxaliplatin, piposulfan, semustine, streptozocin, temozolomide, thiotepa, and treosulfan; ii) an antibiotic selected from bleomycin, dactinomycin, daunorubicin, doxorubicin, epirubicin, idarubicin, menogaril, mitomycin, mitoxantrone, neocarzinostatin, pentostatin, and plicamycin; an antimetabolite selected from the group consisting of azacitidine, capecitabine, cladribine, clofarabine, cytarabine, decitabine, floxuridine, fludarabine, 5-fluorouracil, ftorafur, gemcitabine, hydroxyurea, mercaptopurine,

methotrexate, nelarabine, pemetrexed, raltitrexed, thioguanine, and trimetrexate; iii) an antibody therapy agent selected from alemtuzumab, bevacizumab, cetuximab, galiximab, gemtuzumab, panitumumab, pembrolizumab, pertuzumab, rituximab, tositumomab, trastuzumab, and 90 Y ibritumomab tiuxetan; a hormone or hormone antagonist selected from the group consisting of anastrozole, androgens, buserelin, diethylstilbestrol, exemestane, flutamide, fulvestrant, goserelin, idoxifene, letrozole, leuprolide, magestrol, raloxifene, tamoxifen, and toremifene; iv) a taxane selected from DJ-927, docetaxel, TPI 287, paclitaxel and DHA-paclitaxel; v) a retinoid selected from alitretinoin, bexarotene, fenretinide, isotretinoin, and tretinoin; vi) an alkaloid selected from etoposide, homoharringtonine, teniposide, vinblastine, vincristine, vindesine, and vinorelbine; vii) an antiangiogenic agent selected from AE-941 (GW786034, Neovastat), ABT-510, 2-methoxyestradiol, lenalidomide, and thalidomide; viii) a topoisomerase inhibitor selected from amsacrine, edotecarin, exatecan, irinotecan, SN-38 (7-ethyl-10-hydroxy-camptothecin)), rubitecan, topotecan, and 9-aminocamptothecin; ix) a kinase inhibitor selected from erlotinib, gefitinib, flavopiridol, imatinib mesylate, lapatinib, sorafenib, sunitinib malate, AEE-788, AG-013736, AMG 706, AMN107, BMS-354825, BMS-599626, UCN-01 (7-hydroxystaurosporine), vemurafenib, dabrafenib, trametinib, cobimetinib selumetinib and vatalanib; x) a targeted signal transduction inhibitor selected from bortezomib, geldanamycin, and rapamycin; xi) a biological response modifier selected from imiquimod, interferon-.alpha., and interleukin-2; xii) an IDO inhibitor; and xiii) a chemotherapeutic agent selected from 3-AP (3-amino-2-carboxyaldehyde thiosemicarbazone), altrasentan, aminoglutethimide, anagrelide, asparaginase, bryostatin-1, cilengitide, elesclomol, eribulin mesylate (E7389), ixabepilone, lonidamine, masoprocol, mitoguanazone, oblimersen, sulindac, testolactone, tiazofurin, a mTOR inhibitor, a PI3K inhibitor, a Cdk4 inhibitor, an Akt inhibitor, a Hsp90 inhibitor, a farnesyltransferase inhibitor and an aromatase inhibitor (anastrozole letrozole exemestane); xiii) a Mek inhibitor; xiv) a tyrosine kinase inhibitor; and xv) an EGFR inhibitor.

16. A method for treatment of a disease or condition modulated by a FLT3 protein kinase, wherein the disease or condition is an inflammatory disease, an inflammatory condition, an autoimmune disease or cancer, said method comprising administering to a subject suffering from the disease a therapeutically effective amount of a compound according to any one of claims 1-12, or a pharmaceutically acceptable salt, a solvate, a tautomer, a stereoisomer, or a deuterated analog thereof, or a pharmaceutical composition of any one of claims 13-15.

17. Use of a compound according to any one of claims 1-12, or a pharmaceutically acceptable salt, a solvate, a tautomer, a stereoisomer, or a deuterated analog thereof, or a

pharmaceutical composition of any one of claims 13-15 in the manufacture of a medicament for the treatment of a disease or condition modulated by a FLT3 protein kinase, wherein the disease or condition is an inflammatory disease, an inflammatory condition, an autoimmune disease or cancer.

18. A method for treating a subject with a disease or condition mediated by a FLT3 or c-Kit protein kinase, said method comprising administering to the subject an effective amount of a compound according to any one of claims 1-12, or a pharmaceutically acceptable salt, a solvate, a deuterated analog, a tautomer or a stereoisomer thereof, or a pharmaceutical composition according to any one of claims 13-15, wherein the disease or condition is acute myeloid leukemia, stem cell ablation and myelopreparation for stem cell transplant, primary progressive multiple sclerosis, complex regional pain syndrome, reflex sympathetic dystrophy, muscular dystrophy, duchenne muscular dystrophy, causalgia, neuro-inflammation, neuroinflammatory disorders, benign forgetfulness, HIV, binswager type dementia, dementia with lewy bodie, prosencephaly, microencepahy, cerebral palsy, congenital hydrocephalus, abdominal dropsy, progressive supranuclear palsy, glaucoma, addiction disorders, dependencies, alcoholism, tremors, Wilson's disease, vascular dementias, multi infarct dementia, fronto temporal dementia, pseudo-dementia, bladder cancer, basal cell carcinoma, cholangiocarcinoma, colon cancer, endometrial cancer, esophageal cancer, Ewing's sarcoma, gastric cancer, glioma, hepatocellular carcinoma, Hodgkin lymphoma, laryngeal carcinoma, leukemia, liver cancer, lung cancer, melanoma, mesothelioma, pancreatic cancer, rectal cancer, renal cancer, squamous cell carcinoma, t cell lymphoma, thyroid cancer, monocytic leukemia, pheochromocytoma, malignant peripheral nerve cell tumors, malignant peripheral nerve sheath tumors (MPNST), cutaneous and plexiform neurofibromas, leiomyoadenomatoid tumor, fibroids, uterine fibroids, leiomyosarcoma, papillary thyroid cancer, anaplastic thyroid cancer, medullary thyroid cancer, follicular thyroid cancer, hurthle cell carcinoma, thyroid cancer, ascites, malignant ascites, mesothelioma, salivary gland tumors, mucoepidermoid carcinoma of the salivary gland, acinic cell carcinoma of the salivary gland, gastrointestinal stromal tumors (GIST), tumors that cause effusions in potential spaces of the body, pleural effusions, pericardial effusions, peritoneal effusions aka ascites, giant cell tumors (GCT), GCT of bone, tumor angiogenesis, or paracrine tumor growth.

19. Use of a compound according to any one of claims 1-12, or a pharmaceutically acceptable salt, a solvate, a deuterated analog, a tautomer or a stereoisomer thereof, or a pharmaceutical composition according to any one of claims 13-15 in the manufacture of a

medicament for the treatment of a disease or condition mediated by a FLT3 or c-Kit protein kinase, wherein the disease or condition is acute myeloid leukemia, stem cell ablation and myelopreparation for stem cell transplant, primary progressive multiple sclerosis, complex regional pain syndrome, reflex sympathetic dystrophy, muscular dystrophy, duchenne muscular dystrophy, causalgia, neuro-inflammation, neuroinflammatory disorders, benign forgetfulness, HIV, binswager type dementia, dementia with lewy bodie, prosencephaly, microencepahy, cerebral palsy, congenital hydrocephalus, abdominal dropsy, progressive supranuclear palsy, glaucoma, addiction disorders, dependencies, alcoholism, tremors, Wilson's disease, vascular dementias, multi infarct dementia, fronto temporal dementia, pseudo-dementia, bladder cancer, basal cell carcinoma, cholangiocarcinoma, colon cancer, endometrial cancer, esophageal cancer, Ewing's sarcoma, gastric cancer, glioma, hepatocellular carcinoma, Hodgkin lymphoma, laryngeal carcinoma, leukemia, liver cancer, lung cancer, melanoma, mesothelioma, pancreatic cancer, rectal cancer, renal cancer, squamous cell carcinoma, t cell lymphoma, thyroid cancer, monocytic leukemia, pheochromocytoma, malignant peripheral nerve cell tumors, malignant peripheral nerve sheath tumors (MPNST), cutaneous and plexiform neurofibromas, leiomyoadenomatoid tumor, fibroids, uterine fibroids, leiomyosarcoma, papillary thyroid cancer, anaplastic thyroid cancer, medullary thyroid cancer, follicular thyroid cancer, hurthle cell carcinoma, thyroid cancer, ascites, malignant ascites, mesothelioma, salivary gland tumors, mucoepidermoid carcinoma of the salivary gland, acinic cell carcinoma of the salivary gland, gastrointestinal stromal tumors (GIST), tumors that cause effusions in potential spaces of the body, pleural effusions, pericardial effusions, peritoneal effusions aka ascites, giant cell tumors (GCT), GCT of bone, tumor angiogenesis, or paracrine tumor growth.

20. A method for treating a subject with a disease or condition mediated by a FLT3 protein kinase, said method comprising administering to the subject an effective amount of a compound according to any one of claims 1-12, or a pharmaceutically acceptable salt, a solvate, a deuterated analog, a tautomer or a stereoisomer thereof, or a pharmaceutical composition according to any one of claims 13-15, wherein the disease or condition is a lysosomal storage disorder selected from the group consisting of mucolipidosis, alpha-mannosidosis; aspartylglucosaminuria; Batten disease; beta-mannosidosis; cystinosis; Danon disease; Fabry disease; Farber disease; fucosidosis; galactosialidosis; Gaucher disease; gangliosidosis; Krabbe disease; metachromatic leukodystrophy; mucopolysaccharidoses disorders; aspartylglucosaminuria; Batten disease; beta-mannosidosis; cystinosis; Danon disease; Fabry disease; Farber disease; fucosidosis; galactosialidosis; Gaucher disease; gangliosidosis; Krabbe disease; metachromatic leukodystrophy; mucopolysaccharidoses disorders; mucolipidosis type I

(Sialidosis); Mucolipidosis type II (I-Cell disease); Mucolipidosis type III (Pseudo-Hurler polydystrophy); Mucolipidosis type IV; multiple sulfatase deficiency; Niemann–Pick types A, B, C; Pompe disease (glycogen storage disease); pycnodysostosis; Sandhoff disease; Schindler disease; Salla disease/sialic acid storage disease; Tay–Sachs; and Wolman disease.

21. Use of a compound according to any one of claims 1-12, or a pharmaceutically acceptable salt, a solvate, a deuterated analog, a tautomer or a stereoisomer thereof, or a pharmaceutical composition according to any one of claims 13-15 in the manufacture of a medicament for the treatment of a disease or condition mediated by a FLT3 protein kinase, wherein the disease or condition is a lysosomal storage disorder selected from the group consisting of mucolipidosis, alpha-mannosidosis; aspartylglucosaminuria; Batten disease; beta-mannosidosis; cystinosis; Danon disease; Fabry disease; Farber disease; fucosidosis; galactosialidosis; Gaucher disease; gangliosidosis; Krabbe disease; metachromatic leukodystrophy; mucopolysaccharidoses disorders; aspartylglucosaminuria; Batten disease; beta-mannosidosis; cystinosis; Danon disease; Fabry disease; Farber disease; fucosidosis; galactosialidosis; Gaucher disease; gangliosidosis; Krabbe disease; metachromatic leukodystrophy; mucopolysaccharidoses disorders; mucolipidosis type I (Sialidosis); Mucolipidosis type II (I-Cell disease); Mucolipidosis type III (Pseudo-Hurler polydystrophy); Mucolipidosis type IV; multiple sulfatase deficiency; Niemann–Pick types A, B, C; Pompe disease (glycogen storage disease); pycnodysostosis; Sandhoff disease; Schindler disease; Salla disease/sialic acid storage disease; Tay–Sachs; and Wolman disease.

22. A method for treating a subject with a disease or condition mediated by a (TGF-β) receptor type 2, said method comprising administering to the subject an effective amount of a compound according to any one of claims 1-12, or a pharmaceutically acceptable salt, a solvate, a deuterated analog, a tautomer or a stereoisomer thereof, or a pharmaceutical composition according to any one of claims 13-15, wherein the disease or condition is fibrosis, cardiovascular disease or cancer.

23. Use of a compound according to any one of claims 1-12, or a pharmaceutically acceptable salt, a solvate, a deuterated analog, a tautomer or a stereoisomer thereof, or a pharmaceutical composition according to any one of claims 13-15 in the manufacture of a medicament for the treatment of a disease or condition mediated by a (TGF-β) receptor type 2, wherein the disease or condition is fibrosis, cardiovascular disease or cancer.