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(71) Applicant: **PLEXXIKON INC.** [US/US]; 91 Bolivar Drive, Berkeley, California 94710 (US).

(72) Inventors: **LIN, Jack**; c/o Plexxikon Inc., 91 Bolivar Drive, Berkeley, California 94710 (US). **BUELL, John**; c/o Plexxikon Inc., 91 Bolivar Drive, Berkeley, California 94710 (US). **CHAN, Katrina**; c/o Plexxikon Inc., 91 Bolivar Drive, Berkeley, California 94710 (US). **EWING, Todd**; c/o Plexxikon Inc., 91 Bolivar Drive, Berkeley, California 94710 (US). **IBRAHIM, Prabha N.**; c/o Plexxikon Inc., 91 Bolivar Drive, Berkeley, California 94710 (US). **NESPI, Marika**; c/o Plexxikon Inc., 91 Bolivar Drive, Berkeley, California 94710 (US). **PHAM, Phuongly**; c/o Plexxikon Inc., 91 Bolivar Drive, Berkeley, California 94710 (US). **SHI, Songyuan**; c/o Plexxikon Inc., 91 Bolivar Drive, Berkeley, California 94710 (US). **SPEVAK, Wayne**; c/o Plexxikon Inc., 91 Bolivar Drive, Berkeley, California 94710 (US). **WU, Guoxian**; c/o Plexxikon Inc., 91 Bolivar Drive, Berkeley, California 94710 (US). **ZHANG, Jiazhong**; c/o Plexxikon Inc., 91 Bolivar Drive, Berkeley, California 94710 (US). **ZHANG, Ying**; c/o Plexxikon Inc., 91 Bolivar Drive, Berkeley, California 94710 (US).

(74) Agents: **TANNER, Lorna L.** et al.; Sheppard Mullin Richter & Hampton LLP, 379 Lytton Avenue, Palo Alto, California 94301-1479 (US).

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

(57) Abstract: Compounds active on c-kit protein kinases or mutant c-kit protein kinases having any mutations are described, as well as methods of making and using such compounds to treat diseases and conditions associated with aberrant activity of the c-kit protein kinases and mutant c-kit protein kinases.

COMPOUNDS AND METHODS FOR KINASE MODULATION, AND INDICATIONS THEREFOR

FIELD

[0001] 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

[0002] Receptor protein tyrosine kinases (RPTKs) regulate key signal transduction cascades that control cellular growth and proliferation. The Stem Cell Factor (SCF) receptor c-kit is a type III transmembrane RPTK that includes five extracellular immunoglobulin (IG) domains, a single transmembrane domain, and a split cytoplasmic kinase domain separated by a kinase insert segment. C-kit plays an important role in the development of melanocytes, mast, germ, and hematopoietic cells.

[0003] Stem Cell Factor (SCF) is a protein encoded by the S1 locus, and has also been called kit ligand (KL) and mast cell growth factor (MGF), based on the biological properties used to identify it (reviewed in Tsujimura, *Pathol Int* 1996, **46**:933-938; Loveland, et al., *J. Endocrinol* 1997, **153**:337-344; Vliagoftis, et al., *Clin Immunol* 1997, **100**:435-440; Broudy, *Blood* 1997, **90**:1345-1364; Pignon, *Hermatol Cell Ther* 1997, **39**:114-116; and Lyman, et al., *Blood* 1998, **91**:1101-1134.). Herein the abbreviation SCF is used to refer to the ligand for the c-Kit RTK.

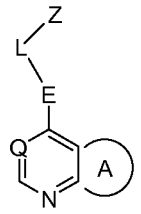
[0004] SCF is synthesized as a transmembrane protein with a molecular weight of 220 or 248 Dalton, depending on alternative splicing of the mRNA to encode exon 6. The larger protein can be proteolytically cleaved to form a soluble, glycosylated protein which noncovalently dimerizes. Both the soluble and membrane-bound forms of SCF can bind to and activate c-Kit. For example, in the skin, SCF is predominantly expressed by fibroblasts, keratinocytes, and endothelial cells, which modulate the activity of melanocytes and mast cells expressing c-Kit. In bone, marrow stromal cells express SCF and regulate hematopoiesis of c-Kit expressing stem cells. In the gastrointestinal tract, intestinal epithelial cells express SCF and affect the interstitial cells of Cajal and intraepithelial lymphocytes. In the testis, sertoli cells and granulosa cells express SCF which regulates spermatogenesis by interaction with c-Kit on germ cells.

[0005] Aberrant expression and/or activation of c-Kit and/or a mutant form(s) of c-kit has been implicated in a variety of pathologic states (Roskoski, 2005, *Biochemical and biophysical Research Comm*. 338: 1307-1315). For example, evidence for a contribution of c-Kit to neoplastic pathology

includes its association with leukemias and mast cell tumors, small cell lung cancer, testicular cancer, and some cancers of the gastrointestinal tract and central nervous system. In addition, c-Kit has been implicated in playing a role in carcinogenesis of the female genital tract sarcomas of neuroectodermal origin, and Schwann cell neoplasia associated with neurofibromatosis. It was found that mast cells are involved in modifying the tumor microenvironment and enhancing tumor growth (Yang et al., *J Clin Invest.* 2003, **112**:1851-1861; Viskochil, *J Clin Invest.* 2003, **112**:1791-1793). Accordingly, there is a need in the art for compounds and methods of use thereof for the modulation of receptor protein kinases. The present disclosure meets this and other needs.

SUMMARY

[0006] In one aspect, the present disclosure provides a compound of formula (I):



I

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

ring A is an optionally substituted 5-membered fused heterocyclic aromatic ring having from 1-2 heteroatoms as ring members selected from O, N or S; or an optionally substituted fused benzene ring; or when ring A is substituted with two or more substituents, two adjacent substituents together with the atoms to which they are attached optionally form a 5- or 6-membered aromatic ring;

E is optionally substituted arylene, optionally substituted heteroarylene, optionally substituted cycloalkylene or optionally substituted heterocyclylene, wherein when E is substituted with two or more substituents, such substituents, together with the atom or atoms to which they attach, form an optionally substituted 3- to 6-membered monocyclic ring or an optionally substituted 7- to 9-membered bicyclic ring;

L is selected from a bond, $-N(R^a)SO_2-$, $-SO_2N(R^a)-$, $-N(R^a)SO_2N(R^a)-$, $-N(R^a)C(O)-$, $-C(O)N(R^a)-$, $-C(O)N(R^a)-SO_2-$, $-SO_2-$, $-C(O)O-$, $-C(O)-$, $-N(R^a)C(O)N(R^a)-$, or $-C(=NR^a)N(R^a)-$, wherein R^a is independently H, C_{1-4}alkyl or C_{1-4} haloalkyl;

Q is N or CH;

Z is selected from H, optionally substituted aryl, optionally substituted aryl-C_{1-4}alkyl, optionally substituted heteroaryl, optionally substituted heteroaryl-C_{1-4} alkyl, optionally substituted heterocycloalkyl, optionally substituted C_{1-6}alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkyl-C_{1-4}alkyl, optionally substituted heterocyclyl or optionally substituted heterocyclyl-C_{1-4}alkyl; or when Z is a

substituted aromatic ring having two or more substituents, two adjacent substituents on the aromatic ring taken together with the atoms to which they are attached optionally form a 5- or 6-membered fused ring.

[0007] In another aspect, the disclosure provides a composition. The composition comprises a compound of any of formulas (I), (II), or any of the formulas and subformulas as described herein, or a compound as recited in any of the claims and described herein, or a pharmaceutically acceptable salt, solvate, tautomer or isomer thereof, and a pharmaceutically acceptable excipient or carrier. The disclosure also provides a composition, which includes a compound as recited in the claims and described herein, a pharmaceutically acceptable excipient or carrier, and another therapeutic agent.

[0008] In another aspect, the disclosure provides a method for preparing a compound of formula (I), (II) and any of the subgeneric formulas.

[0009] In another aspect, the disclosure provides a method for modulating a protein kinase. The method includes administering to a subject in need thereof a compound of any of formulas (I), (II), or any of the formulas and subformulas as described herein, or a compound as recited in any of the claims and described herein, or a pharmaceutically acceptable salt, solvate, tautomer or isomers thereof, or a pharmaceutical composition as described herein. In some embodiments, the protein kinase is a c-kit protein kinase or a mutant c-kit protein kinase.

[0010] In still another aspect, the disclosure provides a method for treating a subject suffering from or at risk of diseases or conditions mediated by a protein kinase. The method includes administering to the subject an effective amount of a compound of any of formulas (I), (II) or any of the subformulas, or a compound as recited in any of the claims and described herein, or a pharmaceutically acceptable salt, solvate, tautomer or isomer thereof, or a composition comprising a compound of any of formulas (I), (II) or any of the subformulas described herein, or a compound as recited in any of the claims or described herein, or a pharmaceutically acceptable salt, solvate, tautomer or isomer thereof.

DETAILED DESCRIPTION

I. Definitions

[0011] As used herein the following definitions apply unless clearly indicated otherwise:

[0012] It is noted here that as used in this specification and the appended claims, the singular forms "a," "an," and "the" include plural reference unless the context clearly dictates otherwise.

[0013] "Halogen" or "halo" refers to all halogens, that is, chloro (Cl), fluoro (F), bromo (Br), or iodo (I).

[0014] "Hydroxyl" or "hydroxy" refers to the group -OH.

[0015] "Thiol" refers to the group -SH.

[0016] "Heteroatom" is meant to include oxygen (O), nitrogen (N), and sulfur (S).

[0017] The term "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, alkylamino, alkylthio, alkylene, haloalkyl, arylalkyl, cycloalkylalkyl, heterocycloalkylalkyl, heteroarylalkyl), 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. "Fluoro substituted alkyl" denotes an alkyl group substituted with one or more fluoro atoms, such as perfluoroalkyl, where preferably the lower alkyl is substituted with 1, 2, 3, 4 or 5 fluoro atoms, also 1, 2, or 3 fluoro atoms. 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.

[0018] The term "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 being preferred in the present disclosure. 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.

[0019] The term "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. Similarly, the term "alkynyl" 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. 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.

[0020] The term "alkenylene" refers to a linear bivalent hydrocarbon moiety or a branched monovalent hydrocarbon moiety having the number of carbon atoms indicated in the prefix and containing at least one double bond. For example, i.e., C_{2-6} means two to six carbons; C_{2-6} alkenylene is meant to include, but is not limited to, –CH=CH-, $-CH_2-CH=CH-$, $-CH_2-CH=C(CH_3)-$, -CH=CH-CH=CH-, and the like). Similarly, the term "alkynylene" refers to a linear bivalent hydrocarbon moiety or a branched monovalent hydrocarbon moiety containing at least one triple bond and having the number of carbon atoms indicated in the prefix. For example, (i.e., C_{2-6} means two to six carbons; C_{2-6} alkynlene is meant to include, but are not limited to, $-C\equiv C-$, $-C\equiv CCH_2-$, $-CH_2-C\equiv CCH_2-$, $-C\equiv CCH(CH_3)-$, and the like. When a prefix is not included to indicate the number of carbon atoms in an alkenylene or alkynlene portion, the alkenylene 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, or 4 or fewer main chain carbon atoms.

[0021] "Cycloalkyl" or "Carbocycle" by itself or as part of another substituent, 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, more preferably 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" refers to a mono- bicyclic or polycyclic group such as,

for example, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, etc. When used in connection with cycloalkyl substituents, the term "polycyclic" refers herein to fused and non-fused alkyl cyclic structures. "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).

[0022] "Cycloalkylene" by itself or as part of another substituent, refers to a divalent cycloalkyl, where the cycloalkyl as defined above as having 3-10, also 3-8, more preferably 3-6, ring members per ring. Exemplary cycloalkylene includes, e.g., 1,2-, 1,3-, or 1,4- cis or trans-cyclohexylene, 2-methyl-1,4-cyclohexylene, 2,2-dimethyl-1,4-cyclohexylene, and the like.

[0023] "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, preferably 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, more preferably 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.

[0024] "Cycloalkylalkenyl" refers to an -(alkenylene)-cycloalkyl group where alkenylene as defined herein has the indicated number of carbon atoms or if unspecified having six or fewer, preferably 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, more preferably 3-6, ring members per ring. C_{3-8}cycloalkyl-C_{2-4}alkenyl is meant to have 3 to 8 ring carbon atoms and 2 to 4 alkenylene chain carbon atoms. Exemplary cycloalkylalkenyl includes, e.g., 2-cyclopropylvinyl, 2-cyclopentylvinyl, and the like.

[0025] "Cycloalkylalkynyl" refers to an -(alkynylene)-cycloalkyl group where alkynylene as defined herein has the indicated number of carbon atoms or if unspecified having six or fewer, preferably 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, more preferably 3-6, ring members per ring. C_{3-8}cycloalkyl-C_{2-4}alkynyl is meant to have 3 to 8 ring carbon atoms and 2 to 4 alkynylene chain carbon atoms. Exemplary cycloalkylalkynyl includes, e.g., 2-cyclopropylethynyl, 2-cyclobutylethynyl, 2-cyclopentylethynyl and the like.

[0026] "Cycloalkenyl" by itself or as part of another substituent, 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, more preferably 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] "Cycloalkenylene" by itself or as part of another substituent, refers to a divalent cycloalkenyl, where the cycloalkenyl as defined herein having 3-10, also 3-8, more preferably 3-6, ring members per ring. Exemplary cycloalkenylene includes, e.g., cyclohexene-1,4-diyl, 2-methyl-cyclohexene-1,4-diyl, 3-methyl-cyclohexene-1,4-diyl, 3,3-dimethyl-cyclohexene-1,4-diyl, cyclohexene-1,2-diyl, cyclohexene-1,3-diyl, and the like.

[0028] "Haloalkyl," is meant to include alkyl substituted by one to seven halogen atoms. Haloalkyl includes monohaloalkyl and polyhaloalkyl. For example, the term "C_{1-6} haloalkyl" is meant to include trifluoromethyl, difluoromethyl, fluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like.

[0029] "Haloalkoxy" refers to a –O-haloalkyl group, where haloalkyl is as defined herein, e. g., trifluoromethoxy, 2,2,2-trifluoroethoxy, difluoromethoxy, and the like.

[0030] "Alkoxy" refers to a –O-alkyl group, where alkyl is as defined herein. "Cycloalkoxy" refers to a –O-cycloalkyl group, where cycloalkyl is as defined herein. "Fluoro substituted alkoxy" denotes alkoxy in which the alkyl is substituted with one or more fluoro atoms, where preferably the alkoxy is substituted with 1, 2, 3, 4 or 5 fluoro atoms, also 1, 2, or 3 fluoro atoms. 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.

[0031] "Amino" or "amine" denotes the group $-NH_2$.

[0032] "Alkylamino" refers to a –NH-alkyl group, where alkyl is as defined herein. Exemplary alkylamino groups include CH_3NH-, ethylamino, and the like.

[0033] "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.

[0034] "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.

[0035] "Alkylthio" refers to -S-alkyl, where alkyl is as defined herein. Exemplary alkylthio groups include CH_3S-, ethylthio, and the like.

[0036] "Aryl" by itself or as part of another substituent 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, 2-naphthyl and 4-biphenyl. Exemplary aryl groups, such as phenyl or naphthyl, may be optionally fused with a cycloalkyl of preferably 5-7, more preferably 5-6, ring members.

[0037] "Arylene" by itself or as part of another substituent, refers to a divalent aryl, where the aryl is as defined herein. Exemplary arylene includes, e.g., phenylene, biphenylene, and the like.

[0038] "Arylalkyl" 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.

[0039] "Arylalkoxy" refers to –O-(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 arylalkoxy include benzyloxy, phenethyloxy, and the like.

[0040] "Aryloxy" refers to –O-aryl, where the aryl group is as defined herein. Exemplary aryloxy includes, e.g., phenoxy.

[0041] "Arylthio" refers to –S-aryl, where the aryl group is as defined herein. Exemplary arylthio includes, e.g., phenylthio.

[0042] "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, preferably 1-4, more preferably 1-3, even more preferably 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, pyridinyl, 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, thienopyridinyl, thienopyrimidinyl, pyrazolopyrimidinyl, imidazopyridines, benzothiaxolyl, benzothienyl, quinolyl, isoquinolyl, indazolyl, pteridinyl and thiadiazolyl. "Nitrogen containing heteroaryl" refers to heteroaryl wherein any of the heteroatoms is N.

[0043] "Heteroarylene" by itself or as part of another substituent, refers to a divalent heteroaryl, where the heteroaryl is as defined herein. Exemplary heteroarylene includes, e.g., pyridine-2,5-diyl, pyrimidine-2,5-diyl, pyridazine-3,5-diyl, pyrazine-2,5-diyl, and the like.

[0044] "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. Non-limiting examples of heteroarylalkyl include 2-pyridylmethyl, 4-pyridylmethyl, 2-thiazolylethyl, and the like.

[0045] "Heterocyclyl", "Heterocycle" or "Heterocyclic" refers to a saturated or unsaturated non-aromatic mono- or bicyclic radical group containing at least one heteroatom independently selected from oxygen (O), nitrogen (N) or sulfur (S). Each heterocycle can be attached at any available ring carbon or heteroatom. Each heterocycle may have one or more rings. When multiple rings are present, they can be fused together or linked covalently. Each heterocycle typically contains 1, 2, 3, 4 or 5, independently selected heteroatoms. Preferably, these groups contain 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms, 0, 1, 2, 3, 4 or 5 nitrogen atoms, 0, 1 or 2 sulfur atoms and 0, 1 or 2 oxygen atoms. More preferably, these groups contain 1, 2 or 3 nitrogen atoms, 0-1 sulfur atoms and 0-1 oxygen atoms. Non-limiting examples of heterocyclyl groups include morpholin-3-one, piperazine-2-one, piperazin-1-oxide, pyridine-2-one, piperidine, morpholine, piperazinyl, isoxazoline, pyrazoline, imidazoline, pyrazol-5-one, pyrrolidine-2,5-dione, imidazolidine-2,4-dione, pyrrolidine, tetrahydroquinolinyl, decahydroquinolinyl, tetrahydrobenzooxazepinyl dihydrodibenzooxepin and the like.

[0046] "Heterocyclylene" by itself or as part of another substituent, refers to a divalent heterocyclyl, where the heterocyclyl is as defined herein. Exemplary heterocyclylene includes, e.g., piperazine-1,4-diyl, piperidine-1,4-diyl, 1,2,3,6-tetrahydropyridine-1,4-diyl, 3-azabicyclo[3.2.1]octane-3,8-diyl, 3,8-diazabicyclo[3.2.1]octane-3,8-diyl, 8-azabicyclo[3.2.1]octane-3,8-diyl, 2-azabicyclo[2.2.2]octane-2,5-diyl, 2,5-diazabicyclo[2.2.2]octane-2,5-diyl, 2,3,6,7-tetrahydro-1H-azepine-1,4-diyl, 2,3,6,7-tetrahydro-1H-azepine-1,5-diyl, 2,5-dihydro-1H-pyrrole-1,3-diyl and the like.

[0047] "Heterocyclylalkyl" refers to -(alkylene)-heterocyclyl, 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 heterocyclyl is as defined herein. Exemplary heterocyclylalkyl includes, e.g., pyrrolidin-1-ylmethyl, 2-piperidinylmethyl, and the like.

[0048] "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, preferably 4 to 10 ring atoms, more preferably 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 with a cycloalkyl, an aryl or a heteroaryl ring. Non limiting examples of heterocycloalkyl groups include pyrrolidinyl, piperidinyl, imidazolidinyl, pyrazolidinyl, butyrolactam moiety, valerolactam moiety, imidazolidinone moiety, hydantoin, dioxolane moiety, phthalimide moiety, piperidine, 1,4-dioxane moiety, morpholinyl, thiomorpholinyl, thiomorpholinyl-S-oxide, thiomorpholinyl-S,S-oxide, piperazinyl, pyranyl, pyridine moiety, 3-pyrrolinyl, thiopyranyl, pyrone moiety, tetrahydrofuranyl, tetrahydrothiophenyl, quinuclidinyl, and the like. A heterocycloalkyl group can be attached to the remainder of the molecule through a ring carbon or a heteroatom. As used herein, the term "Heterocycloalkylene" by itself or as part of another substituent, refers to a divalent heterocycloalkyl, where the heterocycloalkyl is as defined herein. Non-limiting examples of heterocycloalkylene include piperidine-1,4-diyl, 1,2,3,6-tetrahydropyridine-1,4-diyl, 1,2,3,6-tetrahydropyridine-1,5-diyl, 2,3,6,7-tetrahydro-1H-azepine-1,4-diyl, 2,3,6,7-tetrahydro-1H-azepine-1,5-diyl, 2,5-dihydro-1H-pyrrole-1,3-diyl and the like.

[0049] "Heterocycloalkylalkyl" 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. Non-limiting examples of heterocycloalkylalkyl include 2-pyridylmethyl, 2-thiazolylethyl, and the like.

[0050] The substituents for alkyl, alkoxy, haloalkyl, haloalkoxy, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heterocyclyl, alkylene, alkenylene, or alkynlene include, but are not limited to, R', halogen, -OH, $-NH_2$, $-NO_2$, -CN, -C(O)OH, -C(S)OH, $-C(O)NH_2$, $-C(S)NH_2$, $-S(O)_2NH_2$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHS(O)_2NH_2$, $-C(NH)NH_2$, -OR', -SR', -OC(O)R', -OC(S)R', -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -S(O)R', $-S(O)_2R'$, -C(O)NHR', -C(S)NHR', -C(O)NR'R'', -C(S)NR'R'', $-S(O)_2NHR'$, $-S(O)_2NR'R''$, -C(NH)NHR', -C(NH)NR'R'', -NHC(O)R', -NHC(S)R', -NR''C(O)R', -NR'C(S)R'', $-NHS(O)_2R'$, $-NR'S(O)_2R''$, -NHC(O)NHR', -NHC(S)NHR', $-NR'C(O)NH_2$,

-NR'C(S)NH_2, -NR'C(O)NHR", -NR'C(S)NHR", -NHC(O)NR'R", -NHC(S)NR'R", -NR'C(O)NR"R"', -NR"'C(S)NR'R", -NHS(O)$_2$NHR', -NR'S(O)$_2NH_2$, -NR'S(O)$_2$NHR", -NHS(O)$_2$NR'R", -NR'S(O)$_2$NR"R"', -NHR', and -NR'R" in a number ranging from zero to (2m'+1), where m' is the total number of carbon atoms in such group. R', R" and R"' each independently refer to hydrogen, C_{1-8} alkyl, heterocycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, aryl substituted with 1-3 halogens, C_{1-8} alkoxy, haloalkyl, haloalkoxy or C_{1-8} thioalkoxy groups, or unsubstituted aryl-C_{1-4} alkyl groups. When R' and R" are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 3-, 4-, 5-, 6-, or 7-membered ring. For example, -NR'R" is meant to include 1-pyrrolidinyl and 4-morpholinyl. R', R" and R"' can be further substituted with R^{a1}, halogen, -OH, -NH_2, -NO_2, -CN, -C(O)OH, -C(S)OH, -C(O)NH_2, -C(S)NH_2, -S(O)$_2NH_2$, -NHC(O)NH_2, -NHC(S)NH_2, -NHS(O)$_2NH_2$, -C(NH)NH_2, -OR^{a1}, -SR^{a1}, -OC(O)R^{a1}, -OC(S)R^{a1}, -C(O)R^{a1}, -C(S)R^{a1}, -C(O)OR^{a1}, -C(S)OR^{a1}, -S(O)R^{a1}, -S(O)$_2$R^{a1}, -C(O)NHR^{a1}, -C(S)NHR^{a1}, -C(O)NR^{a1}R^{a2}, -C(S)NR^{a1}R^{a2}, -S(O)$_2$NHR^{a1}, -S(O)$_2$NR^{a1}R^{a2}, -C(NH)NHR^{a1}, -C(NH)NR^{a1}R^{a2}, -NHC(O)R^{a1}, -NHC(S)R^{a1}, -NR^{a2}C(O)R^{a1}, -NR^{a1}C(S)R^{a2}, -NHS(O)$_2$R^{a1}, -NR^{a1}S(O)$_2$R^{a2}, -NHC(O)NHR^{a1}, -NHC(S)NHR^{a1}, -NR^{a1}C(O)NH_2, -NR^{a1}C(S)NH_2, -NR^{a1}C(O)NHR^{a2}, -NR^{a1}C(S)NHR^{a2}, -NHC(O)NR^{a1}R^{a2}, -NHC(S)NR^{a1}R^{a2}, -NR^{a1}C(O)NR^{a2}R^{a3}, -NR^{a3}C(S)NR^{a1}R^{a2}, -NHS(O)$_2$NHR^{a1}, -NR^{a1}S(O)$_2NH_2$, -NR^{a1}S(O)$_2$NHR^{a2}, -NHS(O)$_2$NR^{a1}R^{a2}, -NR^{a1}S(O)$_2$NR^{a2}R^{a3}, -NHR^{a1}, and –NR^{a1}R^{a2} in a number ranging from zero to (2n'+1), where n' is the total number of carbon atoms in such group. R^{a1}, R^{a2} and R^{a3} each independently refer to hydrogen, C_{1-8} alkyl, heterocycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, aryl substituted with 1-3 halogens, C_{1-8} alkoxy, haloalkyl, haloalkoxy or C_{1-8} thioalkoxy groups, or unsubstituted aryl-C_{1-4} alkyl groups. R^{a1}, R^{a2} and R^{a3} can be further substituted with R^{b1}, halogen, -OH, -NH_2, -NO_2, -CN, -C(O)OH, -C(S)OH, -C(O)NH_2, -C(S)NH_2, -S(O)$_2NH_2$, -NHC(O)NH_2, -NHC(S)NH_2, -NHS(O)$_2NH_2$, -C(NH)NH_2, -OR^{b1}, -SR^{b1}, -OC(O)R^{b1}, -OC(S)R^{b1}, -C(O)R^{b1}, -C(S)R^{b1}, -C(O)OR^{b1}, -C(S)OR^{b1}, -S(O)R^{b1}, -S(O)$_2$R^{b1}, -C(O)NHR^{b1}, -C(S)NHR^{b1}, -C(O)NR^{b1}R^{b2}, -C(S)NR^{b1}R^{b2}, -S(O)$_2$NHR^{b1}, -S(O)$_2$NR^{b1}R^{b2}, -C(NH)NHR^{b1}, -C(NH)NR^{b1}R^{b2}, -NHC(O)R^{b1}, -NHC(S)R^{b1}, -NR^{b2}C(O)R^{b1}, -NR^{b1}C(S)R^{b2}, -NHS(O)$_2$R^{b1}, -NR^{b1}S(O)$_2$R^{b2}, -NHC(O)NHR^{b1}, -NHC(S)NHR^{b1}, -NR^{b1}C(O)NH_2, -NR^{b1}C(S)NH_2, -NR^{b1}C(O)NHR^{b2}, -NR^{b1}C(S)NHR^{b2}, -NHC(O)NR^{b1}R^{b2}, -NHC(S)NR^{b1}R^{b2}, -NR^{b1}C(O)NR^{b2}R^{b3}, -NR^{b3}C(S)NR^{b1}R^{b2}, -NHS(O)$_2$NHR^{b1}, -NR^{b1}S(O)$_2NH_2$, -NR^{b1}S(O)$_2$NHR^{b2}, -NHS(O)$_2$NR^{b1}R^{b2}, -NR^{b1}S(O)$_2$NR^{b2}R^{b3}, -NHR^{b1}, and –NR^{b1}R^{b2} in a number ranging from zero to (2p'+1), where p' is the total number of carbon atoms in such group. R^{b1}, R^{b2} and R^{b3} each independently refer to hydrogen, C_{1-8} alkyl, heterocycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, aryl substituted with 1-3 halogens, C_{1-8} alkoxy, haloalkyl, haloalkoxy or C_{1-8} thioalkoxy groups, or unsubstituted aryl-C_{1-4} alkyl groups.

[0051] Substituents for the aryl and heteroaryl groups are varied and are generally selected from: R', halogen, -OH, -NH_2, -NO_2, -CN, -C(O)OH, -C(S)OH, -C(O)NH_2, -C(S)NH_2, -S(O)$_2NH_2$, -NHC(O)NH_2, -NHC(S)NH_2, -NHS(O)$_2NH_2$, -C(NH)NH_2, -OR', -SR', -OC(O)R', -OC(S)R', -C(O)R', -C(S)R',

-C(O)OR', -C(S)OR', -S(O)R', -S(O)$_2$R', -C(O)NHR', -C(S)NHR', -C(O)NR'R", -C(S)NR'R", -S(O)$_2$NHR', -S(O)$_2$NR'R", -C(NH)NHR', -C(NH)NR'R", -NHC(O)R', -NHC(S)R', -NR"C(O)R', -NR'C(S)R", -NHS(O)$_2$R', -NR'S(O)$_2$R", -NHC(O)NHR', -NHC(S)NHR', -NR'C(O)NH$_2$, -NR'C(S)NH$_2$, -NR'C(O)NHR", -NR'C(S)NHR", -NHC(O)NR'R", -NHC(S)NR'R", -NR'C(O)NR"R"', -NR"'C(S)NR'R", -NHS(O)$_2$NHR', -NR'S(O)$_2$NH$_2$, -NR'S(O)$_2$NHR", -NHS(O)$_2$NR'R", -NR'S(O)$_2$NR"R"', -NHR', -NR'R", -N$_3$, perfluoro(C$_1$-C$_4$)alkoxy, and perfluoro(C$_1$-C$_4$)alkyl, in a number ranging from zero to the total number of open valences on the aromatic ring system; and where R', R" and R"' are independently selected from hydrogen, haloalkyl, haloalkoxy, C$_{1-8}$ alkyl, C$_{3-6}$ cycloalkyl, cycloalkylalkyl, C$_{2-8}$ alkenyl, C$_{2-8}$ alkynyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryl-C$_{1-4}$ alkyl, and aryloxy-C$_{1-4}$ alkyl. Other suitable substituents include each of the above aryl substituents attached to a ring atom by an alkylene tether of from 1-4 carbon atoms. R', R" and R"' can be further substituted with R^{a1}, halogen, -OH, -NH$_2$, -NO$_2$, -CN, -C(O)OH, -C(S)OH, -C(O)NH$_2$, -C(S)NH$_2$, -S(O)$_2$NH$_2$, -NHC(O)NH$_2$, -NHC(S)NH$_2$, -NHS(O)$_2$NH$_2$, -C(NH)NH$_2$, -OR^{a1}, -SR^{a1}, -OC(O)R^{a1}, -OC(S)R^{a1}, -C(O)R^{a1}, -C(S)R^{a1}, -C(O)OR^{a1}, -C(S)OR^{a1}, -S(O)R^{a1}, -S(O)$_2$R^{a1}, -C(O)NHR^{a1}, -C(S)NHR^{a1}, -C(O)NR^{a1}R^{a2}, -C(S)NR^{a1}R^{a2}, -S(O)$_2$NHR^{a1}, -S(O)$_2$NR^{a1}R^{a2}, -C(NH)NHR^{a1}, -C(NH)NR^{a1}R^{a2}, -NHC(O)R^{a1}, -NHC(S)R^{a1}, -NR^{a2}C(O)R^{a1}, -NR^{a1}C(S)R^{a2}, -NHS(O)$_2$R^{a1}, -NR^{a1}S(O)$_2$R^{a2}, -NHC(O)NHR^{a1}, -NHC(S)NHR^{a1}, -NR^{a1}C(O)NH$_2$, -NR^{a1}C(S)NH$_2$, -NR^{a1}C(O)NHR^{a2}, -NR^{a1}C(S)NHR^{a2}, -NHC(O)NR^{a1}R^{a2}, -NHC(S)NR^{a1}R^{a2}, -NR^{a1}C(O)NR^{a2}R^{a3}, -NR^{a3}C(S)NR^{a1}R^{a2}, -NHS(O)$_2$NHR^{a1}, -NR^{a1}S(O)$_2$NH$_2$, -NR^{a1}S(O)$_2$NHR^{a2}, -NHS(O)$_2$NR^{a1}R^{a2}, -NR^{a1}S(O)$_2$NR^{a2}R^{a3}, -NHR^{a1},–NR^{a1}R^{a2}, -N$_3$, perfluoro(C$_1$-C$_4$)alkoxy, and perfluoro(C$_1$-C$_4$)alkyl, in a number ranging from zero to the total number of open valences on the aromatic ring system; and where R^{a1}, R^{a2} and R^{a3} are each independently selected from hydrogen, haloalkyl, haloalkoxy, C$_{1-8}$ alkyl, C$_{3-6}$ cycloalkyl, cycloalkylalkyl, C$_{2-8}$ alkenyl, C$_{2-8}$ alkynyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryl-C$_{1-4}$ alkyl, or aryloxy-C$_{1-4}$ alkyl. Other suitable substituents include each of the above aryl substituents attached to a ring atom by an alkylene tether of from 1-4 carbon atoms.

[0052] When two substituents are present on adjacent atoms of a substituted aryl or a substituted heteroaryl ring, such substituents may optionally be replaced with a substituent of the formula –T-C(O)-(CH$_2$)$_q$-U-, wherein T and U are independently -NH-, -O-, -CH$_2$- or a single bond, and q is an integer of from 0 to 2. Alternatively, when two substituents are present on adjacent atoms of a substituted aryl or a substituted heteroaryl ring, such substituents may optionally be replaced with a substituent of the formula -A-(CH$_2$)$_r$-B-, wherein A and B are independently -CH$_2$-, -O-, -NH-, -S-, -S(O)-, -S(O)$_2$-, -S(O)$_2$NR'- or a single bond, and r is an integer of from 1 to 3. One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, when two substituents are present on adjacent atoms of a substituted aryl or a substituted heteroaryl ring, such substituents may optionally be replaced with a substituent of the formula -(CH$_2$)$_s$-X-(CH$_2$)$_t$-, where s and t are independently integers

of from 0 to 3, and X is -O-, -NR'-, -S-, -S(O)-, -$S(O)_2$-, or -$S(O)_2$NR'-. The substituent R' in -NR'- and -$S(O)_2$NR'- is selected from hydrogen or unsubstituted C_{1-6} alkyl.

[0053] "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).

[0054] "Optional" or "Optionally" as used throughout the specification 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.

[0055] 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.

[0056] 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.

[0057] "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.

[0058] 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.

[0059] 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.

[0060] In the present context, the term “therapeutically effective” or "effective amount" indicates that a compound or amount of the compound 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.

[0061] Reference to particular amino acid residues in human c-kit polypeptide is defined by the numbering corresponding to the Kit sequence in GenBank NP_000213 (SEQ ID NO:1). Reference to particular nucleotide positions in a nucleotide sequence encoding all or a portion of c-kit is defined by the numbering corresponding to the sequence provided in GenBank NM_000222 (SEQ ID NO:2).

[0062] The terms “kit”, “c-kit”, and "c-Kit" 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 c-kit (e.g., human c-kit, e.g., the sequence NP_000213, 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 c-kit and retains kinase activity. Preferably the sequence identity is at least 95, 97, 98, 99, or even 100%. Preferably 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-kit, allelic variants, and mutated forms (e.g., having activating mutations).

[0063] In the present context, the terms “synergistically effective” or “synergistic effect” indicate that two or more compounds that are therapeutically effective, when used in combination, provide improved

therapeutic effects greater than the additive effect that would be expected based on the effect of each compound used by itself.

[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, or preferably 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. Preferably 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.

[0067] 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.

[0068] 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. Further, by "assaying" is meant the creation of experimental conditions and the gathering of data regarding a particular result of the experimental conditions. For example, enzymes can be assayed based on their ability to act upon a detectable substrate. A compound or ligand can be assayed based on its ability to bind to a particular target molecule or molecules.

[0069] As used herein, the term "modulating" or "modulate" refers to an effect of altering a biological activity, especially a biological activity associated with a particular biomolecule such as a protein kinase. For example, an agonist or antagonist of a particular biomolecule modulates the activity of that

biomolecule, *e.g.*, an enzyme, by either increasing (e.g. agonist, activator), or decreasing (e.g. antagonist, inhibitor) the activity of the biomolecule, such as an enzyme. 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, an enzyme.

[0070] "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.

[0071] "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.

[0072] "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.

[0073] 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.

[0074] 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.

[0075] 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.

[0076] 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.*

[0077] "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.

[0078] 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.

[0079] "Pain" or a "pain condition" can be acute and/or chronic pain, including, without limitation, arachnoiditis; arthritis (e.g. osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, gout); back pain (e.g. sciatica, ruptured disc, spondylolisthesis, radiculopathy); burn pain; cancer pain; dysmenorrhea; headaches (e.g. migraine, cluster headaches, tension headaches); head and facial pain (e.g. cranial neuralgia, trigeminal neuralgia); hyperalgesia; hyperpathia; inflammatory pain (e.g. pain associated with irritable bowel syndrome, inflammatory bowel disease, ulcerative colitis, Crohn's disease, cystitis, pain from bacterial, fungal or viral infection); keloid or scar tissue formation; labor or delivery pain; muscle pain (e.g. as a result of polymyositis, dermatomyositis, inclusion body myositis, repetitive stress injury (e.g. writer's cramp, carpal tunnel syndrome, tendonitis, tenosynovitis)); myofascial pain syndromes (e.g. fibromyalgia); neuropathic pain (e.g. diabetic neuropathy, causalgia, entrapment neuropathy, brachial plexus avulsion, occipital neuralgia, gout, reflex sympathetic dystrophy syndrome, phantom limb or post-amputation pain, postherpetic neuralgia, central pain syndrome, or nerve pain resulting from trauma (e.g.

nerve injury), disease (e.g. diabetes, multiple sclerosis, Guillan-Barre Syndrome, myasthenia gravis, neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, or cancer treatment); pain associated with skin disorders (e.g. shingles, herpes simplex, skin tumors, cysts, neurofibromatosis); sports injuries (e.g. cuts, sprains, strains, bruises, dislocations, fractures, spinal cord, head); spinal stenosis; surgical pain; tactile allodynia; temporomandibular disorders; vascular disease or injury (e.g. vasculitis, coronary artery disease, reperfusion injury (e.g. following ischemia, stroke, or myocardial infarcts)); other specific organ or tissue pain (e.g. ocular pain, corneal pain, bone pain, heart pain, visceral pain (e.g. kidney, gallbladder, gastrointestinal), joint pain, dental pain, pelvic hypersensitivity, pelvic pain, renal colic, urinary incontinence); other disease associated pain (e.g. sickle cell anemia, AIDS, herpes zoster, psoriasis, endometriosis, asthma, chronic obstructive pulmonary disease (COPD), silicosis, pulmonary sarcoidosis, esophagitis, heart burn, gastroesophageal reflux disorder, stomach and duodenal ulcers, functional dyspepsia, bone resorption disease, osteoporosis, cerebral malaria, bacterial meningitis); or pain due to graft v. host rejection or allograft rejections.

[0080] "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.

[0081] As used herein, the term c-kit-mediated disease or condition or kit-mediated disease or condition or KIT-mediated disease or condition refers to a disease or condition in which the biological function of c-kit and/or mutant c-kit affects the development and/or course of the disease or condition, and/or in which modulation of c-kit and/or mutant c-kit alters the development, course, and/or symptoms. For example, mutations in the c-kit gene such as the W42, Wv, and W41 mutations reported by Herbst et al (J. Biol. Chem., 1992, 267: 13210-13216) confer severe, intermediate, and mild phenotypic characteristics, respectively. These mutations attenuate the intrinsic tyrosine kinase activity of the receptor to different degrees and are models for the effect of modulation of c-kit activity. A c-kit mediated disease or condition includes a disease or condition for which c-kit and/or mutant c-kit inhibition provides a therapeutic benefit, e.g. wherein treatment with c-kit inhibitors, including compounds described herein, provides a therapeutic benefit to the subject suffering from or at risk of the disease or condition. As used herein, mutant c-kit, kit or KIT includes kit having one or more of the

mutations selected from D816F, D816H, D816N, D816Y, D816V, K642E, Y823D, Del 550-558, Del 557-561, N822K, V654A, N822H, Del 550-558+V654A, Del 557-561+V654A, Ins503AY, V560G, 558NP, Del 557-558, Del W559-560, F522C, Del 579, R634W, K642E, T801I, C809G, D820Y, N822K, N822H, Y823D, Y823C and T670I. In some instances, KIT mutations include D816F, D816H, D816N, D816Y, D816V, T670I and V654A. In other instances, KIT mutations include D816V and or V560G.

[0082] 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.

[0083] 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.

[0084] 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.

[0085] 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. Preferably the deuterium substituted derivative of the disclosure holds a fully or partially deuterium substituted alkyl, aryl or heteroaryl group.

[0086] 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

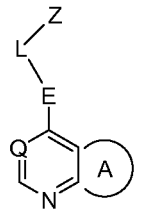
^{14}C) are useful in compound and/or substrate tissue distribution assays. Tritiated (i.e., ^{3}H) and carbon-14 (i.e., ^{14}C) and fluorine-18 (^{18}F) isotopes are useful for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (i.e., ^{2}H) may 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 disclosed in the Schemes and in the Examples herein below, by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

II. General

[0087] The present disclosure concerns compounds of Formulas I, II and all sub-generic formulae, compounds as recited in the claims, and compounds described herein that are modulators of protein kinases, for example without limitation, the compounds are modulators of wild type KIT and/or mutant forms of KIT protein kinases and the use of such compounds in the treatment of diseases or conditions. The kinases can have various levels of inhibitions. In some embodiments, the kinases have less than 20% inhibition at 1 μM. In other embodiments, the kinases have less than 10% inhibition at 1 μM.

III. Compounds

[0088] In one aspect, the present disclosure provides compounds of formula (I):



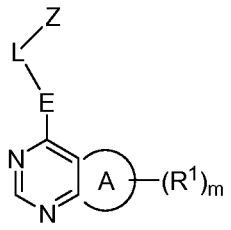
I

or pharmaceutically acceptable salts, hydrates, solvates, tautomers and isomers thereof; wherein the variables and substituents are as defined in the Summary.

[0089] In some embodiments of compounds of formula (I), Q is N and all the other substituents of formula (I) are as defined in any of the embodiments described herein. In other embodiments of the compounds of formula (I), Q is CH and all the other substituents of formula (I) are as defined in any of the embodiments described herein. In some preferred embodiments, the compounds have molecular weights less than 800, preferably, the compounds have molecular weights less than 600, more preferably, the compounds have molecular weights less than 550. In other embodiments, the compounds have molecular weights less than 500. In other embodiments, the compounds have molecular weights less than 450. In yet other embodiments, the compounds have molecular weights less than 400.

[0090] In some embodiments of compounds of formula (I), A is a 5- or 6-membered heterocyclic aromatic ring. In other embodiments, A is a 5- or 6-membered aromatic carbocyclic ring. In some embodiments, the 5- or 6-membered ring in Z is a heterocyclic ring. In other embodiments, the 5- or 6-membered ring in Z is a carbocyclic ring.

[0091] In some embodiments of compounds of formula (I), the disclosure provides compounds having formula (II):



II

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

ring A is 5-membered fused heterocyclic aromatic ring having from 1-2 heteroatoms as ring members selected from O, N or S; or a fused benzene ring;

E is arylene, heteroarylene, cycloalkylene or heterocyclylene, each of which is optionally substituted with from 1-4 R^m substituents, wherein each R^m is independently selected from C_{1-4} alkyl, halogen, -CN, C_{1-4}haloalkyl or C_{1-4}haloalkoxy; or two R^m substituents on the heterocyclylene are taken together to form a $-(CH_2)_n-$ bridging linkage, which together with the atoms to which they are attached forms a 7- to 9-membered bicyclic ring, wherein n is 1, 2 or 3 and wherein the bicyclic ring is optionally substituted with from 1-2 R^n substituents independently selected from C_{1-4} alkyl or halogen, $-OCH_3$, CF_3, CN, $-OCF_3$, $-CHF_2$ or $-OCHF_2$; or two R^m substituents when attaching to the same carbon atom of the cycloalkylene or heterocyclylene are optionally taken together with the atom to which they attach form a 3- to 6-membered monocyclic ring, which is optionally substituted with 1-2 R^n substituents; or two R^m substituents when attaching to the same carbon atom of the cycloalkylene or heterocyclylene are optionally taken together with the atom to which they attach form a –C(=O)- linkage;

L is selected from a bond, $-N(R^a)SO_2-$, $-SO_2N(R^a)-$, $-N(R^a)SO_2N(R^a)-$, $-N(R^a)C(O)-$, $-C(O)N(R^a)-$, $-C(O)N(R^a)SO_2-$, $-SO_2-$, -C(O)O-, -C(O)-, $-N(R^a)C(O)N(R^a)-$, or $-C(=NR^a)N(R^a)-$, wherein R^a, is independently H or C_{1-4}alkyl;

Z is selected from H, aryl, aryl-C_{1-4}alkyl, heteroaryl, heteroaryl-C_{1-4} alkyl, heterocycloalkyl, C_{1-6}alkyl, C_{3-6}cycloalkyl, $-N(R^b)(R^c)$, cycloalkyl-C_{1-4}alkyl, heterocyclyl or heterocyclyl-C_{1-4}alkyl, wherein the aliphatic or aromatic portion of Z is each independently optionally substituted with from 1-3 R^d groups, wherein each R^d is independently selected from C_{1-6}alkyl, C_{1-6} haloalkyl, halogen, C_{1-6}alkoxy, C_{1-6} haloalkoxy, C_{3-6}cycloalkyl, heterocycloalkyl, heteroaryl, or R^2; or two adjacent R^d substituents on an

aromatic ring are taken together to form a 5 or 6-membered ring; wherein each R^d group is optionally further substituted with from 1-2 R^e members selected from C_{1-6}alkyl, C_{1-6} haloalkyl, halogen, C_{1-6}alkoxy, C_{1-6} haloalkoxy, NO_2, CN, -OH, $-NH_2$, -C(O)OH, -C(S)OH, $-C(O)NH_2$, $-C(S)NH_2$, $-S(O)_2NH_2$, $-NHC(O)NH_2$, $-NHS(O)_2NH_2$, $-C(NH)NH_2$, $-OR^f$, $-SR^f$, $-OC(O)R^f$, $-OC(S)R^f$, $-C(O)R^f$, $-C(O)OR^f$, $-C(S)OR^f$, $-S(O)R^f$, $-S(O)_2R^f$, $-C(O)NHR^f$, $-C(S)NHR^f$, $-C(O)NR^fR^f$, $-S(O)_2NHR^f$, $-S(O)_2NR^fR^f$, $-C(NH)NHR^f$, $-C(NH)NR^fR^f$, $-NHC(O)R^f$, $-NHC(S)R^f$, $-NR^fC(O)R^f$, $-NHS(O)_2R^f$, $-NR^fS(O)_2R^f$ or $-NHC(O)NHR^f$, wherein R^f is C_{1-6}alkyl or aryl; and wherein R^b and R^c are each independently C_{1-6}alkyl or R^b and R^c together with the nitrogen atom to which they are attached form a 5 or 6-membered ring, which is optionally substituted with 1-3 R^e; and wherein R^2 is halogen, CN, -OH, $-NH_2$, $-NO_2$, -C(O)OH, -C(S)OH, $-C(O)NH_2$, $-C(S)NH_2$, $-S(O)_2NH_2$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHS(O)_2NH_2$, $-C(NH)NH_2$, $-OR^g$, $-SR^g$, $-OC(O)R^g$, $-OC(S)R^g$, $-C(O)R^g$, $-C(S)R^g$, $-C(O)OR^g$, $-C(S)OR^g$, $-S(O)R^g$, $-S(O)_2R^g$, $-C(O)NHR^g$, $-C(S)NHR^g$, $-C(O)NR^gR^g$, $-C(S)NR^gR^g$, $-S(O)_2NHR^g$, $-S(O)_2NR^gR^g$, $-C(NH)NHR^g$, $-C(NH)NR^gR^g$, $-NHC(O)R^g$, $-NHC(S)R^g$, $-NR^gC(O)R^g$, $-NR^gC(S)R^g$, $-NHS(O)_2R^g$, $-NR^gS(O)_2R^g$, $-NHC(O)NHR^g$, $-NHC(S)NHR^g$, $-NR^gC(O)NH_2$, $-NR^gC(S)NH_2$, $-NR^gC(O)NHR^g$, $-NR^gC(S)NHR^g$, $-NHC(O)NR^gR^g$, $-NHC(S)NR^gR^g$, $-NR^gC(O)NR^gR^g$, $-NR^gC(S)NR^gR^g$, $-NHS(O)_2NHR^g$, $-NR^gS(O)_2NH_2$, $-NR^gS(O)_2NHR^g$, $-NHS(O)_2NR^gR^g$, $-NR^gS(O)_2NR^gR^g$, $-NHR^g$ or $-NR^gR^g$, wherein R^g is C_{1-6}alkyl, aryl, aryl-C_{1-2}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkyl-C_{1-4}alkyl, heteroaryl, heteroaryl-C_{1-4}alkyl, heterocycloalkyl or heterocycloalkyl-C_{1-4}alkyl, wherein each R^g is further optionally substituted with 1-3 R^h substituents independently selected from C_{1-6}alkyl, C_{1-6}alkoxy, halogen, C_{1-6} haloalkyl or C_{1-6} haloalkoxy;

each R^1 is independently selected from C_{1-6}alkyl, C_{1-6}alkoxy, C_{2-6}alkenyl, C_{2-6}alkynyl, $-X^1$-aryl, aryl-C_{1-4}alkyl-X^1-, heteroaryl-X^1-, heteroaryl-C_{1-4} alkyl-X^1-, C_{3-6}cycloalkyl-X^1-, C_{3-6}cycloalkyl-C_{1-4}alkyl-X^1-, C_{3-6}cycloalkenyl-X^1-, CH_2=CH-X^1, C_{3-6}cycloalkyl-C_{2-4}alkenyl-X^1, C_{3-6}cycloalkyl-C_{2-4}alkynyl-X^1, heterocyclyl-X^1-, heterocyclyl-C_{1-4}alkyl-X^1- or R^2, wherein X^1 is a bond or –C(O)- and wherein the aliphatic or aromatic portion of R^1 is optionally substituted with from 1-5 R^3 members selected from halogen, vinyl, CN, -OH, $-NH_2$, $-NO_2$, -C(O)OH, -C(S)OH, $-C(O)NH_2$, $-C(S)NH_2$, $-S(O)_2NH_2$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHS(O)_2NH_2$, $-C(NH)NH_2$, $-OR^i$, $-SR^i$, $-OC(O)R^i$, $-OC(S)R^i$, $-C(O)R^i$, $-C(S)R^i$, $-C(O)OR^i$, $-C(S)OR^i$, $-S(O)R^i$, $-S(O)_2R^i$, $-C(O)NHR^i$, $-C(S)NHR^i$, $-C(O)NR^iR^i$, $-C(S)NR^iR^i$, $-S(O)_2NHR^i$, $-S(O)_2NR^iR^i$, $-C(NH)NHR^i$, $-C(NH)NR^iR^i$, $-NHC(O)R^i$, $-NHC(S)R^i$, $-NR^iC(O)R^i$, $-NR^iC(S)R^i$, $-NHS(O)_2R^i$, $-NR^iS(O)_2R^i$, $-NHC(O)NHR^i$, $-NHC(S)NHR^i$, $-NR^iC(O)NH_2$, $-NR^iC(S)NH_2$, $-NR^iC(O)NHR^i$, $-NR^iC(S)NHR^i$, $-NHC(O)NR^iR^i$, $-NHC(S)NR^iR^i$, $-NR^iC(O)NR^iR^i$, $-NR^iC(S)NR^iR^i$, $-NHS(O)_2NHR^i$, $-NR^iS(O)_2NH_2$, $-NR^iS(O)_2NHR^i$, $-NHS(O)_2NR^iR^i$, $-NR^iS(O)_2NR^iR^i$, $-NHR^i$, R^i or $-NR^iR^i$, wherein R^i is each independently C_{1-6}alkyl, aryl, aryl-C_{1-2}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkyl-C_{1-4}alkyl, heteroaryl, heteroaryl-C_{1-4}alkyl, heterocycloalkyl or heterocycloalkyl-C_{1-4}alkyl, wherein each R^i is further optionally substituted with from 1-3 R^j groups independently selected from CN, -OH, $-N(R^k)(R^k)$, $-NO_2$, -C(O)OH, - $C(O)NH_2$, $-S(O)_2NH_2$, $-NHC(O)NH_2$, $-C(NH)NH_2$, $-OC(O)R^k$, $-OC(S)R^k$, $-C(O)R^k$, $-C(S)R^k$, $-C(O)OR^k$, $-S(O)_2R^k$, $-C(O)NHR^k$, C_{1-6}alkyl, C_{1-6}alkoxy, halogen, C_{1-6} haloalkyl or C_{1-6} haloalkoxy,

wherein R^k is C_{1-6}alkyl; or two adjacent R^1 substituents together with the atom to which they are attached form a 4-, 5- or 6-membered carbocyclic ring or heterocyclic ring having from 1-2 heteroatoms as ring members selected from O, N or S; and the subscript m is 0, 1 or 2. In some embodiments, R^m is C_{1-4} alkyl, halogen, -CN, $-OCH_3$, CF_3, CN, $-OCF_3$, $-CHF_2$, -CH2F, $-OCH_2F$ or $-OCHF_2$. In other embodiments, R^m is C_{1-4}alkyl.

[0092] In some embodiments of compounds of formula (II), the subscript m is 1 or 2 and all the other substituents of formula (II) are as defined in any of the embodiments described herein. In one instance, the subscript m is 1. In another instance, the subscript m is 2. In yet another instance, the subscript m is 0.

[0093] In some embodiments of compounds of formula (II), R^1 is independently selected from C_{1-6}alkyl, C_{1-6}alkoxy, C_{2-6}alkenyl, C_{2-6}alkynyl, $-X^1$-aryl, aryl-C_{1-4}alkyl-X^1-, heteroaryl-X^1-, heteroaryl-C_{1-4} alkyl-X^1-, C_{3-6}cycloalkyl-X^1-, C_{3-6}cycloalkenyl-X^1-, C_{3-6}cycloalkyl-C_{1-4}alkyl-X^1-, heterocyclyl-X^1-, heterocyclyl-C_{1-4}alkyl-X^1-, CH_2=CH-X^1, C_{3-6}cycloalkyl-C_{2-4}alkenyl-X^1, C_{3-6}cycloalkyl-C_{2-4}alkynyl-X^1, halogen, CN, -OH, $-NH_2$, $-NO_2$, -C(O)OH, -C(S)OH, $-C(O)NH_2$, $-C(S)NH_2$, $-S(O)_2NH_2$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHS(O)_2NH_2$, $-C(NH)NH_2$, $-OR^g$, $-SR^g$, $-OC(O)R^g$, $-OC(S)R^g$, $-C(O)R^g$, $-C(S)R^g$, $-C(O)OR^g$, $-C(S)OR^g$, $-S(O)R^g$, $-S(O)_2R^g$, $-C(O)NHR^g$, $-C(S)NHR^g$, $-C(O)NR^gR^g$, $-C(S)NR^gR^g$, $-S(O)_2NHR^g$, $-S(O)_2NR^gR^g$, $-C(NH)NHR^g$, $-C(NH)NR^gR^g$, $-NHC(O)R^g$, $-NHC(S)R^g$, $-NR^gC(O)R^g$, $-NR^gC(S)R^g$, $-NHS(O)_2R^g$, $-NR^gS(O)_2R^g$, $-NHC(O)NHR^g$, $-NHC(S)NHR^g$, $-NR^gC(O)NH_2$, $-NR^gC(S)NH_2$, $-NR^gC(O)NHR^g$, $-NR^gC(S)NHR^g$, $-NHC(O)NR^gR^g$, $-NHC(S)NR^gR^g$, $-NR^gC(O)NR^gR^g$, $-NR^gC(S)NR^gR^g$, $-NHS(O)_2NHR^g$, $-NR^gS(O)_2NH_2$, $-NR^gS(O)_2NHR^g$, $-NHS(O)_2NR^gR^g$, $-NR^gS(O)_2NR^gR^g$, $-NHR^g$ or $-NR^gR^g$, wherein R^g is C_{1-6}alkyl, aryl, aryl-C_{1-2}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkyl-C_{1-4}alkyl, heteroaryl, heteroaryl-C_{1-4}alkyl, heterocycloalkyl or heterocycloalkyl-C_{1-4}alkyl, wherein each R^g is further optionally substituted with 1-3 R^h substituents independently selected from C_{1-6}alkyl, $-OCH_3$, $-OCH_2CH_3$, $-O-CH(CH_3)_2$, -Cl, -F, $-CH_2F$, $-CHF_2$, CF_3, $-OCF_3$, $-OCHF_2$ or $-OCH_2F$; wherein X^1 is a bond or –C(O)- and wherein the aliphatic or aromatic portion of R^1 is optionally substituted with from 1-5 R^3 members selected from halogen, CN, -OH, $-NH_2$, $-NO_2$, -C(O)OH, -C(S)OH, $-C(O)NH_2$, $-C(S)NH_2$, $-S(O)_2NH_2$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHS(O)_2NH_2$, $-C(NH)NH_2$, $-OR^i$, $-SR^i$, $-OC(O)R^i$, $-OC(S)R^i$, $-C(O)R^i$, $-C(S)R^i$, $-C(O)OR^i$, $-C(S)OR^i$, $-S(O)R^i$, $-S(O)_2R^i$, $-C(O)NHR^i$, $-C(S)NHR^i$, $-C(O)NR^iR^i$, $-C(S)NR^iR^i$, $-S(O)_2NHR^i$, $-S(O)_2NR^iR^i$, $-C(NH)NHR^i$, $-C(NH)NR^iR^i$, $-NHC(O)R^i$, $-NHC(S)R^i$, $-NR^iC(O)R^i$, $-NR^iC(S)R^i$, $-NHS(O)_2R^i$, $-NR^iS(O)_2R^i$, $-NHC(O)NHR^i$, $-NHC(S)NHR^i$, $-NR^iC(O)NH_2$, $-NR^iC(S)NH_2$, $-NR^iC(O)NHR^i$, $-NR^iC(S)NHR^i$, $-NHC(O)NR^iR^i$, $-NHC(S)NR^iR^i$, $-NR^iC(O)NR^iR^i$, $-NR^iC(S)NR^iR^i$, $-NHS(O)_2NHR^i$, $-NR^iS(O)_2NH_2$, $-NR^iS(O)_2NHR^i$, $-NHS(O)_2NR^iR^i$, $-NR^iS(O)_2NR^iR^i$, $-NHR^i$, R^i or $-NR^iR^i$, wherein R^i is each independently C_{1-6}alkyl, aryl, aryl-C_{1-2}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkyl-C_{1-4}alkyl, heteroaryl, heteroaryl-C_{1-4}alkyl, heterocycloalkyl or heterocycloalkyl-C_{1-4}alkyl, wherein each R^i is further optionally substituted with from 1-3 R^j groups independently selected from CN, -OH, $-N(R^k)(R^k)$, $-NO_2$, -C(O)OH, -

$C(O)NH_2$, $-S(O)_2NH_2$, $-NHC(O)NH_2$, $-C(NH)NH_2$, $-OC(O)R^k$, $-OC(S)R^k$, $-C(O)R^k$, $-C(S)R^k$, $-C(O)OR^k$, $-S(O)_2R^k$, $-C(O)NHR^k$, C_{1-6}alkyl, C_{1-6}alkoxy, halogen, C_{1-6} haloalkyl or C_{1-6} haloalkoxy, wherein R^k is C_{1-6}alkyl; or two adjacent R^1 substituents together with the atom to which they are attached form a 4-, 5- or 6-membered carbocyclic ring or heterocyclic ring having from 1-2 heteroatoms as ring members selected from O, N or S; and the subscript m is 0, 1 or 2. In some instances, X^1 is a bond. In other instances, X^1 is –C(O)-. In some instances, R^g or R^i is each independently $–CH_3$, $-OCH_3$, $-OCH_2CH_3$, $-O-CH(CH_3)_2$, -Cl, -F, $-CH_2F$, $-CHF_2$, CF_3, $-OCF_3$, $-OCHF_2$ or $-OCH_2F$, C_{1-6}alkyl, phenyl, benzyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 3-pyrazolyl, 4-pyrazolyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 2-oxazolyl, 5-oxazolyl, 4-oxazolyl, 2-thiophenyl, 3-thiophenyl, 1-piperidinyl, 4-piperidinyl or 4-morpholinyl. In other instances, R^g or R^i is each independently C_{1-6}alkyl optionally substituted with a member selected from phenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 3-pyrazolyl, 4-pyrazolyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 2-oxazolyl, 5-oxazolyl, 4-oxazolyl, 2-thiophenyl, 3-thiophenyl, 1-piperidinyl, 4-piperidinyl or 4-morpholinyl. In yet other instances, R^j is selected from C_{1-6}alkyl, -CN, $-OCH_3$, $-OCH_2CH_3$, $-O-CH(CH_3)_2$, -Cl, -F, $-CH_2F$, $-CHF_2$, CF_3, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, $-NH-C_{1-6}$alkyl, $-N(C_{1-6}$alkyl$)(C_{1-6}$alkyl). All the other variables Z, L, E and A of formula (II) are as defined in any of the embodiments described herein.

[0094] In some embodiments of compounds of formula (II), R^1 is selected from halogen, -CN, vinyl-X^1, C_{1-6}alkyl-X^1, C_{1-6}alkoxy-X^1, C_{2-6} alkynyl-X^1, C_{3-6} cycloalkyl-X^1, C_{3-6}cycloalkenyl-X^1-, C_{3-6} cycloalkyl-C_{1-4}alkyl-X^1, C_{3-6} cycloalkyl-C_{2-4}alkynyl-X^1, aryl-X^1, aryl-C_{1-4}alkyl-X^1, heteroaryl-X^1, heteroaryl-C_{1-4} alkyl-X^1, heterocyclyl-X^1, heterocyclyl-C_{1-4}alkyl, $-C(O)-R^g$, $-C(O)NHR^g$, $-C(O)NR^gR^g$, $-NHC(O)R^g$, $-NHC(O)NHR^g$, $-NHC(O)NR^gR^g$, $-NR^gR^g$, $-NHR^g$, $-C(O)OR^g$, $-OC(O)R^g$, $-SO_2R^g$, $-NHSO_2R^g$, $-NHSO_2NHR^g$, $-NHSO_2NR^gR^g$, $-SO_2NHR^g$ or $-SO_2NR^gR^g$, wherein at each occurrence R^1 is optionally substituted with from 1-4 R^3 members. In some instances, each R^3 is independently selected from halogen, -CN, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{3-6}cycloalkyl, C_{3-6} cycloalkyl-C_{1-4}alkyl, aryl, aryl-C_{1-4}alkyl, heteroaryl, heteroaryl-C_{1-4} alkyl, heterocyclyl or heterocyclyl-C_{1-4}alkyl or R^2. In other instances, two adjacent R^3 substituents on an aromatic ring are taken together to form a 5 or 6-membered ring having from 0-2 heteroatoms selected from O, N or S. All the other variables Z, L, E and A of formula (II) are as defined in any of the embodiments described herein.

[0095] In some embodiments of compounds of formula (II), R^1 is selected from halogen, CN, vinyl, C_{1-6}alkyl, C_{1-6}alkoxy, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{3-6}cycloalkenyl, C_{3-6} cycloalkyl-C_{1-4}alkyl, C_{3-6} cycloalkyl-C_{2-4}alkynyl, aryl, aryl-C_{1-4}alkyl, heteroaryl, heteroaryl-C_{1-4} alkyl, heterocycloalkyl, heterocycloalkyl-C_{1-4}alkyl, $-C(O)-R^g$, $-C(O)NHR^g$, $-C(O)NR^gR^g$, $-NHC(O)R^g$, $-NHC(O)NHR^g$, $-NHC(O)NR^gR^g$, $-NR^gR^g$, $-NHR^g$, $-C(O)OR^g$, $-OC(O)R^g$, $-SO_2R^g$, $-NHSO_2R^g$, $-NHSO_2NHR^g$, -

$NHSO_2NR^gR^g$, $-SO_2NHR^g$ or $-SO_2NR^gR^g$, each of which is optionally independently substituted with from 1-4 R^3 substituents; or optionally independently substituted with from 1-4 R^i substituents; or optionally independently substituted with from 1-4 R^j substituents; or optionally substituted with from 1-4 R^7 substituents selected from halogen, -CN, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{3-6}cycloalkyl, C_{3-6}cycloalkyl-C_{1-4}alkyl, heterocycloalkyl-C_{1-4}alkyl, $-C(O)-R^i$, $-C(O)NHR^i$, $-C(O)NR^iR^i$, $-NHC(O)R^i$, $-NR^iR^i$, $-NHR^i$, $-C(O)OR^i$, $-OC(O)R^i$, $-SO_2R^i$, $-NHSO_2R^i$, $-SO_2NHR^i$ or $-SO_2NR^iR^i$; or optionally independently substituted with from 1-4 R^8 substituents selected from C_{1-6}alkyl, -OH, -CN, $-NO_2$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-OCH_3$, $-OCH_2CH_3$, $-O-CH(CH_3)_2$, -Cl, -F, $-CH_2F$, $-CHF_2$, CF_3, $-OCF_3$, $-OCHF_2$, or $-OCH_2F$. All the other variables Z, L, E and A of formula (II) are as defined in any of the embodiments as described herein. In some instances, R^i is C_{3-6}cycloalkyl, C_{3-6}cycloalkyl-C_{1-4}alkyl, heterocycloalkyl or heterocycloalkyl-C_{1-4}alkyl.

[0096] In some embodiments of compounds of formula (II), R^1 is selected from aryl, heteroaryl, C_{2-6} alkynyl, C_{3-6}cycloalkenyl, heterocycloalkyl, $-C(O)-R^g$, $-C(O)NHR^g$, $-C(O)NR^gR^g$, $-C(O)OR^g$, $-SO_2NHR^g$ or $-SO_2NR^gR^g$, each of which is optionally substituted with from (i) 1-4 R^3 substituents; or (ii) 1-4 R^i substituents; or (iii) 1-4 R^j substituents; or (iv) 1-4 R^7 substituents selected from halogen, -CN, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{3-6}cycloalkyl, C_{3-6}cycloalkyl-C_{1-4}alkyl, heterocycloalkyl-C_{1-4}alkyl, $-C(O)-R^i$, $-C(O)NHR^i$, $-C(O)NR^iR^i$, $-NHC(O)R^i$, $-NR^iR^i$, $-NHR^i$, $-C(O)OR^i$, $-OC(O)R^i$, $-SO_2R^i$, $-NHSO_2R^i$, $-SO_2NHR^i$ or $-SO_2NR^iR^i$; or (v) 1-4 R^8 substituents independently selected from C_{1-6}alkyl, -OH, -CN, $-NO_2$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-OCH_3$, $-OCH_2CH_3$, $-O-CH(CH_3)_2$, -Cl, -F, $-CH_2F$, $-CHF_2$, CF_3, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, 4-morpholinyl, 1-piperidinyl, cyclopropyl, 1-cyanocyclopropyl, $-C_{1-2}$alkyl-R^o, $C(O)-R^o$, $-C(O)NHR^o$, $-C(O)NR^oR^o$, $-NHC(O)R^o$, $-C(O)OR^o$, $-OC(O)R^o$, $-SO_2R^o$, $-NHSO_2R^o$, $-SO_2NHR^o$, $-SO_2NR^oR^o$, wherein each R^o is independently C_{1-6}alkyl, C_{3-6}cycloalkyl, phenyl or heterocycloalkyl, wherein R^o is further optionally substituted with from 1-3 R^j group; or (vi) 1-4 R^9 substituents selected from F, Cl, I, $-CH_3$, $-OCH_3$, OCH_2CH_3, $-O-CH(CH_3)_2$, -OH, -CN, $-NO_2$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-CH_2F$, $-CHF_2$, CF_3, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, cyclopropyl, 1-cyanocyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, $-NHSO_2CH_3$, $-NH_2C(O)-$, $CH_3NHC(O)-$, NH_2SO_2-, CH_3SO_2-, $(CH_3)_2NC(O)-$, benzyl, benzyl-C(O), $(C_{1-4}$alkyl$)OC(O)-$, cyclopropyl-C(O)-, cyclopropylethyl-C(O)-, cyclobutyl-C(O)-, cyclobutylmethyl-C(O)-, Ph-NH-C(O)-, 4-morpholinyl, 4-morpholinylmethyl, 4-morpholinylethyl, 4-morpholinyl-C(O)-, 1-piperidinyl, 1-piperidinyl-C(O)-, p-CH_3-Ph-SO_2NH-, cyclopropyl-SO_2NH-, cyclobutyl-SO_2NH- or butylSO_2NH-, wherein at each occurrence, R^9 is further optionally substituted with from 1-3 substituents independently selected from –CN, F, Cl, I, $-OCH_3$, C_{1-6}alkyl, cyclopropyl, -OH, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-CH_2F$, $-CHF_2$, CF_3, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, $CH_3C(O)-$, $CH_3C(O)O-$, $CH_3OC(O)-$, $CH_3NHC(O)-$, $CH_3C(O)NH-$, $(CH_3)_2NC(O)-$, $(CH_3)_2NS(O)_2-$, $(CH_3)_2S(O)_2NH-$ or CH_3SO_2. All the other variables Z, L, E and A of formula (II) are as defined in any of the embodiments as described herein.

[0097] In some embodiments of compounds of formula (II), R^1 is selected from halogen, -CN, C_{1-6}alkyl, C_{1-6}alkoxy, 2-pyridyl, 3-pyridyl, 4-pyridyl, phenyl, 1-pyrazolyl, 3-1H-pyrazolyl, 4-1H-pyrazolyl, vinyl, cyclopropyl-ethynyl, cyclobutyl-ethynyl, cyclopentyl-ethynyl, cyclohexyl-ethynyl, 1-cyclopentenyl-ethynyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, 1-piperazinyl, 1-piperidinyl, morpholinyl, 1,2,5,6-terahydropyridin-4-yl, 1,2,5,6-terahydropyridin-3-yl, 2,3-dihydro-1,4-benzodioxin-5-yl, 1,3-benzodioxol-4-yl, 1,3-benzodioxol-5-yl, indanyl, 1,2-benzoxazolyl, 1,3-benzoxazolyl, 1-cyclohexenyl, 1-cyclopentenyl, 1-cyclooctenyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 2-pyrazinyl, 3-pyridazinyl, 4-pyridazinyl, 5,6-dihydro-2H-pyran-4-yl, 5,6-dihydro-2H-pyran-3-yl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 2-imidazolyl, 4-imidazolyl, 1-pyrazolyl, 2-pyrazolyl, 3-pyrazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 3-isothiazolyl, 4-isothiazolyl, 5-isothiazolyl, 1,2,3-triazol-1-yl, 1,2,3-triazol-2-yl, 1,2,3-triazol-3-yl, 1,2,3-triazol-4-yl, 1,2,3-triazol-5-yl, 1,2,4-triazol-1-yl, 1,2,4-triazol-2-yl, 1,2,4-triazol-3-yl, 1,2,4-triazol-4-yl, 1,2,4-triazol-5-yl, 1-oxa-2,3-diazol-4-yl, 1-oxa-2,3-diazol-5-yl, 1-oxa-2,4-diazol-3-yl, 1-oxa-2,4-diazol-5-yl, 1-oxa-2,5-diazol-3-yl, 1-oxa-2,5-diazol-4-yl, 1-thia-2,3-diazol-4-yl, 1-thia-2,3-diazol-5-yl, 1-thia-2,4-diazol-3-yl, 1-thia-2,4-diazol-5-yl, 1-thia-2,5-diazol-3-yl, 1-thia-2,5-diazol-4-yl, 1-tetrazolyl, 3-tetrazolyl, 1H-5-tetrazolyl, 3H-5-tetrazolyl, 2-furanyl, 3-furanyl, 2-thiophenyl or 3-thiophenyl, each of which is optionally substituted with from (i) 1-4 R^3 substituents; or (ii) 1-4 R^i substituents; or (iii) 1-4 R^j substituents; or (iv) 1-4 R^7 substituents selected from halogen, -CN, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{3-6}cycloalkyl, C_{3-6}cycloalkyl-C_{1-4}alkyl, heterocycloalkyl-C_{1-4}alkyl, -C(O)-R^i, -C(O)NHR^i, -C(O)N$R^i R^i$, -NHC(O)R^i, -N$R^i R^i$, -NHR^i, -C(O)OR^i, -OC(O)R^i, -SO_2R^i, -NHSO_2R^i, -SO_2NHR^i or -SO_2N$R^i R^i$; or (v) 1-4 R^8 substituents independently selected from C_{1-6}alkyl, -OH, -CN, -NO_2, -NH_2, -$NHCH_3$, -$N(CH_3)_2$, -OCH_3, -OCH_2CH_3, -O-$CH(CH_3)_2$, -Cl, -F, -CH_2F, -CHF_2, CF_3, -OCF_3, -$OCHF_2$, -OCH_2F, 4-morpholinyl, 1-piperidinyl, cyclopropyl, 1-cyanocyclopropyl, 1-methylcyclopropyl, -C_{1-2}alkyl-R^o, C(O)-R^o, -C(O)NHR^o, -C(O)N$R^o R^o$, -NHC(O)R^o, -C(O)OR^o, -OC(O)R^o, -SO_2R^o, -NHSO_2R^o, -SO_2NHR^o, -SO_2N$R^o R^o$, wherein each R^o is independently C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkylalkyl, phenyl, benzyl or heterocycloalkyl, wherein R^o is further optionally substituted with from 1-3 R^j group; or (vi) 1-4 R^9 substituents selected from F, Cl, I, -CH_3, CD_3, -OCH_3, OCH_2CH_3, -O-$CH(CH_3)_2$, -OH, -CN, -NO_2, -NH_2, -$NHCH_3$, -$N(CH_3)_2$, -CH_2F, -CHF_2, CF_3, -OCF_3, -$OCHF_2$, -OCH_2F, cyclopropyl, 1-methylcyclopropyl, 1-cyanocyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, -$NHSO_2CH_3$, -$NH_2C(O)$-, $CH_3NHC(O)$-, NH_2SO_2-, CH_3SO_2-, $(CH_3)_2NC(O)$-, benzyl, benzyl-C(O), (C_{1-4}alkyl)OC(O)-, cyclopropyl-C(O)-, cyclopropylmethyl-C(O)-, 2-cyclopropylethyl-C(O)-, cyclopropylethyl-C(O)-, cyclobutyl-C(O)-, cyclobutylmethyl-C(O)-, Ph-NH-C(O)-, 4-morpholinyl, 4-morpholinylmethyl, 2-(4-morpholinyl)ethyl 4-morpholinylethyl, 4-morpholinyl-C(O)-, 1-piperidinyl, 1-piperidinyl-C(O)-, p-CH_3-Ph-SO_2NH-, cyclopropyl-SO_2NH-, cyclobutyl-SO_2NH- or butylSO_2NH-, wherein at each occurrence, R^9 is further optionally substituted with from 1-3 R^{10} substituents independently selected from –CN, F, Cl, I, -OCH_3,

C_{1-6}alkyl, cyclopropyl, -OH, -NH_2, -$NHCH_3$, -$N(CH_3)_2$, -CH_2F, -CHF_2, CF_3, -OCF_3, -$OCHF_2$, -OCH_2F, $CH_3C(O)$-, $CH_3C(O)O$-, $CH_3OC(O)$-, $CH_3NHC(O)$-, $CH_3C(O)NH$-, $(CH_3)_2NC(O)$-, $(CH_3)_2NS(O)_2$-,$(CH_3)_2S(O)_2NH$- or CH_3SO_2. All the other variables Z, L, E and A of formula (II) are as defined in any of the embodiments as described herein.

[0098] In some embodiments of compounds of formula (II), R^1 is selected from halogen, -CN, C_{1-6}alkyl, C_{1-6}alkoxy, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-methoxy-4-pyridyl, phenyl, 1-pyrazolyl, 3-1H-pyrazolyl, 4-1H-pyrazolyl, 1-methyl-4-pyrazolyl, 1,3-dimethyl-5-pyrazolyl, vinyl, cyclopropyl-ethynyl, cyclobutyl-ethynyl, cyclopentyl-ethynyl, cyclohexyl-ethynyl, 1-cyclopentenyl-ethynyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, 2-cyclopropylethyl, 2-cyclobutylethyl, 1-methyl-1-cyclopropyl, 1-cyclopropylethyl, 1-methyl-1-cyclobutyl, 1-cyclobutylethyl, methoxymethoxy, 4-morpholinylmethoxy, 1-piperidinylmethoxy, 4,4-difluoropiperidinyl, 4-ethoxycarbonyl-1-piperazinyl, 1-piperazinyl, 1-piperidinyl, 4-morpholinyl, 1,2,3,6-terahydropyridin-4-yl, 1,2,3,6-terahydropyridin-5-yl, 1-cyclopropylcarbonyl-2,3,6-trihydropyridin-4-yl, 2,2,6,6-tetramethyl-1,5-dihydropyridin-4-yl, 2,2,6,6-tetramethyl-1,5-dihydropyridin-3-yl, 1-cyclopropylcarbonyl-2,3,6-trihydropyridin-5-yl, 1-methylsulfonyl-2,3,6-trihydropyridin-4-yl, 1-methylsulfonyl-2,3,6-trihydropyridin-5-yl, 1-(4-morpholinylcarbonyl)-2,3,6-trihydropyridin-4-yl, 1-(4-morpholinylcarbonyl)-2,3,6-trihydropyridin-5-yl, 1-t-butoxycarbonyl-2,3,6-trihydropyridin-4-yl, 1-t-butoxycarbonyl-2,3,6-trihydropyridin-5-yl, 2,3-dihydro-1,4-benzodioxin-5-yl, 1,3-benzodioxol-4-yl, 1,3-benzodioxol-5-yl, indanyl, 1,2-benzoxazolyl, 1,3-benzoxazolyl, 1-cyclohexenyl, 1-cyclopentenyl, 1-cyclooctenyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 2-cyclopropyl-5-pyrimidinyl, 2-cyclopropyl-pyrimidin-5-yl, 2-pyrazinyl, 3-pyridazinyl, 4-pyridazinyl, 5,6-dihydro-2H-pyran-4-yl, 5,6-dihydro-2H-pyran-3-yl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 2-imidazolyl, 4-imidazolyl, 1-pyrazolyl, 2-pyrazolyl, 3-pyrazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 3-isothiazolyl, 4-isothiazolyl, 5-isothiazolyl, 1,2,3-triazol-1-yl, 1,2,3-triazol-2-yl, 1,2,3-triazol-3-yl, 1,2,3-triazol-4-yl, 1,2,3-triazol-5-yl, 1,2,4-triazol-1-yl, 1,2,4-triazol-2-yl, 1,2,4-triazol-3-yl, 1,2,4-triazol-4-yl, 1,2,4-triazol-5-yl, 1-oxa-2,3-diazol-4-yl, 1-oxa-2,3-diazol-5-yl, 1-oxa-2,4-diazol-3-yl, 1-oxa-2,4-diazol-5-yl, 1-oxa-2,5-diazol-3-yl, 1-oxa-2,5-diazol-4-yl, 1-thia-2,3-diazol-4-yl, 1-thia-2,3-diazol-5-yl, 1-thia-2,4-diazol-3-yl, 1-thia-2,4-diazol-5-yl, 1-thia-2,5-diazol-3-yl, 1-thia-2,5-diazol-4-yl, 1-tetrazolyl, 3-tetrazolyl, 1H-5-tetrazolyl, 3H-5-tetrazolyl, 2-furanyl, 3-furanyl, 2-thiophenyl, 3-thiophenyl, 3-chloro-5-thiophenyl or 1-cyclopropylcarbonyl-piperidin-4-yl, each of which is optionally substituted with from 1-4 R^8 substituents; or 1-4 R^9 substituents, wherein at each occurrence, R^9 is further optionally substituted with from 1-3 R^{10} substituents. In some instances, R^o is C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkyl-C_{1-2}alkyl, 4-morpholinyl, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-oxo-1-pyrrolidinyl, phenyl or benzyl, each of which is optionally substituted with 1-3 substituents selected from

–CH_3, -OCH_3, F, Cl, CN, CF_3, CHF_2, CH_2F, -OCF_3, -$N(CH_3)_2$, -$NHCH_3$. All the other variables Z, L, E and A of formula (II) are as defined in any of the embodiments as described herein.

[0099] In some embodiments of compounds of formula (II), R^1 is H, CN, vinyl, deuterated C_{1-6}alkyl, C_{1-6}alkyl, halogen, C_{1-6}alkoxy, 2-cyclopropylethynyl, pyridyl, phenyl, benzyl, pyrazolyl, oxazolyl, thiozolyl, pyrimidinyl, pyrazinyl, pyridazinyl, cyclopropyl, cyclopropylmethyl, cyclopropylcarbonyl, cyclobutyl, cyclobutylmethyl, cyclopentyl, cyclopentylmethyl, cyclohexyl, cyclohexylmethyl, benzoyl, phenylcarbamoyl, piperidinyl, piperazinyl, morpholinyl, cyclopentenyl, cyclohexenyl, 1,2,3,6-tetrahydropyridin-4-yl, 2,3-dihydro-1,4-benzodioxin-5-yl, 1,3-benzodioxol-4-yl, 1,3-benzodioxol-5-yl, indanyl, 1,2-benzoxazolyl, 1,3-benzoxazolyl, each of which is optionally substituted with from 1-4 members independently selected from halogen, –CH_3, CD_3, -OCH_3, CN, CF_3, CF_3O-, -CF_2H, CHF_2O-, -$N(CH_3)_2$, -$NHCH_3$, CH_3CONH-, $NH_2C(O)$-, $CH_3NHC(O)$-, $(CH_3)_2NC(O)$-, cyclopropyl, 1-cyanocyclopropyl, CH_3SO_2NH-, cyclopropyl-SO_2NH-, butyl- SO_2NH-, p-$CH_3C_6H_4SO_2NH$-, NH_2SO_2-, CH_3NHSO_2-, $(CH_3)_2NSO_2$-, morpholinyl, piperidinyl, cyclopropylcarbonyl, cyclobuylcarbonyl, cyclopentylcarbonyl, cyclohexylcarbonyl, 4-morpholinylcarbonyl, piperdinylcarbonyl, piperazinylcarbonyl, t-butoxycarbonyl or 2-(4-morpholinyl)-ethyl. All the other variables Z, L, E and A of formula (II) are as defined in any of the embodiments as described herein.

[0100] In some embodiments of compounds of formula (II), R^1 is aryl optionally substituted with from: (i) 1-3 R^3 substituents; or two adjacent R^3 substituents on R^1, together with the atoms to which they are attached, form a 5- or 6-membered ring having from 0-2 additional heteroatoms selected from O, N or S and optionally substituted with from 1-3 R^j substituents; or (ii) 1-3 R^i substituents; or (iii) 1-3 R^j substituents; or (iv) 1-3 R^7 substituents; or (v) 1-3 R^8 substituents; or (vi) 1-3 R^9 substituents, wherein each of R^1, R^i, R^j, R^7, R^8 or R^9 substituent is further optionally substituted with from 1-3 R^{10} substituents independently selected from –CN, F, Cl, I, -OCH_3, C_{1-6}alkyl, cyclopropyl, -OH, -NH_2, -$NHCH_3$, -$N(CH_3)_2$, -CH_2F, -CHF_2, CF_3, -OCF_3, -$OCHF_2$, -OCH_2F, $CH_3C(O)$-, $CH_3C(O)O$-, $CH_3OC(O)$-, $CH_3NHC(O)$-, $CH_3C(O)NH$-, $(CH_3)_2NC(O)$-, $(CH_3)_2NS(O)_2$-,$(CH_3)_2S(O)_2NH$- or CH_3SO_2. In some instances, R^1 is phenyl, which is optionally substituted with from 1-3 R^8 substituents; or 1-3 R^9 substituents, wherein R^8 and R^9 are each further optionally substituted with 1-3 R^{10} groups. In other instances, R^1 is 1-naphthyl, or 2-naphthyl, each of which is optionally substituted with from 1-3 R^8 substituents; or 1-3 R^9 substituents, wherein R^8 and R^9 are each further optionally substituted with 1-3 R^{10} groups. All the other variables Z, L, E and A of formula (II) are as defined in any of the embodiments as described herein.

[0101] In some embodiments of compounds of formula (II), R^1 is 1H-4-benzotriazolyl, 1H-5-benzotriazolyl, 1H-4-benzimidazolyl, 1H-5-benzimidazolyl, 1H-4-indazolyl, 1H-5-indazolyl, 1H-6-indazolyl, 1H-7-indazolyl, 1H-4-indolyl, 1H-5-indolyl, 1H-6-indolyl, 1H-7-indolyl, 2-oxo-6-indolinyl, 2-

oxo-4-indolinyl, 2-oxo-5-indolinyl, 2-oxo-7-indolinyl, 1,2-benzoxazol-4-yl, 1,2-benzoxazol-5-yl, 1,2-benzoxazol-6-yl, 1,2-benzoxazol-7-yl, 1,3-benzoxazol-4-yl, 1,3-benzoxazol-5-yl, 1,3-benzoxazol-6-yl, 1,3-benzoxazol-7-yl, 1,2-benzothiazol-4-yl, 1,2-benzothiazol-5-yl, 1,2-benzothiazol-6-yl, 1,2-benzothiazol-7-yl, 5-quinolinyl, 6-quinolinyl, 7-quinolinyl, 8-quinolinyl, 5-isoquinolinyl, 6-isoquinolinyl, 7-isoquinolinyl, 8-isoquinolinyl, 5-cinnolinyl, 6-cinnolinyl, 7-cinnolinyl, 8-cinnolinyl, 5-quinazolinyl, 6-quinazolinyl, 7-quinazolinyl, 8-quinazolinyl, 5-quinoxalinyl, 6-quinoxalinyl, 7-quinoxalinyl, 8-quinoxalinyl, 4-indanyl, 5-indanyl, 5-tetralinyl, 6-tetralinyl, 1,3-dihydroisobenzofuran-4-yl, 1,3-dihydroisobenzofuran-5-yl, 2,3-dihydrobenzofuran-4-yl, 2,3-dihydrobenzofuran-5-yl, 2,3-dihydrobenzofuran-6-yl, 2,3-dihydrobenzofuran-7-yl, 1,3-dihydroisobenzothiophen-4-yl, 1,3-dihydroisobenzothiophen-5-yl, 2,3-dihydrobenzothiophen-4-yl, 2,3-dihydrobenzothiophen-5-yl, 2,3-dihydrobenzothiophen-6-yl, 2,3-dihydrobenzothiophen-7-yl, 4-indolinyl, 5-indolinyl, 6-indolinyl, 7-indolinyl, 5-isochromanyl, 6-isochromanyl, 7-isochromanyl, 8-isochromanyl, 5-chromanyl, 6-chromanyl, 7-chromanyl, 8-chromanyl, 2,3-dihydro-1,3-benzothiazo-4-yl, 2,3-dihydro-1,3-benzothiazo-5-yl, 2,3-dihydro-1,3-benzothiazo-6-yl, 2,3-dihydro-1,3-benzothiazo-7-yl, 2,3-dihydro-1,2-benzothiazo-4-yl, 2,3-dihydro-1,2-benzothiazo-5-yl, 2,3-dihydro-1,2-benzothiazo-6-yl, 2,3-dihydro-1,2-benzothiazo-7-yl, 2,3-dihydro-1,3-benzoxazol-4-yl, 2,3-dihydro-1,3-benzoxazol-5-yl, 2,3-dihydro-1,3-benzoxazol-6-yl, 2,3-dihydro-1,3-benzoxazol-7-yl, 2,3-dihydro-1,2-benzoxazol-4-yl, 2,3-dihydro-1,2-benzoxazol-5-yl, 2,3-dihydro-1,2-benzoxazol-6-yl, 2,3-dihydro-1,2-benzoxazol-7-yl, 4-benzofuranyl, 5-benzofuranyl, 6-benzofuranyl, 7-benzofuranyl, 4-benzo[b]thiophenyl, 5-benzo[b]thiophenyl, 6-benzo[b]thiophenyl, 7-benzo[b]thiophenyl, 4-benzo[c]thiophenyl, 5-benzo[c]thiophenyl 2,3-dihydro-1,4-benzodioxin-5-yl, 1,3-benzodioxol-4-yl, 1,3-benzodioxol-5-yl, indanyl, 1,2-benzoxazol-4-yl, 1,2-benzoxazol-5-yl, 1,2-benzoxazol-6-yl, 1,2-benzoxazol-7-yl, 1,3-benzoxazol-4-yl, 1,3-benzoxazol-5-yl, 1,3-benzoxazol-6-yl or 1,3-benzoxazol-7-yl, each of which is optionally substituted with from: (i) 1-3 R^3 substituents; or (ii) 1-3 R^i substituents; or (iii) 1-3 R^j substituents; or (iv) 1-3 R^7 substituents; or (v) 1-3 R^8 substituents; or (vi) 1-3 R^9 substituents, wherein each of R^3, R^i, R^j, R^7, R^8 or R^9 substituent is further optionally substituted with from 1-3 substituents independently selected from –CN, F, Cl, I, -OCH_3, C_{1-6}alkyl, cyclopropyl, -OH, -NH_2, -$NHCH_3$, -$N(CH_3)_2$, -CH_2F, -CHF_2, CF_3, -OCF_3, -$OCHF_2$, -OCH_2F, $CH_3C(O)$-, $CH_3C(O)O$-, $CH_3OC(O)$-, $CH_3NHC(O)$-, $CH_3C(O)NH$-, $(CH_3)_2NC(O)$-, $(CH_3)_2NS(O)_2$-,$(CH_3)_2S(O)_2NH$- or CH_3SO_2. All the other variables Z, L, E and A of formula (II) are as defined in any of the embodiments as described herein.

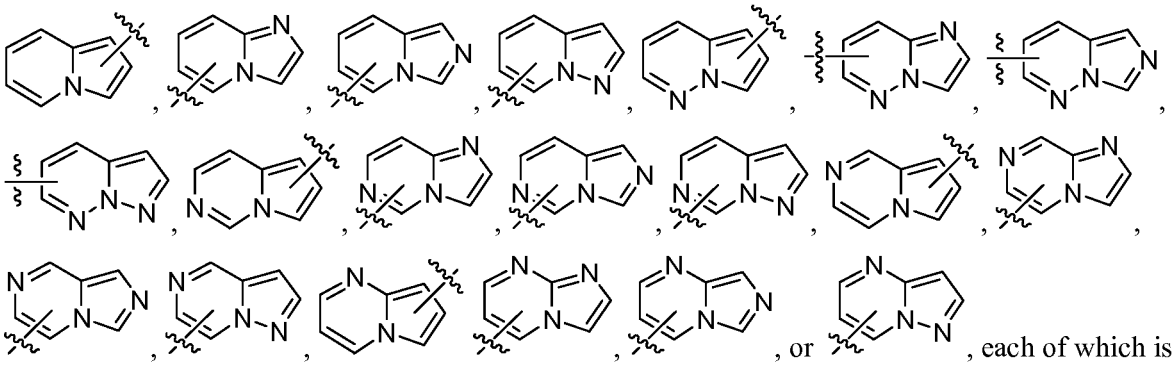
[0102] In some embodiments of compounds of formula (II), R^1 is heteroaryl optionally substituted with from: (i) 1-3 R^3 substituents; or two adjacent R^3 substituents on R^1, together with the atoms to which they are attached, form a 5- or 6-membered ring having from 0-2 additional heteroatoms selected from O, N or S and optionally substituted with from 1-3 R^j substituents; or (ii) 1-3 R^i substituents; or (iii) 1-3 R^j substituents; or (iv) 1-3 R^7 substituents; or (v) 1-3 R^8 substituents; or (vi) 1-3 R^9 substituents, wherein

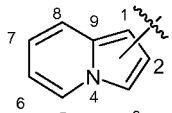
each of R^3, R^i, R^j, R^7, R^8 or R^9 substituent is further optionally substituted with from 1-3 R^{10} substituents independently selected from –CN, F, Cl, I, -OCH_3, C_{1-6}alkyl, cyclopropyl, -OH, -NH_2, -$NHCH_3$, -$N(CH_3)_2$, -CH_2F, -CHF_2, CF_3, -OCF_3, -$OCHF_2$, -OCH_2F, $CH_3C(O)$-, $CH_3C(O)O$-, $CH_3OC(O)$-, $CH_3NHC(O)$-, $CH_3C(O)NH$-, $(CH_3)_2NC(O)$-, $(CH_3)_2NS(O)_2$-,$(CH_3)_2S(O)_2NH$- or CH_3SO_2. In some instances, R^1 is an optionally substituted 5- or 6-membered heteroaryl. All the other variables Z, L, E and A of formula (II) are as defined in any of the embodiments as described herein.

[0103] In some embodiments of compounds of formula (II), R^1 is 5-pyrimidinyl, 2-pyrimidinyl, 4-pyrimidinyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrazinyl, 2-pyridazinyl, 3-pyridazinyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 2-imidazolyl, 4-imidazolyl, 1-pyrazolyl, 2-pyrazolyl, 3-pyrazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 3-isothiazolyl, 4-isothiazolyl, 5-isothiazolyl, 1,2,3-triazol-1-yl, 1,2,3-triazol-2-yl, 1,2,3-triazol-3-yl, 1,2,3-triazol-4-yl, 1,2,3-triazol-5-yl, 1,2,4-triazol-1-yl, 1,2,4-triazol-2-yl, 1,2,4-triazol-3-yl, 1,2,4-triazol-4-yl, 1,2,4-triazol-5-yl, 1-oxa-2,3-diazol-4-yl, 1-oxa-2,3-diazol-5-yl, 1-oxa-2,4-diazol-3-yl, 1-oxa-2,4-diazol-5-yl, 1-oxa-2,5-diazol-3-yl, 1-oxa-2,5-diazol-4-yl, 1-thia-2,3-diazol-4-yl, 1-thia-2,3-diazol-5-yl, 1-thia-2,4-diazol-3-yl, 1-thia-2,4-diazol-5-yl, 1-thia-2,5-diazol-3-yl, 1-thia-2,5-diazol-4-yl, 1-tetrazolyl, 3-tetrazolyl, 1H-5-tetrazolyl, 3H-5-tetrazolyl, 2-furanyl, 3-furanyl, 2-thiophenyl or 3-thiophenyl, each of which is optionally substituted with from: (i) 1-3 R^3 substituents; or (ii) 1-3 R^i substituents; or (iii) 1-3 R^j substituents; or (iv) 1-3 R^7 substituents; or (v) 1-3 R^8 substituents; or (vi) 1-3 R^9 substituents, wherein each of R^3, R^i, R^j, R^7, R^8 or R^9 substituent is further optionally substituted with from 1-3 R^{10} substituents independently selected from –CN, F, Cl, I, -OCH_3, C_{1-6}alkyl, cyclopropyl, -OH, -NH_2, -$NHCH_3$, -$N(CH_3)_2$, -CH_2F, -CHF_2, CF_3, -OCF_3, -$OCHF_2$, -OCH_2F, $CH_3C(O)$-, $CH_3C(O)O$-, $CH_3OC(O)$-, $CH_3NHC(O)$-, $CH_3C(O)NH$-, $(CH_3)_2NC(O)$-, $(CH_3)_2NS(O)_2$-,$(CH_3)_2S(O)_2NH$- or CH_3SO_2. All the other variables Z, L, E and A of formula (II) are as defined in any of the embodiments as described herein.

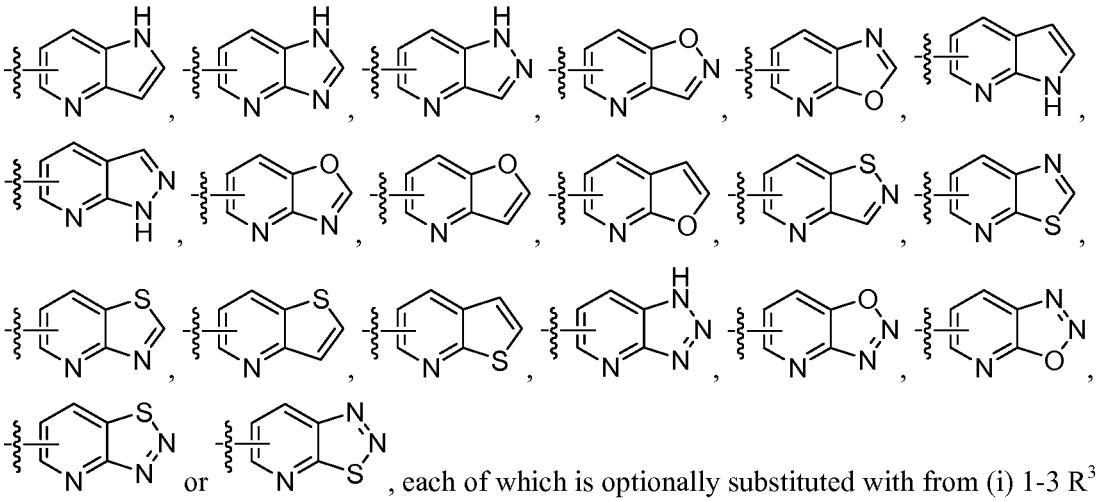
[0104] In some embodiments of compounds of formula (II), R^1 is selected from 1-benzotriazolyl, 1-benzimidazolyl, 1H-2-benzimidazolyl, 1-indazolyl, 1H-3-indazolyl, 1-indolyl, 1H-2-indolyl, 1H-3-indolyl, 1,2-benzoxazol-3-yl, 1,3-benzoxazol-2-yl, 1,2-benzothiazol-3-yl, 1,3-benzothiazol-2-yl, 2-quinolinyl, 3-quinolinyl, 4-quinolinyl, 1-isoquinolinyl, 3-isoquinolinyl, 4-isoquinolinyl, 3-cinnolinyl, 4-cinnolinyl, 2-quinazolinyl, 4-quinazolinyl, 2-quinoxalinyl, 2-benzofuranyl, 3-benzofuranyl, 2-benzo[b]thiophenyl, 3-benzo[b]thiophenyl or 1-benzo[c]thiophenyl each of which is optionally substituted with from: (i) 1-3 R^3 substituents; or (ii) 1-3 R^i substituents; or (iii) 1-3 R^j substituents; or (iv) 1-3 R^7 substituents; or (v) 1-3 R^8 substituents; or (vi) 1-3 R^9 substituents, wherein each of R^3, R^i, R^j, R^7, R^8 or R^9 substituents is further optionally substituted with from 1-3 R^{10} substituents. All the other variables Z, L, E and A of formula (II) are as defined in any of the embodiments as described herein.

[0105] In some embodiments of compounds of formula (II), R^1 is selected from:



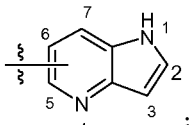
, each of which is optionally substituted with from (i) 1-3 R^3 substituents; or (ii) 1-3 R^i substituents; or (iii) 1-3 R^j substituents; or (iv) 1-3 R^7 substituents; or (v) 1-3 R^8 substituents; or (vi) 1-3 R^9 substituents, wherein each of R^3, R^i, R^j, R^7, R^8 or R^9 substituent is further optionally substituted with from 1-3 R^{10} substituents independently selected from –CN, F, Cl, I, -OCH_3, $C_{1\text{-}6}$alkyl, cyclopropyl, -OH, -NH_2, -$NHCH_3$, -$N(CH_3)_2$, -CH_2F, -CHF_2, CF_3, -OCF_3, -$OCHF_2$, -OCH_2F, $CH_3C(O)$-, $CH_3C(O)O$-, $CH_3OC(O)$-, $CH_3NHC(O)$-, $CH_3C(O)NH$-, $(CH_3)_2NC(O)$-, $(CH_3)_2NS(O)_2$-,$(CH_3)_2S(O)_2NH$- or CH_3SO_2, where the wavy line indicate the point of attachment to the rest of the molecule. The notation  means R^1 can be attached to the rest of the molecule at any of the available positions of the R^1 group set forth above. For example,  is meant to include 1-indolizinyl, 2-indolizinyl, 3-indolizinyl, 4-indolizinyl, 5-indolizinyl, 6-indolizinyl, 7-indolizinyl, and 8-indolizinyl (i.e., substitutions can be at 1, 2, 3, 5, 6, 7 or 8 positions of the indolizine ring).

[0106] In some embodiments of compounds of formula (II), R^1 is selected from:



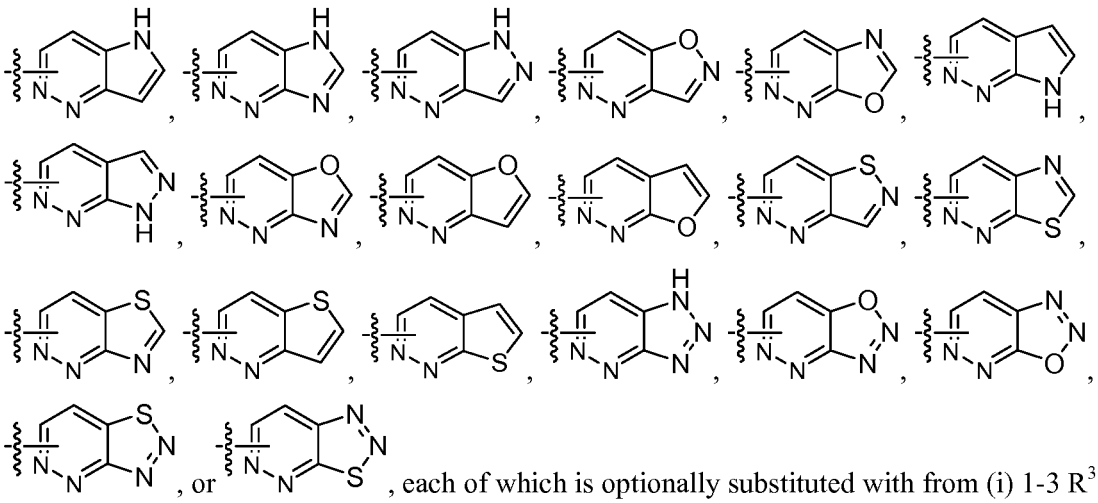
, each of which is optionally substituted with from (i) 1-3 R^3 substituents; or (ii) 1-3 R^i substituents; or (iii) 1-3 R^j substituents; or (iv) 1-3 R^7 substituents; or (v) 1-3 R^8 substituents; or (vi) 1-3 R^9 substituents, wherein each of R^3, R^i, R^j, R^7, R^8 or R^9 substituent is further optionally

substituted with from 1-3 R^{10} substituents independently selected from –CN, F, Cl, I, -OCH_3, C_{1-6}alkyl, cyclopropyl, -OH, -NH_2, -$NHCH_3$, -$N(CH_3)_2$, -CH_2F, -CHF_2, CF_3, -OCF_3, -$OCHF_2$, -OCH_2F, $CH_3C(O)$-, $CH_3C(O)O$-, $CH_3OC(O)$-, $CH_3NHC(O)$-, $CH_3C(O)NH$-, $(CH_3)_2NC(O)$-, $(CH_3)_2NS(O)_2$-,$(CH_3)_2S(O)_2NH$- or CH_3SO_2, where the wavy line indicates the point of attachment to the rest of the molecule. The notation —§— means R^1 can be attached to the rest of the molecule at any of the available positions of the

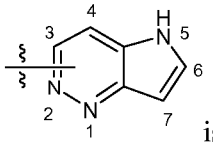


R^1 group set forth above. For example, is meant to include 1H-pyrrolo[3,2-b]pyridin-1-yl, 1H-pyrrolo[3,2-b]pyridin-2-yl, 1H-pyrrolo[3,2-b]pyridin-3-yl, 1H-pyrrolo[3,2-b]pyridin-5-yl, 1H-pyrrolo[3,2-b]pyridin-6-yl and 1H-pyrrolo[3,2-b]pyridin-7-yl (i.e., substitutions can be at 1, 2, 3, 5, 6, or 7 positions of the pyrrolo[3,2-b]pyridine ring). All the other variables Z, L, E and A of formula (II) are as defined in any of the embodiments as described herein.

[0107] In some embodiments of compounds of formula (II), R^1 is selected from:



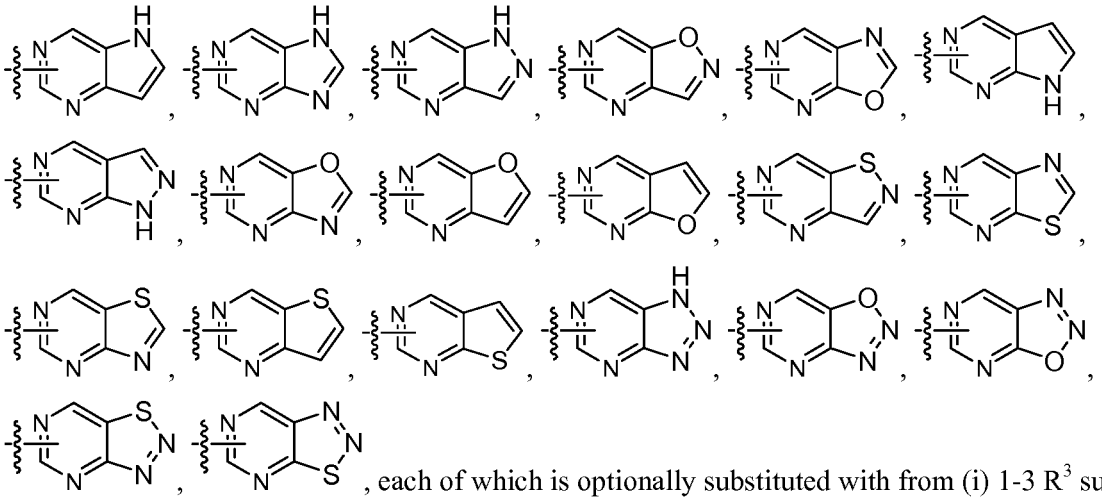
, each of which is optionally substituted with from (i) 1-3 R^3 substituents; or (ii) 1-3 R^i substituents; or (iii) 1-3 R^j substituents; or (iv) 1-3 R^7 substituents; or (v) 1-3 R^8 substituents; or (vi) 1-3 R^9 substituents, wherein each of R^3, R^i, R^j, R^7, R^8 or R^9 substituent is further optionally substituted with from 1-3 R^{10} substituents independently selected from –CN, F, Cl, I, -OCH_3, C_{1-6}alkyl, cyclopropyl, -OH, -NH_2, -$NHCH_3$, -$N(CH_3)_2$, -CH_2F, -CHF_2, CF_3, -OCF_3, -$OCHF_2$, -OCH_2F, $CH_3C(O)$-, $CH_3C(O)O$-, $CH_3OC(O)$-, $CH_3NHC(O)$-, $CH_3C(O)NH$-, $(CH_3)_2NC(O)$-, $(CH_3)_2NS(O)_2$-,$(CH_3)_2S(O)_2NH$- or CH_3SO_2, where the wavy line indicates the point of attachment to the rest of the molecule. The notation —§— means R^1 can be attached to the rest of the molecule at any of the available positions of the

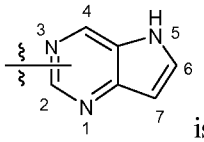


R^1 group set forth above. For example, is meant to include 5H-pyrrolo[3,2-c]pyridazin-

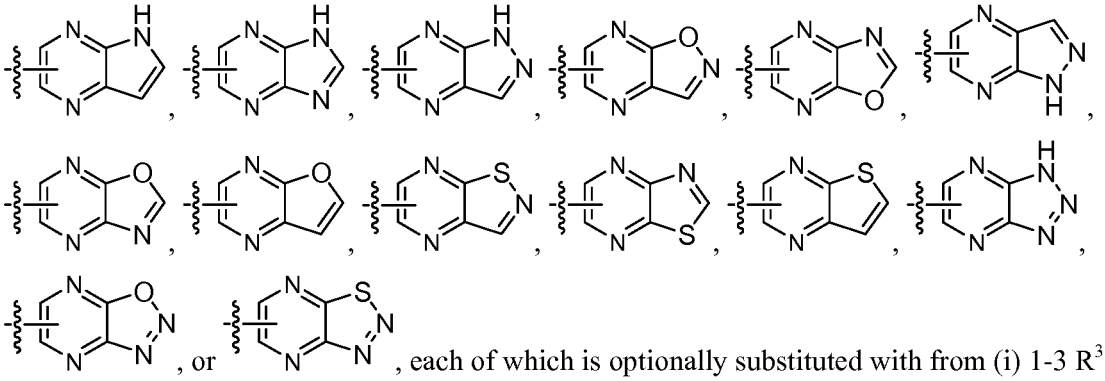
3-yl, 5H-pyrrolo[3,2-c]pyridazin-4-yl, 5H-pyrrolo[3,2-c]pyridazin-5-yl, 5H-pyrrolo[3,2-c]pyridazin-6-yl, 5H-pyrrolo[3,2-c]pyridazin-7-yl (i.e., substitutions can be at 3, 4, 5, 6, or 7 positions of the 5H-pyrrolo[3,2-c]pyridazine ring). All the other variables Z, L, E and A of formula (II) are as defined in any of the embodiments as described herein.

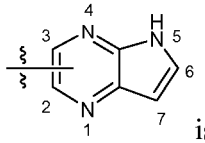
[0108] In some embodiments of compounds of formula (II), R^1 is selected from:



, each of which is optionally substituted with from (i) 1-3 R^3 substituents; or (ii) 1-3 R^i substituents; or (iii) 1-3 R^j substituents; or (iv) 1-3 R^7 substituents; or (v) 1-3 R^8 substituents; or (vi) 1-3 R^9 substituents, wherein each of R^3, R^i, R^j, R^7, R^8 or R^9 substituent is further optionally substituted with from 1-3 R^{10} substituents independently selected from –CN, F, Cl, I, -OCH_3, $C_{1\text{-}6}$alkyl, cyclopropyl, -OH, -NH_2, -$NHCH_3$, -$N(CH_3)_2$, -CH_2F, -CHF_2, CF_3, -OCF_3, -$OCHF_2$, -OCH_2F, $CH_3C(O)$-, $CH_3C(O)O$-, $CH_3OC(O)$-, $CH_3NHC(O)$-, $CH_3C(O)NH$-, $(CH_3)_2NC(O)$-, $(CH_3)_2NS(O)_2$-,$(CH_3)_2S(O)_2NH$- or CH_3SO_2, where the wavy line indicates the point of attachment to the rest of the molecule. The notation means R^1 can be attached to the rest of the molecule at any of the available positions of the R^1 group set forth above. For example,  is meant to include 5H-pyrrolo[3,2-c]pyrimidin-2-yl, 5H-pyrrolo[3,2-c]pyrimidin-4-yl, 5H-pyrrolo[3,2-c]pyrimidin-5-yl, 5H-pyrrolo[3,2-c]pyrimidin-6-yl and 5H-pyrrolo[3,2-c]pyrimidin-7-yl (i.e., substitutions can be at 2, 4, 5, 6, or 7 positions of the 5H-pyrrolo[3,2-c]pyrimidine ring). All the other variables Z, L, E and A of formula (II) are as defined in any of the embodiments as described herein.

[0109] In some embodiments of compounds of formula (II), R^1 is selected from:



, each of which is optionally substituted with from (i) 1-3 R^3 substituents; or (ii) 1-3 R^i substituents; or (iii) 1-3 R^j substituents; or (iv) 1-3 R^7 substituents; or (v) 1-3 R^8 substituents; or (vi) 1-3 R^9 substituents, wherein each of R^3, R^i, R^j, R^7, R^8 or R^9 substituent is further optionally substituted with from 1-3 R^{10} substituents independently selected from –CN, F, Cl, I, -OCH_3, $C_{1\text{-}6}$alkyl, cyclopropyl, -OH, -NH_2, -$NHCH_3$, -$N(CH_3)_2$, -CH_2F, -CHF_2, CF_3, -OCF_3, -$OCHF_2$, -OCH_2F, $CH_3C(O)$-, $CH_3C(O)O$-, $CH_3OC(O)$-, $CH_3NHC(O)$-, $CH_3C(O)NH$-, $(CH_3)_2NC(O)$-, $(CH_3)_2NS(O)_2$-, $(CH_3)_2S(O)_2NH$- or CH_3SO_2, where the wavy line indicates the point of attachment to the rest of the molecule. The notation  means R^1 can be attached to the rest of the molecule at any of the available positions of the R^1 group set forth above. For example,  is meant to include 5H-pyrrolo[2,3-b]pyrazin-2-yl, 5H-pyrrolo[2,3-b]pyrazin-3-yl, 5H-pyrrolo[2,3-b]pyrazin-5-yl, 5H-pyrrolo[2,3-b]pyrazin-6-yl, 5H-pyrrolo[2,3-b]pyrazin-7-yl, (i.e., substitutions can be at 2, 3, 5, 6, or 7 positions of the 5H-pyrrolo[2,3-b]pyrazine ring). All the other variables Z, L, E and A of formula (II) are as defined in any of the embodiments as described herein.

[0110] In some embodiments of compounds of formula (II), R^1 is cycloalkyl or cycloalkenyl, each of which is optionally substituted with from: (i) 1-3 R^3 substituents; or (ii) 1-3 R^i substituents; or (iii) 1-3 R^j substituents; or (iv) 1-3 R^7 substituents; or (v) 1-3 R^8 substituents; or (vi) 1-3 R^9 substituents, wherein each of R^3, R^i, R^j, R^7, R^8 or R^9 substituent is further optionally substituted with from 1-3 R^{10} substituents. All the other variables Z, L, E and A of formula (II) are as defined in any of the embodiments as described herein.

[0111] In some embodiments of compounds of formula (II), R^1 is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 1-cyclopentenyl, 3-cyclopentenyl, 4-cyclopentenyl, 1-cyclohexenyl, 3-cyclohexenyl, 4-cyclohexenyl, 1-cyclohexenyl, 1-octenyl, 1,4-cyclohexadienyl, 1,4-cyclohexadien-3-yl or cyclooctatetraene, each of which is optionally substituted with from: (i) 1-4 R^3 substituents; or (ii) 1-34 R^i substituents; or (iii) 1-4 R^j substituents; or (iv) 1-4 R^7 substituents; or (v) 1-4 R^8 substituents; or (vi) 1-4 R^9 substituents, wherein each of R^3, R^i, R^j, R^7, R^8 or R^9 substituent is further optionally substituted with

from 1-3 R^{10} substituents. In some instances, R^1 is optionally substituted cyclopentenyl, cyclohexenyl or cyclopropyl. All the other variables Z, L, E and A of formula (II) are as defined in any of the embodiments as described herein.

[0112] In some embodiments of compounds of formula (II), R^1 is heterocycloalkyl, optionally substituted with from: (i) 1-4 R^3 substituents; or (ii) 1-4 R^i substituents; or (iii) 1-4 R^j substituents; or (iv) 1-4 R^7 substituents; or (v) 1-4 R^8 substituents; or (vi) 1-4 R^9 substituents, wherein each of R^3, R^i, R^j, R^7, R^8 or R^9 substituent is further optionally substituted with from 1-3 R^{10} substituents. All the other variables Z, L, E and A of formula (II) are as defined in any of the embodiments as described herein.

[0113] In some embodiments of compounds of formula (II), R^1 is 1-aziridinyl, 2-aziridinyl, 1-azetidinyl, 2-azetidinyl, 3-azetidinyl, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2,3-dihydro-1H-pyrrol-1-yl, 2,3-dihydro-1H-pyrrol-2-yl, 2,3-dihydro-1H-pyrrol-3-yl, 2,3-dihydro-1H-pyrrol-4-yl, 2,3-dihydro-1H-pyrrol-5-yl, 2,5-dihydro-1H-pyrrol-1-yl, 2,5-dihydro-1H-pyrrol-2-yl, 2,5-dihydro-1H-pyrrol-3-yl, 2,3-dihydro-1H-imidazol-1-yl, 2,3-dihydro-1H-imidazol-2-yl, 2,3-dihydro-1H-imidazol-4-yl, 2,3-dihydrothiazol-2-yl, 2,3-dihydrothiazol-4-yl, 2,3-dihydrothiazol-5-yl, 2,3-dihydrofuran-2-yl, 2,3-dihydrofuran-3-yl, 2,3-dihydrofuran-4-yl, 2,3-dihydrofuran-5-yl, 2,5-dihydrofuran-2-yl, 2,5-dihydrofuran-3-yl, 2,3-dihydropyran-2-yl, 2,3-dihydropyran-3-yl, 2,3-dihydropyran-4-yl, 2,3-dihydropyran-5-yl, 2,3-dihydropyran-6-yl, 3,6-dihydro-2H-pyran-2-yl, 3,6-dihydro-2H-pyran-3-yl, 3,6-dihydro-2H-pyran-4-yl, 3,6-dihydro-2H-pyran-5-yl, 3,6-dihydro-2H-pyran-6-yl, 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl, 1-piperazinyl, 2-piperazinyl, 2-morpholinyl, 3-morpholinyl, 4-morpholinyl, 1,2,3,6-tetrahydropyridin-1-yl, 1,2,3,6-tetrahydropyridin-1-yl, 1,2,3,6-tetrahydropyridin-2-yl, 1,2,3,6-tetrahydropyridin-3-yl, 1,2,3,6-tetrahydropyridin-4-yl, 1,2,3,6-tetrahydropyridin-5-yl, or 1,2,3,6-tetrahydropyridin-6-yl, each of which is optionally substituted with from: (i) 1-4 R^3 substituents; or (ii) 1-4 R^i substituents; or (iii) 1-4 R^j substituents; or (iv) 1-4 R^7 substituents; or (v) 1-4 R^8 substituents; or (vi) 1-4 R^9 substituents, wherein each of R^3, R^i, R^j, R^7, R^8 or R^9 substituent is further optionally substituted with from 1-3 R^{10} substituents. In some instances, R_1 is 1-aziridinyl, 2-aziridinyl, 2,3-dihydro-1H-pyrrol-5-yl, 2,5-dihydro-1H-pyrrol-3-yl, 2,3-dihydro-1H-imidazol-4-yl, 2,3-dihydrofuran-4-yl, 2,3-dihydrofuran-5-yl, 2,3-dihydrofuran-4-yl, 2,3-dihydrofuran-5-yl, 2,5-dihydrofuran-3-yl, 2,3-dihydropyran-5-yl, 2,3-dihydropyran-6-yl, 3,6-dihydro-2H-pyran-4-yl, 3,6-dihydro-2H-pyran-5-yl, 1,2,3,6-tetrahydropyridin-4-yl or 1,2,3,6-tetrahydropyridin-5-yl, each of which is optionally substituted with from (i) 1-4 R^3 substituents; or (ii) 1-4 R^i substituents; or (iii) 1-4 R^j substituents; or (iv) 1-4 R^7 substituents; or (v) 1-4 R^8 substituents; or (vi) 1-4 R^9 substituents, wherein each of R^3, R^i, R^j, R^7, R^8 or R^9 substituent is further optionally substituted with from 1-3 R^{10} substituents. All the other variables Z, L, E and A of formula (II) are as defined in any of the embodiments as described herein.

[0114] In some embodiments of compounds of formula (II), R^1 is C_{2-4}alkenyl or C_{2-4}alkynyl, each of which is optionally substituted with from: (i) 1-2 R^3 substituent; or (ii) 1-2 R^i substituents; or (iii) 1-2 R^j substituents; or (iv) 1-2 R^7 substituents; or (v) 1-2 R^8 substituents; or (vi) 1-2 R^9 substituents, wherein each of R^3, R^i, R^j, R^7, R^8 or R^9 substituent is further optionally substituted with from 1-3 R^{10} substituents. All the other variables Z, L, E and A of formula (II) are as defined in any of the embodiments as described herein.

[0115] In some embodiments of compounds of formula (II), R^1 is vinyl or cyclopropylethynyl, each of which is optionally substituted with from: (i) 1-2 R^3 substituent; or (ii) 1-2 R^i substituents; or (iii) 1-2 R^j substituents; or (iv) 1-2 R^7 substituents; or (v) 1-2 R^8 substituents; or (vi) 1-2 R^9 substituents, wherein each of R^3, R^i, R^j, R^7, R^8 or R^9 substituent is further optionally substituted with from 1-3 R^{10} substituents. All the other variables Z, L, E and A of formula (II) are as defined in any of the embodiments as described herein.

[0116] In some embodiments of compounds of formula (II), R^1 is halogen, C_{1-6}alkyl, CN, -C_{1-2}alkyl-R^o, -C(O)-R^o, -C(O)NHR^o, -C(O)NR^{o}R^o, -NHC(O)R^o, -C(O)OR^o, -OC(O)R^o, -SO_2R^o, -$NHSO_2R^o$, -SO_2NHR^o, -$SO_2NR^oR^o$, wherein each R^o is independently C_{1-6}alkyl, C_{3-6}cycloalkyl, phenyl or heterocycloalkyl, wherein R^o is further optionally substituted with from 1-3 R^j groups. In some instances, R^o is C_{1-6}alkyl, C_{3-6}cycloalkyl, phenyl, 4-morpholinyl, 1-piperidinyl, 3-piperidinyl, 4-piperidinyl, 1-piperazinyl or 2-piperazinyl, wherein R^o is further optionally substituted with from 1-3 R^j group. All the other variables Z, L, E and A of formula (II) are as defined in any of the embodiments as described herein.

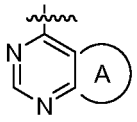
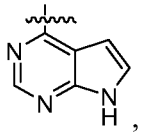
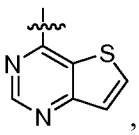
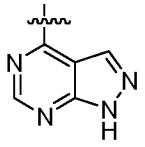
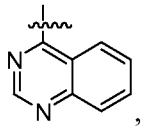
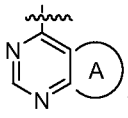
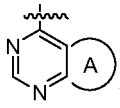
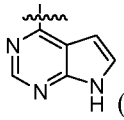
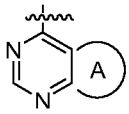
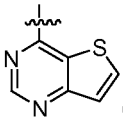
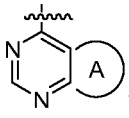
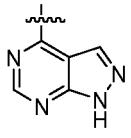
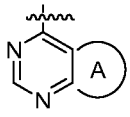
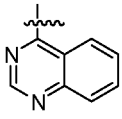
[0117] In some embodiments of compounds of formula (II), two adjacent R^1 substituents together with the atoms to which they are attached form a 5- or 6-membered ring having from 0-2 heteroatoms selected from N, O or S, wherein in the ring is optionally substituted with from (i) 1-3 R^3 substituents; or (ii) 1-3 R^i substituents; or (iii) 1-3 R^j substituents; or (iv) 1-3 R^7 substituents; or (v) 1-3 R^8 substituents; or (vi) 1-4 R^9 substituents, wherein each of R^3, R^i, R^j, R^7, R^8 or R^9 substituent is further optionally substituted with from 1-3 R^{10} substituents. In certain embodiments, the 5- or 6-membered ring is selected from cyclopentane, cyclohexane, pyrrolidine, pyrrole, pyrazole, imidazole, oxazole, isoxazole, thiazole, isothiazole, tetrahydrofuran, tetrahydropyran, 1,4-dioxane, pyridine, pyrazine, piperidine, piperazine, pyrimidine or pyridazine ring system, each of which is optionally substituted with from 1-3 R^8; or 1-3 R^9 substituents wherein R^8 or R^9 substituent is further optionally substituted with from 1-3 R^{10} substituents. All the other variables Z, L, E and A of formula (II) are as defined in any of the embodiments as described herein.

[0118] In some embodiments of compounds of formula (I), ring A is an optionally substituted 5-membered fused heterocyclic aromatic ring having from 1-2 heteroatoms as ring members selected from

O, N or S; or an optionally substituted fused benzene ring; or when ring A is substituted with two or more substituents, two such substituents, together with the atoms to which they are attached, optionally form a 5- or 6-membered ring. All the other variables Z, Q, L and E of formula (I) are as defined in any of the embodiments as described herein.

[0119] In some embodiments of compounds of formula (II), ring A is 5-membered fused heterocyclic aromatic ring having from 1-2 heteroatoms as ring members selected from O, N or S; or a fused benzene ring. All the other variables Z, L, E and R^1 of formula (II) are as defined in any of the embodiments as described herein.

[0120] In certain embodiments of compounds of formula (II), the moiety:

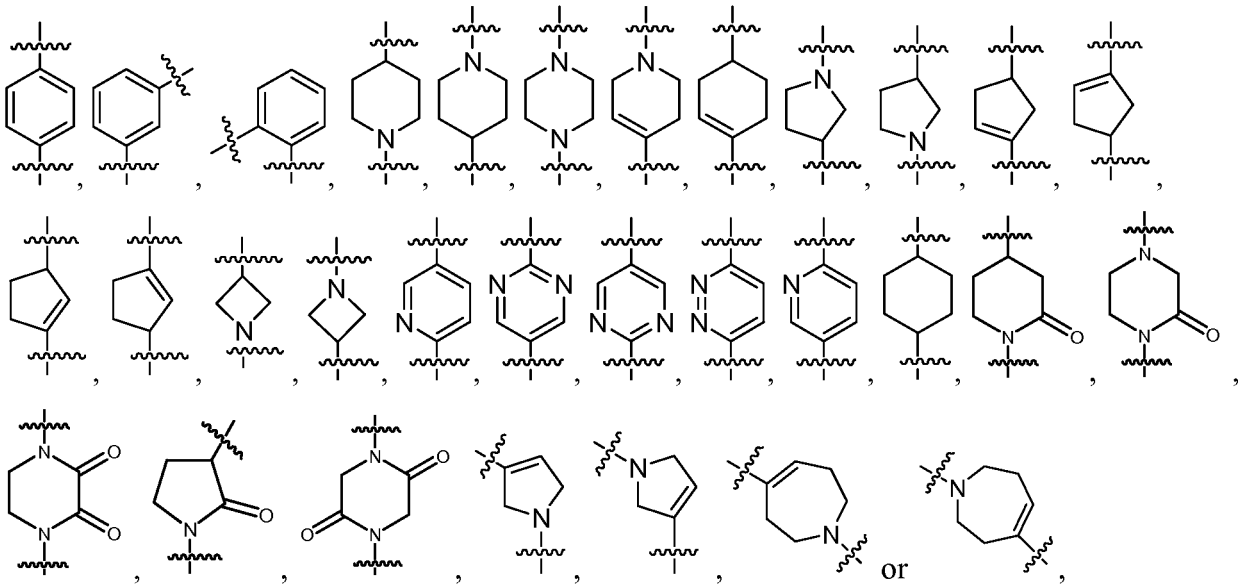

is selected from  ,  ,  or  , each of which is optionally substituted with from 1-2 R^1 groups and the wavy line indicates the point of attachment to the rest of the molecule. In some embodiments,  is substituted with from 1-2 R^1 groups. In one embodiment,  is  (pyrrolo[2,3-d]pyrimidine moiety), optionally substituted with from 1-2 R^1 groups. In other embodiment,  is  (thieno[2,3-d]pyrimidine moiety), optionally substituted with from 1-2 R^1 groups. In yet other embodiment,  is  (pyrazolo[3,4-d]pyrimidine moiety), optionally substituted with from 1-2 R^1 groups. In yet other embodiment,  is  (quinazoline moiety), optionally substituted with from 1-2 R^1 groups. All the other variables Z, L, E and R^1 of formula (II) are as defined in any of the embodiments as described herein.

[0121] In some embodiments of compounds of formula (I), E is optionally substituted arylene, optionally substituted heteroarylene, optionally substituted cycloalkylene or optionally substituted heterocyclylene, wherein when E is substituted with two or more substituents, two such substituents, together with the atom or atoms to which they attach, form an optionally substituted 3- to 6-membered

monocyclic ring or an optionally substituted 7- to 9-membered bicyclic ring. All the other variables A, Z, Q and L of formula (I) are as defined in any of the embodiments as described herein.

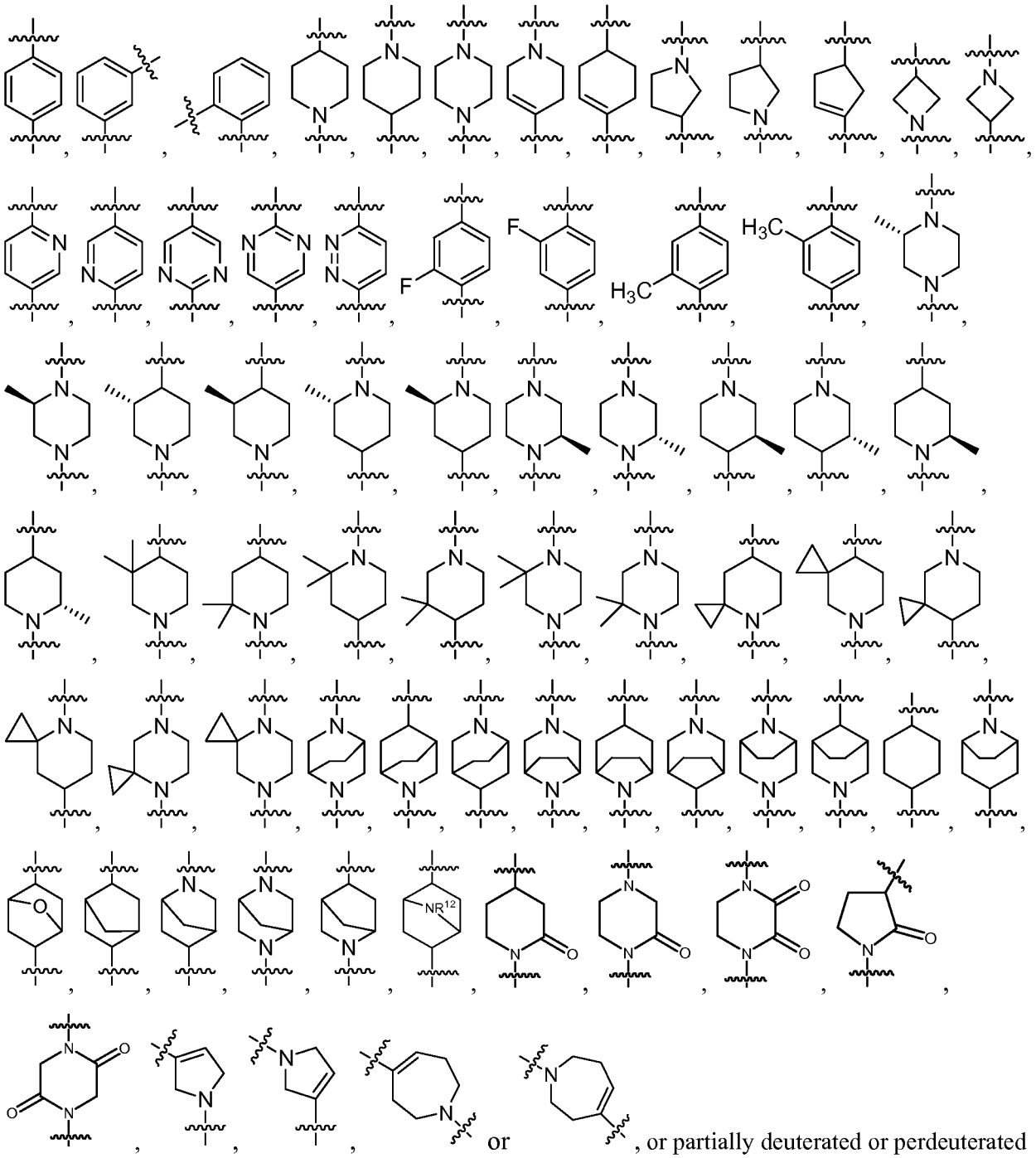
[0122] In some embodiments of compounds of formula (II), E is arylene, heteroarylene, cycloalkylene or heterocyclylene, each of which is optionally substituted with from 1-4 R^m substituents, wherein each R^m is independently selected from C_{1-4} alkyl, C_{1-4}alkoxy, halogen, -CN, C_{1-4}haloalkyl or C_{1-4}haloalkoxy; or two R^m substituents on E are taken together to form a $-(CH_2)_n-$ bridging linkage, which together with the atoms to which they are attached forms a 7- to 9-membered bicyclic ring, wherein the subscript n is 1, 2 or 3 and wherein the bicyclic ring is optionally substituted with from 1-2 R^n substituents independently selected from C_{1-4} alkyl, C_{1-4}alkoxy, halogen, -CN, C_{1-4}haloalkyl or C_{1-4}haloalkoxy; or two R^m substituents, when attaching to the same carbon atom of cycloalkylene or heterocyclylene, are taken together with the atom to which they attach form a 3- to 6-membered monocyclic ring, which is optionally substituted with 1-2 R^n substituents; or two R^m substituents, when attaching to the same carbon atom of cycloalkylene or heterocyclylene, are optionally taken together with the carbon atom to which they are attached form –C(=O)-. In one embodiment, E is arylene. In another embodiment, E is heteroarylene. In yet another embodiment, E is cycloalkylene. In still another embodiment, E is heterocycloalkylene. In some instances, R^m is C_{1-4} alkyl, halogen, -OCH_3, - CF_3, -CN, -OCF_3, -CHF_2, -CH_2F, -OCH_2F or –$OCHF_2$. In other instances, R^m is -OCH_3, - CF_3, -CN, -OCF_3, -CHF_2, -CH_2F, -OCH_2F or –$OCHF_2$. In yet other instances, two R^m substituents, when attaching to the same carbon atom of cycloalkylene or heterocyclylene, are optionally taken together with the carbon atom to which they are attached form a –C(=O)- linkage. In other instances, R^n is C_{1-4} alkyl, halogen, -CN, -OCH_3, CF_3, CN, -OCF_3, -CHF_2 or –$OCHF_2$. In yet other instances, R^n is -OCH_3, CF_3, CN, -OCF_3, -CHF_2 or –$OCHF_2$. All the other variables A, Z, L and R^1 of formula (II) are as defined in any of the embodiments as described herein.

[0123] In some embodiments of compounds of formula (II), E is selected from:



each of which is optionally substituted with 1-2 R^m substituents; or two R^m substituents are taken together to form a $-(CH_2)_n-$ bridging linkage, which together with the atoms to which they are attached forms a 5- to 9-membered bicyclic ring, wherein n is 1, 2 or 3 and wherein the bicyclic ring is optionally substituted with from 1-2 R^n substituents; or two R^m substituents, when attaching to the same carbon atom of the cycloalkylene or heterocyclylene, are taken together with the atom to which they attach form a 3- to 6-membered monocyclic carbocyclic ring, which is optionally substituted with R^n; or two R^m substituents, when attaching to the same carbon atom of the cycloalkylene or heterocycloalkylene, are taken together with the carbon atom to which they are attached form a –C(=O)- linkage; and the wavy line indicates the point of attachment to the rest of the molecule; or the hydrogen atoms in E are optionally replaced with from 1 to 8 deuteriums with at least 52.5%, 60%, 70%, 75%, 80%, 90%, 95%, 99%, 99.5% or 99.9% deuterium incorporation for each deuterium. R^m and R^n are as defined in any of the embodiments as described herein. In certain instances, R^m is C_{1-4} alkyl, halogen, $-OCH_3$, $-CF_3$, -CN, $-OCF_3$, $-CHF_2$, $-CH_2F$, $-OCH_2F$ or $-OCHF_2$. In some instances, each R^m is independently selected from C_{1-4} alkyl or halogen. In one instance, R^m is CH_3, F or Cl. In certain instances, R^n is C_{1-4} alkyl, halogen, -CN, $-OCH_3$, CF_3, CN, $-OCF_3$, $-CHF_2$ or $-OCHF_2$. In one instance, R^n is CH_3, F, Cl, $-OCH_3$, $-CF_3$, -CN, $-OCF_3$, $-CHF_2$ or $-OCHF_2$. In some embodiments, each hydrogen atom in E is optionally replaced by a deuterium atom with at least 52.5%, 60%, 70%, 75%, 80%, 90%, 95%, 99%, 99.5% or 99.9% deuterium incorporation for each deuterium. All the other variables A, Z, L and R^1 of formula (II) are as defined in any of the embodiments as described herein.

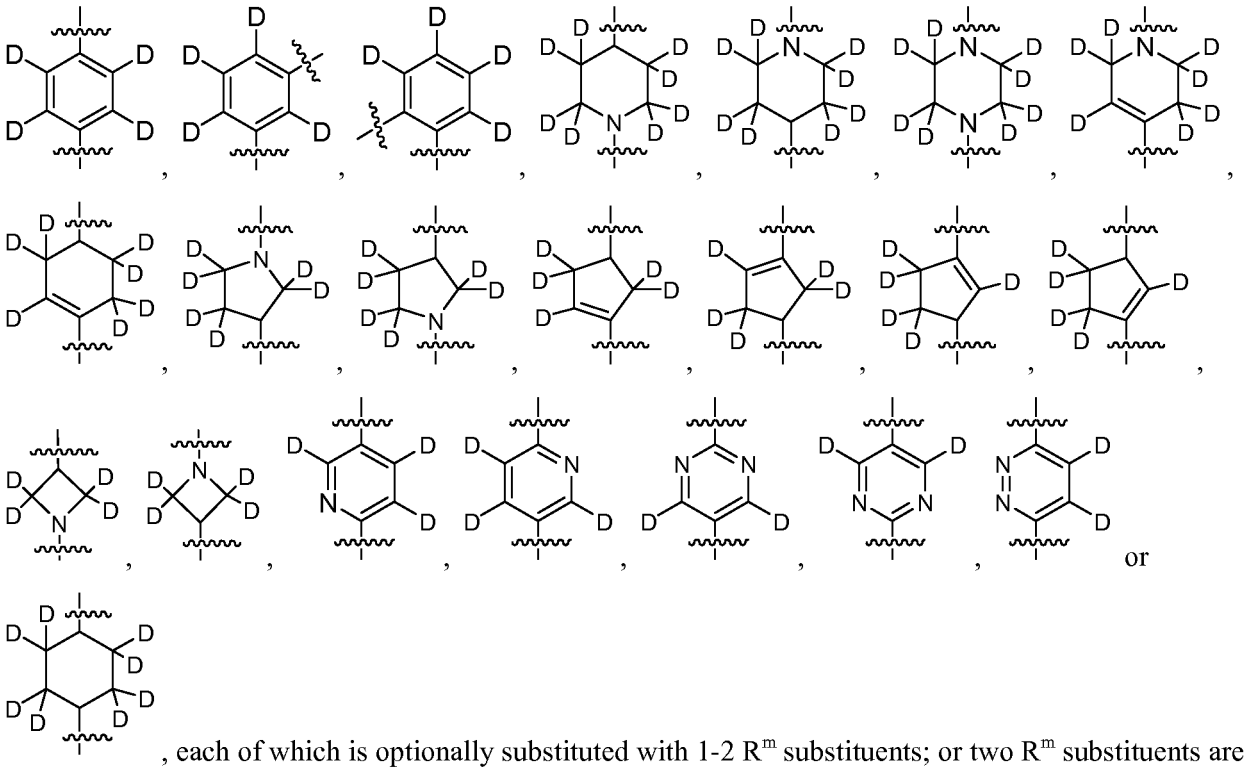
[0124] In some embodiments of compounds of formula (II), E is selected from:



or , or partially deuterated or perdeuterated analogs thereof, each of which is optionally substituted with from 1-2 R^m groups, wherein R^{12} is H or C_{1-4}alkyl and wherein the hydrogen atoms in E are optionally replaced with from 1 to 8 deuteriums with at least 52.5%, 60%, 70%, 75%, 80%, 90%, 95%, 99%, 99.5% or 99.9% deuterium incorporation for each deuterium. R^m is as defined in any of the embodiments as described herein. In certain instances, R^m is selected from –F, $-CF_3$, CN, $-OCF_3$, $-CHF_2$, $-CH_2F$, $-OCH_2F$ or $-OCHF_2$, $-OCH_3$ or $-CH_3$. In one instance, R^m is –F or $-CH_3$. In some embodiments, each hydrogen atom in E is optionally replaced by a deuterium atom with at least 52.5%, 60%, 70%, 75%, 80%, 90%, 95%, 99%, 99.5% or 99.9% deuterium

incorporation for each deuterium. All the other variables A, Z, L and R^1 of formula (II) are as defined in any of the embodiments as described herein.

[0125] In some embodiments of compounds of formula (II), E is partially deuterated arylene, cycloalkylene or heterocycloalkylene having from 1 to 8 deuterium atoms or a perdeuterated arylene, cycloalkylene or heterocycloalkylene selected from:



, each of which is optionally substituted with 1-2 R^m substituents; or two R^m substituents are taken together to form a $-(CH_2)_n-$ or $-(CD_2)_n$ bridging linkage, which together with the atoms to which they are attached forms a 5- to 9-membered bicyclic ring, wherein n is 1, 2 or 3 and wherein the bicyclic ring is optionally substituted with from 1-2 R^n substituents; or two R^m substituents, when attaching to the same carbon atom of the heterocyclylene, are taken together with the atom to which they attach form a 3- to 6-membered monocyclic ring, which is optionally substituted with R^n; and the wavy line indicates the point of attachment to the rest of the molecule. R^m and R^n are as defined in any of the embodiments as described herein. In certain instances, R^m is C_{1-4} alkyl, halogen, $-OCH_3$, $-CF_3$, -CN, $-OCF_3$, $-CHF_2$, $-CH_2F$, $-OCH_2F$, $-OCHF_2$ or deuterated analogs thereof. In some instances, each R^m is independently selected from C_{1-4} alkyl or halogen or deuterated analogs thereof. In one instance, R^m is CH_3, CD_3, F or Cl. In certain instances, R^n is C_{1-4} alkyl, halogen, -CN, $-OCH_3$, CF_3, CN, $-OCF_3$, $-CHF_2$, $-OCHF_2$ or deuterated analogs thereof. In one instance, R^n is CD_3, CH_3, F, Cl, $-OCD_3$, $-OCH_3$, $-CF_3$, -CN, $-OCF_3$, $-CHF_2$, $-CDF_2$, $-OCDF_2$ or $-OCHF_2$. All the other variables A, Z, L and R^1 of formula (II) are as defined in any of the embodiments as described herein.

[0126] In some embodiments of compounds of formula (I), L is selected from a bond, –N(R^a)SO_2-, -SO_2N(R^a)-, -N(R^a)SO_2N(R^a)-, -N(R^a)C(O)-, -C(O)N(R^a)-, -SO_2-, -C(O)O-, -C(O)-, -N(R^a)C(O)N(R^a)-, or -C(=NR^a)N(R^a)-, wherein R^a is independently H, C_{1-4}alkyl or C_{1-4} haloalkyl. In some embodiments, R^a is independently H, C_{1-4}alkyl. All the other variables A, Z, E and Q of formula (I) are as defined in any of the embodiments as described herein.

[0127] In some embodiments of compounds of formula (II), L is selected from a bond, –N(R^a)SO_2-, -SO_2N(R^a)-, -N(R^a)SO_2N(R^a)-, -N(R^a)C(O)-, -C(O)N(R^a)-, -SO_2-, -C(O)O-, -C(O)-, -N(R^a)C(O)N(R^a)-, or -C(=NR^a)N(R^a)-, wherein R^a is independently H, C_{1-4}alkyl or C_{1-4} haloalkyl. In certain embodiments, L is selected from –N(R^a)SO_2-, -SO_2N(R^a)-, -N(R^a)SO_2N(R^a)-, -N(R^a)C(O)-, -C(O)N(R^a)-, -SO_2-, -C(O)O-, -C(O)-, -N(R^a)C(O)N(R^a)-, -C(=NR^a)N(R^a)-. In certain embodiments, R^a is H or C_{1-4}alkyl. In some embodiments, R^a is H, -CH_3, -CHF_2, -CH_2F or -CF_3. In one embodiment, R^a is H. In another embodiment, R^a is CH_3. All the other variables A, Z, E and R^1 of formula (II) are as defined in any of the embodiments as described herein.

[0128] In some embodiments of compounds of formula (II), L is –NHSO_2-, -SO_2NH-, -NHC(O)NH-, -NHC(O)-, -C(O)NH-, -SO_2-, -C(O)O-, -C(O)-, -C(=NH)NH- or -NHC(=NH)-. In certain embodiments, L is –NHSO_2-, -SO_2NH-, -NHC(O)NH-, -NHC(O)-, -C(O)NH-, -SO_2-, -C(O)O-, -OC(O)-, -C(O)- or -C(=NH)NH-. In certain instances, L is –NHSO_2-, -SO_2NH-, -NHC(O)NH- or -NHC(O)-. In other instances, L is -C(O)NH-, -SO_2-, -SO_2NH-, -C(O)O- or -C(O)-. In other instances, L is –NHSO_2- or -SO_2NH-. In yet other instances, L is -C(O)NH-, –NHSO_2-, -SO_2NH- or -C(=NH)NH-. In still other instances, L is –NHSO_2-, -SO_2NH- or –SO_2-. All the other variables A, Z, E and R^1 of formula (II) are as defined in any of the embodiments as described herein.

[0129] In some embodiments of compounds of formula (I), Z is selected from H, optionally substituted aryl, optionally substituted aryl-C_{1-4}alkyl, optionally substituted heteroaryl, optionally substituted heteroaryl-C_{1-4} alkyl, optionally substituted heterocycloalkyl, optionally substituted C_{1-6}alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkyl-C_{1-4}alkyl, optionally substituted heterocyclyl or optionally substituted heterocyclyl-C_{1-4}alkyl; or when Z is a substituted aromatic ring, two adjacent substituents on the aromatic ring, taken together with the atoms to which they are attached, optionally form a 5- or 6-membered ring. In certain instances, the cycloalkyl has 3 to 8 or 3 to 7 or 3 to 6 ring carbon atoms. All the other variables A, L, E and Q of formula (I) are as defined in any of the embodiments as described herein.

[0130] In some embodiments of compounds of formula (II), Z is selected from H, aryl, aryl-C_{1-4}alkyl, heteroaryl, heteroaryl-C_{1-4} alkyl, heterocycloalkyl, C_{1-6}alkyl, C_{3-6}cycloalkyl, -N(R^b)(R^c), cycloalkyl-C_{1-4}alkyl, heterocyclyl or heterocyclyl-C_{1-4}alkyl, wherein the aliphatic or aromatic portion of Z is each independently optionally substituted with from 1-3 R^d groups, wherein each R^d is independently selected

from C_{1-6}alkyl, C_{1-6} haloalkyl, halogen, C_{1-6}alkoxy, C_{1-6} haloalkoxy, C_{3-6}cycloalkyl, heterocycloalkyl, heteroaryl, or R^2; or two adjacent R^d substituents on an aromatic ring are taken together to form a 5 or 6-membered ring; wherein each R^d group is optionally further substituted with from 1-2 R^e members selected from C_{1-6}alkyl, C_{1-6} haloalkyl, halogen, C_{1-6}alkoxy, C_{1-6} haloalkoxy, NO_2, CN, -OH, $-NH_2$, -C(O)OH, -C(S)OH, $-C(O)NH_2$, $-C(S)NH_2$, $-S(O)_2NH_2$, $-NHC(O)NH_2$, $-NHS(O)_2NH_2$, $-C(NH)NH_2$, $-OR^f$, $-SR^f$, $-OC(O)R^f$, $-OC(S)R^f$, $-C(O)R^f$, $-C(O)OR^f$, $-C(S)OR^f$, $-S(O)R^f$, $-S(O)_2R^f$, $-C(O)NHR^f$, $-C(S)NHR^f$, $-C(O)NR^fR^f$, $-S(O)_2NHR^f$, $-S(O)_2NR^fR^f$, $-C(NH)NHR^f$, $-C(NH)NR^fR^f$, $-NHC(O)R^f$, $-NHC(S)R^f$, $-NR^fC(O)R^f$, $-NHS(O)_2R^f$, $-NR^fS(O)_2R^f$ or $-NHC(O)NHR^f$, wherein R^f is C_{1-6}alkyl or aryl; and wherein R^b and R^c are each independently C_{1-6}alkyl or R^b and R^c together with the nitrogen atom to which they are attached form a 5 or 6-membered ring, which is optionally substituted with 1-3 R^e; and wherein R^2 is halogen, CN, -OH, $-NH_2$, $-NO_2$, -C(O)OH, -C(S)OH, $-C(O)NH_2$, $-C(S)NH_2$, $-S(O)_2NH_2$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHS(O)_2NH_2$, $-C(NH)NH_2$, $-OR^g$, $-SR^g$, $-OC(O)R^g$, $-OC(S)R^g$, $-C(O)R^g$, $-C(S)R^g$, $-C(O)OR^g$, $-C(S)OR^g$, $-S(O)R^g$, $-S(O)_2R^g$, $-C(O)NHR^g$, $-C(S)NHR^g$, $-C(O)NR^gR^g$, $-C(S)NR^gR^g$, $-S(O)_2NHR^g$, $-S(O)_2NR^gR^g$, $-C(NH)NHR^g$, $-C(NH)NR^gR^g$, $-NHC(O)R^g$, $-NHC(S)R^g$, $-NR^gC(O)R^g$, $-NR^gC(S)R^g$, $-NHS(O)_2R^g$, $-NR^gS(O)_2R^g$, $-NHC(O)NHR^g$, $-NHC(S)NHR^g$, $-NR^gC(O)NH_2$, $-NR^gC(S)NH_2$, $-NR^gC(O)NHR^g$, $-NR^gC(S)NHR^g$, $-NHC(O)NR^gR^g$, $-NHC(S)NR^gR^g$, $-NR^gC(O)NR^gR^g$, $-NR^gC(S)NR^gR^g$, $-NHS(O)_2NHR^g$, $-NR^gS(O)_2NH_2$, $-NR^gS(O)_2NHR^g$, $-NHS(O)_2NR^gR^g$, $-NR^gS(O)_2NR^gR^g$, $-NHR^g$ or $-NR^gR^g$, wherein each R^g is independently C_{1-6}alkyl, aryl, aryl-C_{1-2}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkyl-C_{1-4}alkyl, heteroaryl, heteroaryl-C_{1-4}alkyl, heterocycloalkyl or heterocycloalkyl-C_{1-4}alkyl, wherein each R^g is further optionally substituted with 1-3 R^h substituents independently selected from C_{1-6}alkyl, C_{1-6}alkoxy, halogen, C_{1-6} haloalkyl or C_{1-6} haloalkoxy. In one instance, Z is H. All the other variables A, L, E and R^1 of formula (II) are as defined in any of the embodiments as described herein.

[0131] In some embodiments of compounds of formula (II), Z is selected from C_{1-6}alkyl, perdeuterated C_{1-6}alkyl, aryl, aryl-C_{1-4}alkyl, heteroaryl, heteroaryl-C_{1-4} alkyl, heterocycloalkyl, heterocycloalkyl-C_{1-4}alkyl, C_{3-6}cycloalkyl, $-N(R^b)(R^c)$ or cycloalkyl-C_{1-4}alkyl, each of which is optionally substituted with from: (i) 1-3 R^d groups; or (ii) 1-3 R^e substituents; or (iii) 1-3 R^g substituents; or (iv) 1-3 R^{13} substituents independently selected from C_{1-6}alkyl, -OH, -CN, $-NO_2$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-OCH_3$, $-OCH_2CH_3$, $-O-CH(CH_3)_2$, -Cl, -F, $-CH_2F$, $-CHF_2$, CF_3, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, 4-morpholinyl, 1-piperidinyl, cyclopropyl, 1-methylcyclopropyl, 1-cyanocyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 2-oxo-1-pyrrolidinyl, $-C_{1-2}$alkyl-R^p, C(O)-R^p, $-C(O)NHR^p$, $-C(O)NR^pR^p$, $-NHC(O)R^p$, $-C(O)OR^p$, $-OC(O)R^p$, $-SO_2R^p$, $-NHSO_2R^p$, $-SO_2NHR^p$, $-SO_2NR^pR^p$, wherein each R^p is independently C_{1-6}alkyl, C_{3-6}cycloalkyl, phenyl or heterocycloalkyl, wherein R^p is further optionally substituted with from 1-3 R^j groups; or (v) 1-3 R^{14} substituents independently selected from F, Cl, I, $-CH_3$, $-CD_3$, $-OCD_3$, $-OCH_3$, OCH_2CH_3, $-O-CH(CH_3)_2$, -OH, -CN, $-NO_2$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-CH_2F$, $-CHF_2$, CF_3, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, cyclopropyl, 1-methylcyclopropyl, 1-cyanocyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, -

$NHSO_2CH_3$, $-NH_2C(O)-$, $CH_3NHC(O)-$, NH_2SO_2-, CH_3SO_2-, $(CH_3)_2NC(O)-$, benzyl, benzyl-C(O), (C_{1-4}alkyl)OC(O)-, cyclopropyl-C(O)-, cyclopropylethyl-C(O)-, cyclobutyl-C(O)-, cyclobutylmethyl-C(O)-, Ph-NH-C(O)-, 4-morpholinyl, 4-morpholinylmethyl, 4-morpholinylethyl, 4-morpholinyl-C(O)-, 1-piperidinyl, 1-piperidinyl-C(O)-, p-CH_3-Ph-SO_2NH-, cyclopropyl-SO_2NH-, cyclobutyl-SO_2NH- or butylSO_2NH-; or (vi) 1-3 R^{15} substituents selected from F, Cl, -CN, $-NO_2$, $-CH_3$, $-CD_3$, $-OCH_3$,-OCH_2CH_3, $-OCD_3$, ethyl, propyl, butyl, t-butyl, isopropyl, $-OCH(CH_3)_2$, $-OCHF_2$, $-OCF_3$, $-CF_3$, $-CH_2F$, -OCH_2F, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl or $-N(CH_3)_2$; wherein at each occurrence, each of R^d, R^e, R^{13}, R^{14} or R^{15} substituents is further optionally substituted with from 1-3 R^{16} substituents independently selected from –CN, F, Cl, I, CD_3, $-OCD_3$, $-OCH_3$, C_{1-6}alkyl, cyclopropyl, -OH, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-CH_2F$, -CHF_2, CF_3, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, $CH_3C(O)-$, $CH_3C(O)O-$, $CH_3OC(O)-$, $CH_3NHC(O)-$, $CH_3C(O)NH-$, $(CH_3)_2NC(O)-$, $(CH_3)_2NS(O)_2-$,$(CH_3)_2S(O)_2NH-$ or CH_3SO_2; or (vii) two adjacent R^d substituents on an aromatic ring are taken together to form a 5 or 6-membered ring having from 0-2 heteroatoms selected from N, O or S, wherein the 5- or 6-membered ring is optionally substituted with 1-2 R^e or R^h groups. All the other variables A, L, E and R^1 of formula (II) are as defined in any of the embodiments as described herein.

[0132] In some embodiments of compounds of formula (II), Z is aryl, aryl-C_{1-4}alkyl, heteroaryl or heteroaryl-C_{1-4}alkyl, each of which is optionally substituted with from 1-3 R^d groups, wherein two adjacent substituents on an aromatic ring are taken together to form a 5 or 6-membered ring having from 0-2 heteroatoms selected from N, O or S, wherein the 5- or 6-membered ring is optionally substituted with 1-2 R^e or R^h groups. All the other variables A, L, E and R^1 of formula (II) are as defined in any of the embodiments as described herein.

[0133] In some embodiments of compounds of formula (II), Z is selected from 1H-4-benzotriazolyl, 1H-5-benzotriazolyl, 1H-4-benzimidazolyl, 1H-5-benzimidazolyl, 1H-4-indazolyl, 1H-5-indazolyl, 1H-6-indazolyl, 1H-7-indazolyl, 1H-4-indolyl, 1H-5-indolyl, 1H-6-indolyl, 1H-7-indolyl, 2-oxo-6-indolinyl, 2-oxo-4-indolinyl, 2-oxo-5-indolinyl, 2-oxo-7-indolinyl, 1,2-benzoxazol-4-yl, 1,2-benzoxazol-5-yl, 1,2-benzoxazol-6-yl, 1,2-benzoxazol-7-yl, 1,3-benzoxazol-4-yl, 1,3-benzoxazol-5-yl, 1,3-benzoxazol-6-yl, 1,3-benzoxazol-7-yl, 1,2-benzothiazol-4-yl, 1,2-benzothiazol-5-yl, 1,2-benzothiazol-6-yl, 1,2-benzothiazol-7-yl, 5-quinolinyl, 6-quinolinyl, 7-quinolinyl, 8-quinolinyl, 5-isoquinolinyl, 6-isoquinolinyl, 7-isoquinolinyl, 8-isoquinolinyl, 5-cinnolinyl, 6-cinnolinyl, 7-cinnolinyl, 8-cinnolinyl, 5-quinazolinyl, 6-quinazolinyl, 7-quinazolinyl, 8-quinazolinyl, 5-quinoxalinyl, 6-quinoxalinyl, 7-quinoxalinyl, 8-quinoxalinyl, 4-indanyl, 5-indanyl, 5-tetralinyl, 6-tetralinyl, 1,3-dihydroisobenzofuran-4-yl, 1,3-dihydroisobenzofuran-5-yl, 2,3-dihydrobenzofuran-4-yl, 2,3-dihydrobenzofuran-5-yl, 2,3-dihydrobenzofuran-6-yl, 2,3-dihydrobenzofuran-7-yl, 1,3-dihydroisobenzothiophen-4-yl, 1,3-dihydroisobenzothiophen-5-yl, 2,3-dihydrobenzothiophen-4-yl, 2,3-dihydrobenzothiophen-5-yl, 2,3-

dihydrobenzothiophen-6-yl, 2,3-dihydrobenzothiophen-7-yl, 4-indolinyl, 5-indolinyl, 6-indolinyl, 7-indolinyl, 5-isochromanyl, 6-isochromanyl, 7-isochromanyl, 8-isochromanyl, 5-chromanyl, 6-chromanyl, 7-chromanyl, 8-chromanyl, 2,3-dihydro-1,3-benzothiazo-4-yl, 2,3-dihydro-1,3-benzothiazo-5-yl, 2,3-dihydro-1,3-benzothiazo-6-yl, 2,3-dihydro-1,3-benzothiazo-7-yl, 2,3-dihydro-1,2-benzothiazo-4-yl, 2,3-dihydro-1,2-benzothiazo-5-yl, 2,3-dihydro-1,2-benzothiazo-6-yl, 2,3-dihydro-1,2-benzothiazo-7-yl, 2,3-dihydro-1,3-benzoxazol-4-yl, 2,3-dihydro-1,3-benzoxazol-5-yl, 2,3-dihydro-1,3-benzoxazol-6-yl, 2,3-dihydro-1,3-benzoxazol-7-yl, 2,3-dihydro-1,2-benzoxazol-4-yl, 2,3-dihydro-1,2-benzoxazol-5-yl, 2,3-dihydro-1,2-benzoxazol-6-yl, 2,3-dihydro-1,2-benzoxazol-7-yl, 4-benzofuranyl, 5-benzofuranyl, 6-benzofuranyl, 7-benzofuranyl, 4-benzo[b]thiophenyl, 5-benzo[b]thiophenyl, 6-benzo[b]thiophenyl, 7-benzo[b]thiophenyl, 2,3-dihydro-1,4-benzodioxin-5-yl, 1,3-benzodioxol-4-yl, 1,3-benzodioxol-5-yl, 4-indanyl, 5-indanyl, 1,2-benzoxazol-4-yl, 1,2-benzoxazol-5-yl, 1,2-benzoxazol-6-yl, 1,2-benzoxazol-7-yl, 1,3-benzoxazol-4-yl, 1,3-benzoxazol-5-yl, 1,3-benzoxazol-6-yl, 1,3-benzoxazol-7-yl, 1,3-benzodioxol-4-yl or 1,3-benzodioxol-5-yl, each of which is optionally substituted with from: (i) 1-3 R^d substituents; or (ii) 1-3 R^e substituents; or (iii) 1-3 R^g substituents; or (iv) 1-3 R^{13} substituents; or (v) 1-3 R^{14} substituents; or (vi) 1-3 R^{15} substituents, wherein at each occurrence, each of R^d, R^e, R^{13}, R^{14} or R^{15} substituents is further optionally substituted with from 1-3 substituents independently selected from –CN, F, Cl, I, CD_3, -OCD_3, -OCH_3, $C_{1\text{-}6}$alkyl, cyclopropyl, -OH, -NH_2, -$NHCH_3$, -$N(CH_3)_2$, -CH_2F, -CHF_2, CF_3, -OCF_3, -$OCHF_2$, -OCH_2F, $CH_3C(O)$-, $CH_3C(O)O$-, $CH_3OC(O)$-, $CH_3NHC(O)$-, $CH_3C(O)NH$-, $(CH_3)_2NC(O)$-, $(CH_3)_2NS(O)_2$-,$(CH_3)_2S(O)_2NH$- or CH_3SO_2. In some instances, Z is 1,3-benzodioxol-4-yl, 1,3-benzodioxol-5-yl, 4-indanyl, 5-indanyl, 1,2-benzoxazol-4-yl, 1,2-benzoxazol-5-yl or 1,2-benzoxazol-6-yl, each of which is optionally substituted with R^d, R^e, R^g, R^{13} or R^{14}. In some embodiments, the hydrogen atoms in Z are optionally replaced by 1 to 12, or 1 to 8, or 1 to 6, or 1 to 3 or 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 deuterium atoms with at least 52.5%, 60%, 70%, 75%, 80%, 90%, 95%, 99%, 99.5% or 99.9% deuterium incorporation for each deuterium. In certain embodiments, each hydrogen atom in Z is optionally replaced by a deuterium atom with at least 52.5%, 60%, 70%, 75%, 80%, 90%, 95%, 99%, 99.5% or 99.9% deuterium incorporation for each deuterium. All the other variables A, L, E and R^1 of formula (II) are as defined in any of the embodiments as described herein.

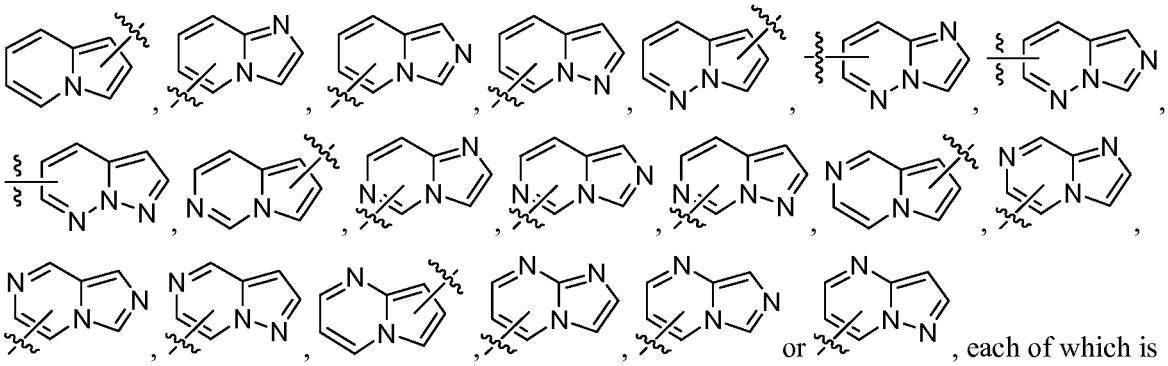
[0134] In some embodiments of compounds of formula (II), Z is selected from 2-pyridyl, 3-pyridyl, 4-pyridyl, 5-pyrimidinyl, 2-pyrimidinyl, 4-pyrimidinyl, 2-pyrazinyl, 2-pyridazinyl, 3-pyridazinyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 2-imidazolyl, 4-imidazolyl, 1-pyrazolyl, 2-pyrazolyl, 3-pyrazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 3-isothiazolyl, 4-isothiazolyl, 5-isothiazolyl, 1,2,3-triazol-1-yl, 1,2,3-triazol-2-yl, 1,2,3-triazol-3-yl, 1,2,3-triazol-4-yl, 1,2,3-triazol-5-yl, 1,2,4-triazol-1-yl, 1,2,4-triazol-2-yl, 1,2,4-triazol-3-yl, 1,2,4-triazol-4-yl, 1,2,4-triazol-5-yl, 1-oxa-2,3-diazol-4-yl, 1-oxa-2,3-diazol-5-yl, 1-oxa-2,4-diazol-3-yl, 1-oxa-2,4-diazol-5-yl, 1-oxa-2,5-diazol-3-yl, 1-oxa-2,5-diazol-4-yl, 1-thia-2,3-diazol-4-yl, 1-thia-2,3-diazol-5-

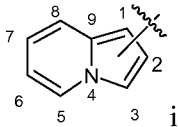
yl, 1-thia-2,4-diazol-3-yl, 1-thia-2,4-diazol-5-yl, 1-thia-2,5-diazol-3-yl, 1-thia-2,5-diazol-4-yl, 1-tetrazolyl, 3-tetrazolyl, 1H-5-tetrazolyl, 3H-5-tetrazolyl, 2-furanyl, 3-furanyl, 2-thiophenyl or 3-thiophenyl, each of which is optionally substituted with from: (i) 1-3 R^d substituents; or (ii) 1-3 R^e substituents; or (iii) 1-3 R^g substituents; or (iv) 1-3 R^{13} substituents; or (v) 1-3 R^{14} substituents; or (vi) 1-3 R^{15} substituents, wherein at each occurrence, each of R^d, R^e, R^{13}, R^{14} or R^{15} substituents is further optionally substituted with from 1-3 substituents independently selected from –CN, F, Cl, I, CD_3, -OCD_3, -OCH_3, C_{1-6}alkyl, cyclopropyl, -OH, -NH_2, -$NHCH_3$, -$N(CH_3)_2$, -CH_2F, -CHF_2, CF_3, -OCF_3, -$OCHF_2$, -OCH_2F, $CH_3C(O)$-, $CH_3C(O)O$-, $CH_3OC(O)$-, $CH_3NHC(O)$-, $CH_3C(O)NH$-, $(CH_3)_2NC(O)$-, $(CH_3)_2NS(O)_2$-,$(CH_3)_2S(O)_2NH$- or CH_3SO_2. In some instances, Z is 2-thiophenyl, 3-thiophenyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 1-pyrazolyl, 2-pyrazolyl, 3-pyrazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl or 1-oxo-2,4-diazol-3-yl, each of which is optionally substituted with R^d, R^e, R^g, R^{13} or R^{14}. In some embodiments, the hydrogen atoms in Z are optionally replaced by 1 to 12, or 1 to 8, or 1 to 6, or 1 to 3 or 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 deuterium atoms with at least 52.5%, 60%, 70%, 75%, 80%, 90%, 95%, 99%, 99.5% or 99.9% deuterium incorporation for each deuterium. In certain embodiments, each hydrogen atom in Z is optionally replaced by a deuterium atom with at least 52.5%, 60%, 70%, 75%, 80%, 90%, 95%, 99%, 99.5% or 99.9% deuterium incorporation for each deuterium. All the other variables A, L, E and R^1 of formula (II) are as defined in any of the embodiments as described herein.

[0135] In some embodiments of compounds of formula (II), Z is selected from 1-benzotriazolyl, 1-benzimidazolyl, 1H-2-benzimidazolyl, 1-indazolyl, 1H-3-indazolyl, 1-indolyl, 1H-2-indolyl, 1H-3-indolyl, 1,2-benzoxazol-3-yl, 1,3-benzoxazol-2-yl, 1,2-benzothiazol-3-yl, 1,3-benzothiazol-2-yl, 2-quinolinyl, 3-quinolinyl, 4-quinolinyl, 1-isoquinolinyl, 3-isoquinolinyl, 4-isoquinolinyl, 3-cinnolinyl, 4-cinnolinyl, 2-quinazolinyl, 4-quinazolinyl, 2-quinoxalinyl, 2-benzofuranyl, 3-benzofuranyl, 2-benzo[b]thiophenyl or 3-benzo[b]thiophenyl, each of which is optionally substituted with from (i) 1-3 R^d substituents; or (ii) 1-3 R^e substituents; or (iii) 1-3 R^g substituents; or (iv) 1-3 R^{13} substituents; or (v) 1-3 R^{14} substituents; or (vi) 1-3 R^{15} substituents, wherein at each occurrence, each of R^d, R^e, R^{13}, R^{14} or R^{15} substituents is further optionally substituted with from 1-3 substituents independently selected from –CN, F, Cl, I, CD_3, -OCD_3, -OCH_3, C_{1-6}alkyl, cyclopropyl, -OH, -NH_2, -$NHCH_3$, -$N(CH_3)_2$, -CH_2F, -CHF_2, CF_3, -OCF_3, -$OCHF_2$, -OCH_2F, $CH_3C(O)$-, $CH_3C(O)O$-, $CH_3OC(O)$-, $CH_3NHC(O)$-, $CH_3C(O)NH$-, $(CH_3)_2NC(O)$-, $(CH_3)_2NS(O)_2$-,$(CH_3)_2S(O)_2NH$- or CH_3SO_2. In certain embodiments, Z is 2-benzo[b]thiophenyl or 3-benzo[b]thiophenyl, each of which is optionally substituted with from 1-3 R^{13}, R^{14}, R^{15} substituents. In some embodiments, the hydrogen atoms in Z are optionally replaced by 1 to 12, or 1 to 8, or 1 to 6, or 1 to 3 or 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 deuterium atoms with at least 52.5%, 60%, 70%, 75%, 80%, 90%, 95%, 99%, 99.5% or 99.9% deuterium incorporation for each deuterium. In certain embodiments, each hydrogen atom in Z is optionally replaced by a deuterium atom with at least 52.5%, 60%, 70%, 75%, 80%, 90%, 95%, 99%, 99.5% or 99.9% deuterium incorporation for each

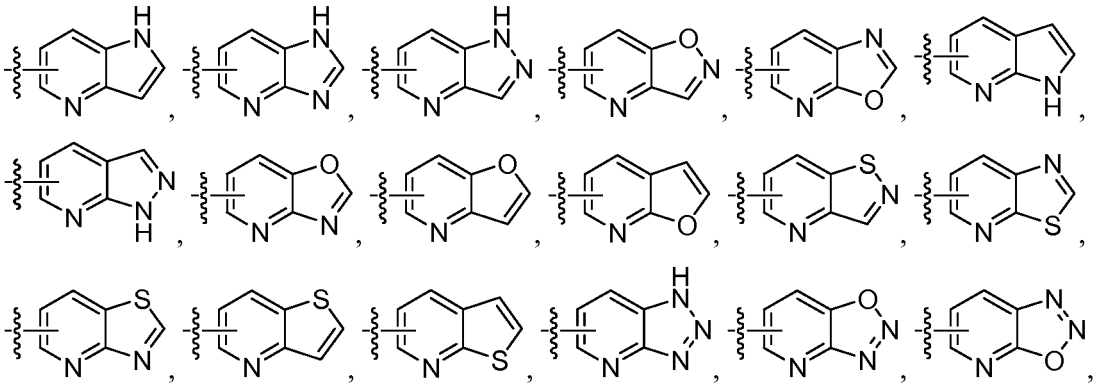
deuterium. All the other variables A, L, E and R^1 of formula (II) are as defined in any of the embodiments as described herein.

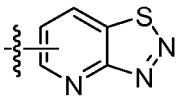
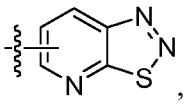
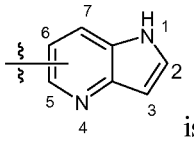
[0136] In some embodiments of compounds of formula (II), Z is selected from:



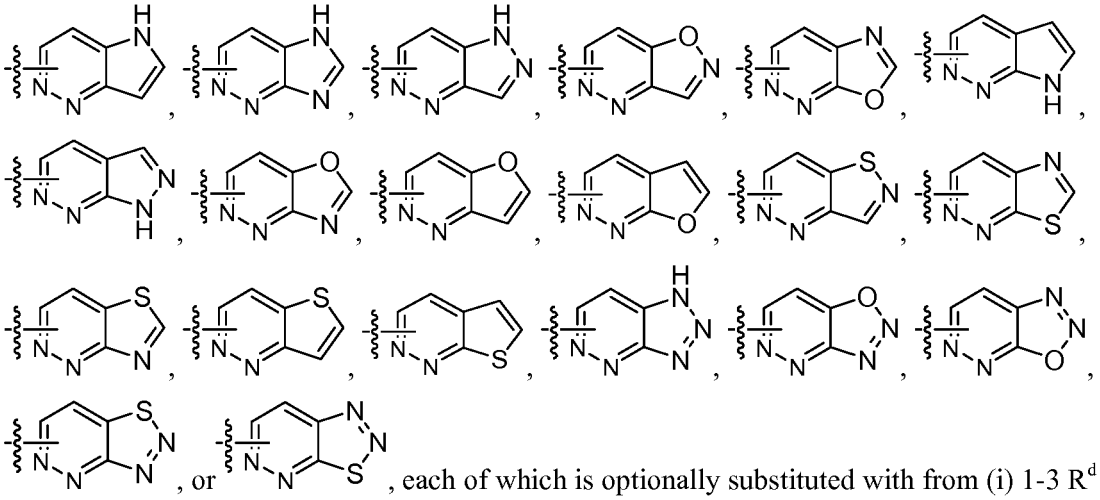
optionally substituted with from: (i) 1-3 R^d substituents; or (ii) 1-3 R^e substituents; or (iii) 1-3 R^g substituents; or (iv) 1-3 R^{13} substituents; or (v) 1-3 R^{14} substituents; or (vi) 1-3 R^{15} substituents, wherein at each occurrence, each of R^d, R^e, R^{13}, R^{14} or R^{15} substituents is further optionally substituted with from 1-3 substituents independently selected from –CN, F, Cl, I, CD_3, -OCD_3, -OCH_3, $C_{1\text{-}6}$alkyl, cyclopropyl, -OH, -NH_2, -$NHCH_3$, -$N(CH_3)_2$, -CH_2F, -CHF_2, CF_3, -OCF_3, -$OCHF_2$, -OCH_2F, $CH_3C(O)$-, $CH_3C(O)O$-, $CH_3OC(O)$-, $CH_3NHC(O)$-, $CH_3C(O)NH$-, $(CH_3)_2NC(O)$-, $(CH_3)_2NS(O)_2$-,$(CH_3)_2S(O)_2NH$- or CH_3SO_2, where the wavy line indicate the point of attachment to the rest of the molecule. The notation —≋— means Z can be attached to the rest of the molecule at any of the available positions of the Z group set forth above. For example,  is meant to include 1-indolizinyl, 2-indolizinyl, 3-indolizinyl, 4-indolizinyl, 5-indolizinyl, 6-indolizinyl, 7-indolizinyl, and 8-indolizinyl (i.e., substitutions can be at 1, 2, 3, 5, 6, 7 or 8 positions of the indolizine ring). All the other variables A, L, E and R^1 of formula (II) are as defined in any of the embodiments as described herein.

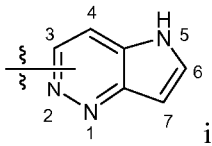
[0137] In some embodiments of compounds of formula (II), Z is selected from:



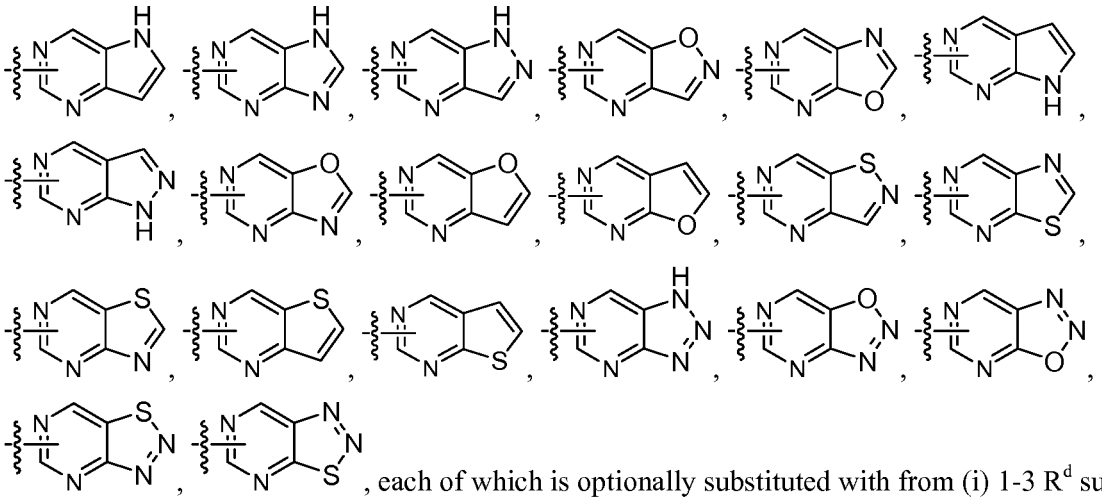
 or  , (i) 1-3 R^d substituents; or (ii) 1-3 R^e substituents; or (iii) 1-3 R^g substituents; or (iv) 1-3 R^{13} substituents; or (v) 1-3 R^{14} substituents; or (vi) 1-3 R^{15} substituents, wherein at each occurrence, each of R^d, R^e, R^{13}, R^{14} or R^{15} substituents is further optionally substituted with from 1-3 substituents independently selected from –CN, F, Cl, I, CD_3, -OCD_3, -OCH_3, $C_{1\text{-}6}$alkyl, cyclopropyl, -OH, -NH_2, -$NHCH_3$, -$N(CH_3)_2$, -CH_2F, -CHF_2, CF_3, -OCF_3, -$OCHF_2$, -OCH_2F, $CH_3C(O)$-, $CH_3C(O)O$-, $CH_3OC(O)$-, $CH_3NHC(O)$-, $CH_3C(O)NH$-, $(CH_3)_2NC(O)$-, $(CH_3)_2NS(O)_2$-,$(CH_3)_2S(O)_2NH$- or CH_3SO_2, where the wavy line indicates the point of attachment to the rest of the molecule. The notation means Z can be attached to the rest of the molecule at any of the available positions of the Z group set forth above. For example,  is meant to include 1H-pyrrolo[3,2-b]pyridin-1-yl, 1H-pyrrolo[3,2-b]pyridin-2-yl, 1H-pyrrolo[3,2-b]pyridin-3-yl, 1H-pyrrolo[3,2-b]pyridin-5-yl, 1H-pyrrolo[3,2-b]pyridin-6-yl and 1H-pyrrolo[3,2-b]pyridin-7-yl (i.e., substitutions can be at 1, 2, 3, 5, 6, or 7 positions of the pyrrolo[3,2-b]pyridine ring). All the other variables Z, L, E and A of formula (II) are as defined in any of the embodiments as described herein.

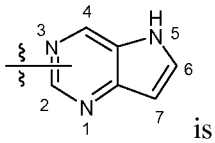
[0138] In some embodiments of compounds of formula (II), Z is selected from:

 , each of which is optionally substituted with from (i) 1-3 R^d substituents; or (ii) 1-3 R^e substituents; or (iii) 1-3 R^g substituents; or (iv) 1-3 R^{13} substituents; or (v) 1-3 R^{14} substituents; or (vi) 1-3 R^{15} substituents, wherein at each occurrence, each of R^d, R^e, R^{13}, R^{14} or R^{15} substituents is further optionally substituted with from 1-3 substituents independently selected from –CN, F, Cl, I, CD_3, -OCD_3, -OCH_3, $C_{1\text{-}6}$alkyl, cyclopropyl, -OH, -NH_2, -$NHCH_3$, -$N(CH_3)_2$, -CH_2F, -CHF_2, CF_3, -OCF_3, -$OCHF_2$, -OCH_2F, $CH_3C(O)$-, $CH_3C(O)O$-, $CH_3OC(O)$-, $CH_3NHC(O)$-, $CH_3C(O)NH$-, $(CH_3)_2NC(O)$-, $(CH_3)_2NS(O)_2$-,$(CH_3)_2S(O)_2NH$- or CH_3SO_2, where the wavy line indicates the point of

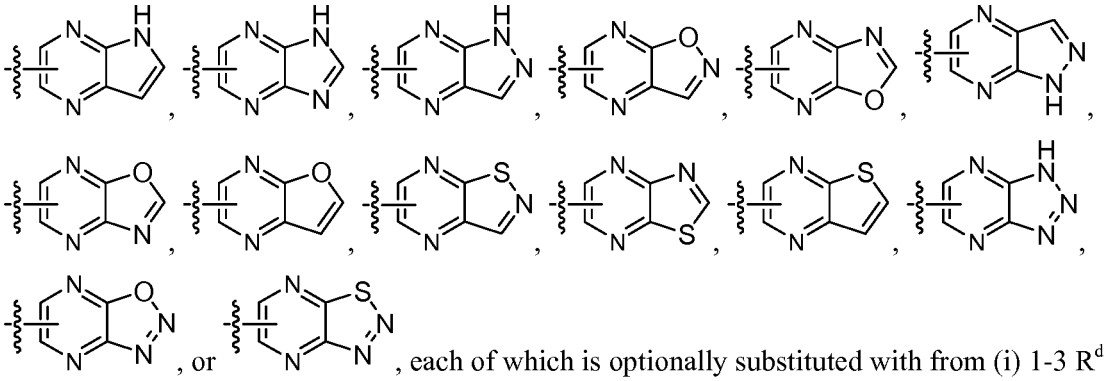
attachment to the rest of the molecule. The notation —§— means Z can be attached to the rest of the molecule at any of the available positions of the Z group set forth above. For example,  is meant to include 5H-pyrrolo[3,2-c]pyridazin-3-yl, 5H-pyrrolo[3,2-c]pyridazin-4-yl, 5H-pyrrolo[3,2-c]pyridazin-5-yl, 5H-pyrrolo[3,2-c]pyridazin-6-yl, 5H-pyrrolo[3,2-c]pyridazin-7-yl (i.e., substitutions can be at 3, 4, 5, 6, or 7 positions of the 5H-pyrrolo[3,2-c]pyridazine ring). All the other variables A, L, E and R^1 of formula (II) are as defined in any of the embodiments as described herein.

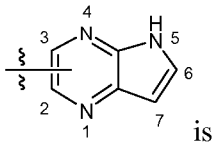
[0139] In some embodiments of compounds of formula (II), Z is selected from:



, each of which is optionally substituted with from (i) 1-3 R^d substituents; or (ii) 1-3 R^e substituents; or (iii) 1-3 R^g substituents; or (iv) 1-3 R^{13} substituents; or (v) 1-3 R^{14} substituents; or (vi) 1-3 R^{15} substituents, wherein at each occurrence, each of R^d, R^e, R^{13}, R^{14} or R^{15} substituents is further optionally substituted with from 1-3 substituents independently selected from –CN, F, Cl, I, CD_3, -OCD_3, -OCH_3, $C_{1\text{-}6}$alkyl, cyclopropyl, -OH, -NH_2, -$NHCH_3$, -$N(CH_3)_2$, -CH_2F, -CHF_2, CF_3, -OCF_3, -$OCHF_2$, -OCH_2F, $CH_3C(O)$-, $CH_3C(O)O$-, $CH_3OC(O)$-, $CH_3NHC(O)$-, $CH_3C(O)NH$-, $(CH_3)_2NC(O)$-, $(CH_3)_2NS(O)_2$-,$(CH_3)_2S(O)_2NH$- or CH_3SO_2, where the wavy line indicates the point of attachment to the rest of the molecule. The notation —§— means Z can be attached to the rest of the molecule at any of the available positions of the Z group set forth above. For example,  is meant to include 5H-pyrrolo[3,2-c]pyrimidin-2-yl, 5H-pyrrolo[3,2-c]pyrimidin-4-yl, 5H-pyrrolo[3,2-c]pyrimidin-5-yl, 5H-pyrrolo[3,2-c]pyrimidin-6-yl and 5H-pyrrolo[3,2-c]pyrimidin-7-yl (i.e., substitutions can be at 2, 4, 5, 6, or 7 positions of the 5H-pyrrolo[3,2-c]pyrimidine ring). All the other variables A, L, E and R^1 of formula (II) are as defined in any of the embodiments as described herein.

[0140] In some embodiments of compounds of formula (II), Z is selected from:



, each of which is optionally substituted with from (i) 1-3 R^d substituents; or (ii) 1-3 R^e substituents; or (iii) 1-3 R^g substituents; or (iv) 1-3 R^{13} substituents; or (v) 1-3 R^{14} substituents; or (vi) 1-3 R^{15} substituents, wherein at each occurrence, each of R^d, R^e, R^{13}, R^{14} or R^{15} substituents is further optionally substituted with from 1-3 substituents independently selected from –CN, F, Cl, I, CD_3, -OCD_3, -OCH_3, C_{1-6}alkyl, cyclopropyl, -OH, -NH_2, -$NHCH_3$, -$N(CH_3)_2$, -CH_2F, -CHF_2, CF_3, -OCF_3, -$OCHF_2$, -OCH_2F, $CH_3C(O)$-, $CH_3C(O)O$-, $CH_3OC(O)$-, $CH_3NHC(O)$-, $CH_3C(O)NH$-, $(CH_3)_2NC(O)$-, $(CH_3)_2NS(O)_2$-,$(CH_3)_2S(O)_2NH$- or CH_3SO_2, where the wavy line indicates the point of attachment to the rest of the molecule. The notation  means Z can be attached to the rest of the molecule at any of the available positions of the Z group set forth above. For example,  is meant to include 5H-pyrrolo[2,3-b]pyrazin-2-yl, 5H-pyrrolo[2,3-b]pyrazin-3-yl, 5H-pyrrolo[2,3-b]pyrazin-5-yl, 5H-pyrrolo[2,3-b]pyrazin-6-yl, 5H-pyrrolo[2,3-b]pyrazin-7-yl, (i.e., substitutions can be at 2, 3, 5, 6, or 7 positions of the 5H-pyrrolo[2,3-b]pyrazine ring). All the other variables A, L, E and R^1 of formula (II) are as defined in any of the embodiments as described herein.

[0141] In some embodiments of compounds of formula (II), Z is C_{3-6}cycloalkyl, C_{3-6}cycloalkyl-C_{1-4}alkyl, aryl-C_{1-4}alkyl, heterocycloalkyl, heterocycloalkyl-C_{1-4}alkyl, heteroaryl-C_{1-4}alkyl, each of which is optionally substituted with from (i) 1-3 R^d substituents; or (ii) 1-3 R^e substituents; or (iii) 1-3 R^g substituents; or (iv) 1-3 R^{13} substituents; or (v) 1-3 R^{14} substituents; or (vi) 1-3 R^{15} substituents, wherein at each occurrence, each of R^d, R^e, R^{13}, R^{14} or R^{15} substituents is further optionally substituted with from 1-3 R^{15} substituents. All the other variables A, L, E and R^1 of formula (II) are as defined in any of the embodiments as described herein.

[0142] In some embodiments of compounds of formula (II), Z is selected from benzyl, phenyl-CD_2-, 1-methylbenzyl, 1,1-dimethylbenzyl, 1-ethylbenzyl, 2-phenylethyl, 1-naphthylmethyl, 2-naphthylmethyl, 1-naphthylethyl, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, cyclopropylmethyl, cyclopropylethyl, 2-cyclopropylethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, 2-pyridylmethyl, 3-

pyridylmethyl, 4-pyridylmethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl, 1-piperazinyl, 2-piperazinyl, 3-piperazinyl, 4-piperazinyl, 2-oxo-1-pyrrolidinyl, 2-oxo-3-pyrrolidinyl, 2-oxo-4-pyrrolidinyl or 2-oxo-5-pyrrolidinyl, each of which is optionally substituted with from (i) 1-3 R^d substituents; or (ii) 1-3 R^e substituents; or (iii) 1-3 R^g substituents; or (iv) 1-3 R^{13} substituents; or (v) 1-3 R^{14} substituents; or (vi) 1-3 R^{15} substituents, wherein at each occurrence, each of R^d, R^e, R^{13}, R^{14} or R^{15} substituents is further optionally substituted with from 1-3 R^{16} substituents; or (vii) 1-3 substituents selected from F, Cl, -CN, $-NO_2$, $-CH_3$, $-CD_3$, $-OCH_3$,-OCH_2CH_3, $-OCD_3$, ethyl, propyl, butyl, t-butyl, isopropyl, $-OCH(CH_3)_2$, $-OCHF_2$, $-OCF_3$, $-CF_3$, $-CH_2F$, -OCH_2F, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, $-N(CH_3)_2$, phenyl or benzyl. In some embodiments, the hydrogen atoms in Z are optionally replaced by 1 to 12, or 1 to 8, or 1 to 6, or 1 to 3 or 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 deuterium atoms with at least 52.5%, 60%, 70%, 75%, 80%, 90%, 95%, 99%, 99.5% or 99.9% deuterium incorporation for each deuterium. In certain embodiments, each hydrogen atom in Z is optionally replaced by a deuterium atom with at least 52.5%, 60%, 70%, 75%, 80%, 90%, 95%, 99%, 99.5% or 99.9% deuterium incorporation for each deuterium. All the other variables A, L, E and R^1 of formula (II) are as defined in any of the embodiments as described herein.

[0143] In some embodiments of compounds of formula (II), Z is phenyl, phenylCD_2-, benzyl, phenyl-CD_2-, 2-phenylethyl, 1,3-benzodioxol-4-yl, 1,3-benzodioxol-5-yl, 4-indanyl, 5-indanyl, 1,2-benzoxazol-4-yl, 1,2-benzoxazol-5-yl, 1,2-benzoxazol-6-yl, 1,2-benzoxazol-7-yl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-thiophenyl, 3-thiophenyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-benzo[b]thiophenyl, 3-benzo[b]thiophenyl, 1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl, 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl, 1-piperazinyl, 2-piperazinyl, 3-piperazinyl, methyl, ethyl, propyl, butyl, t-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-oxo-1-pyrrolidinyl, $-CD_3$, 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethyl, 1-cyanocyclopropyl, 1-methylcyclopropyl, 1-oxa-2,4-diazol-3-yl, 1-oxa-2,4-diazol-5-yl, 1-naphthylmethyl, 2-naphthylmethyl, 1-naphthylethyl or dimethylamino, each of which is optionally substituted with from (i) 1-3 R^d substituents; or (ii) 1-3 R^e substituents; or (iii) 1-3 R^g substituents; or (iv) 1-3 R^{13} substituents; or (v) 1-3 R^{14} substituents; or (vi) 1-3 R^{15} substituents, wherein at each occurrence, each of R^d, R^e, R^{13}, R^{14} or R^{15} substituents is further optionally substituted with from 1-3 R^{16} substituents. In certain embodiments, Z is hydrogen. In some embodiments, the hydrogen atoms in Z are optionally replaced by 1 to 12, or 1 to 8, or 1 to 6, or 1 to 3 or 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 deuterium atoms with at least 52.5%, 60%, 70%, 75%, 80%, 90%, 95%, 99%, 99.5% or 99.9% deuterium incorporation for each deuterium. In certain embodiments, each hydrogen atom in Z is optionally replaced by a deuterium atom with at least 52.5%, 60%, 70%, 75%,

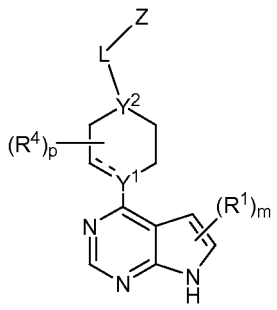
80%, 90%, 95%, 99%, 99.5% or 99.9% deuterium incorporation for each deuterium. All the other variables A, L, E and R^1 of formula (II) are as defined in any of the embodiments as described herein.

[0144] In some embodiments of compounds of formula (II), Z is phenyl, phenyl-CD_2-, benzyl, 4-methoxybenzyl, 1,1-dimethylbenzyl, 1-ethylbenzyl, (S)-1-ethylbenzyl, (R)-1-ethylbenzyl, 1-methylbenzyl, (S)-1-methylbenzyl, (R)-1-methylbenzyl, 1-methyl-3-methoxybenzyl, (S)-1-methyl-3-methoxybenzyl, (R)-1-methyl-3-methoxybenzyl, 2-phenylethyl, 1,3-benzodioxol-4-yl, 1,3-benzodioxol-5-yl, 4-indanyl, 5-indanyl, 1,2-benzoxazol-4-yl, 1,2-benzoxazol-5-yl, 1,2-benzoxazol-6-yl, 1,2-benzoxazol-7-yl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-thiophenyl, 3-thiophenyl, 4-chloro-2-thiophenyl, 4,5-dichloro-2-thiophenyl, 2,4-dimethyl-2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 5-methyl-2-benzo[b]thiophenyl, 6-methyl-2-benzo[b]thiophenyl, 4-methyl-2-benzo[b]thiophenyl, 7-methyl-2-benzo[b]thiophenyl, 3-benzo[b]thiophenyl, 1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl, 1-(difluoromethyl)-4-pyrazolyl, 1-(cyclopentyl)-4-pyrazolyl, 1-(ethyl)-4-pyrazolyl, 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl, 1-piperazinyl, 2-piperazinyl, 3-piperazinyl, methyl, ethyl, propyl, butyl, t-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-oxo-1-pyrrolidinyl, -CD_3, 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethyl, 1-(2-pyridyl)ethyl, (S)-1-(2-pyridyl)ethyl, (R)-1-(2-pyridyl)ethyl, 1-(3-pyridyl)ethyl, (S)-1-(3-pyridyl)ethyl, (R)-1-(3-pyridyl)ethyl, 1-(4-pyridyl)ethyl, (S)-1-(4-pyridyl)ethyl, (R)-1-(4-pyridyl)ethyl, 1-cyanocyclopropyl, 1-methylcyclopropyl, 1-oxa-2,4-diazol-3-yl, 1-oxa-2,4-diazol-5-yl, dimethylamino, 1-naphthylmethyl, 2-naphthylmethyl, 1-naphthylethyl, (R)-1-(1-naphthyl)ethyl or (S)-1-(1-naphthyl)ethyl, each of which is optionally substituted with from (i) 1-3 R^d substituents; or (ii) 1-3 R^e substituents; or (iii) 1-3 R^g substituents; or (iv) 1-3 R^{13} substituents; or (v) 1-3 R^{14} substituents; or (vi) 1-3 R^{15} substituents, wherein at each occurrence, each of R^d, R^e, R^{13}, R^{14} or R^{15} substituents is further optionally substituted with from 1-3 R^{16} substituents. In some instances, Z is phenyl substituted with from 1-2 substituents selected from F, Cl, CHF_2, CH_2F, CF_3, CH_3, -CN, NO_2, ethyl, propyl, butyl, isopropyl, -CD_3, -OCH_3, -OCD_3, -$OCH(CH_3)_2$, $N(CH_3)_2$, -$OCHF_2$ or -OCH_2F. In other instances, Z is 1,3-benzodioxol-4-yl, 1,3-benzodioxol-5-yl, 4-indanyl, 5-indanyl, 1,2-benzoxazol-4-yl, 1,2-benzoxazol-5-yl, 1,2-benzoxazol-6-yl, 1,2-benzoxazol-7-yl, 2-benzo[b]thiophenyl or 3-benzo[b]thiophenyl, each of which is optionally substituted with from 1-2 groups selected from CH_3, Cl, F, or OCH_3. In other instances, Z is 2-thiophenyl, 3-thiophenyl, 3-pyrazolyl, 4-pyrazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl or 1-oxa-2,4-diazol-3-yl or 1-oxa-2,4-diazol-5-yl, each of which is optionally substituted with 1-2 substituents selected from Cl, F, CHF_2, CF_3, CH_3, -OCH_3, ethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl. In yet other instances, Z is 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyridylmethyl, 3-pyridylmethyl, or 4-pyridylmethyl, each of which is optionally substituted with from 1-2 substituents selected from F, Cl, CHF_2, CH_2F, CF_3, CH_3, -CN, NO_2, ethyl, propyl, butyl, isopropyl, -CD_3, -OCH_3, -OCD_3, -$OCH(CH_3)_2$, $N(CH_3)_2$, -$OCHF_2$ or -OCH_2F. In other instances, Z is 1-ethylbenzyl, (S)-

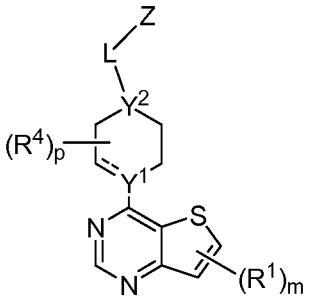
1-ethylbenzyl, (R)-1-ethylbenzyl, 1-methylbenzyl, (S)-1-methylbenzyl, (R)-1-methylbenzyl, 1-methyl-3-methoxybenzyl, (S)-1-methyl-3-methoxybenzyl, (R)-1-methyl-3-methoxybenzyl, 1-naphthylmethyl, 2-naphthylmethyl, 1-naphthylethyl, (R)-1-(1-naphthyl)ethyl or (S)-1-(1-naphthyl)ethyl, each of which is optionally substituted with from 1-2 substituents selected from F, Cl, CHF_2, CH_2F, CF_3, CH_3, $N(CH_3)_2$, -CN, NO_2, ethyl, propyl, butyl, isopropyl, $-CD_3$, $-OCH_3$, $-OCD_3$, $-OCH(CH_3)_2$, $-OCHF_2$ or $-OCH_2F$. In other instances, Z is C_{1-6}alkyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, 1-cyclopropylethyl, 1-cyclobutylethyl, 1-cyclopentylethyl, 1-cyclohexylethyl, each of which is optionally substituted with from 1-2 substituents selected from F, Cl, CHF_2, CH_2F, CF_3, CH_3, -CN, NO_2, ethyl, propyl, butyl, isopropyl, $-CD_3$, $-OCH_3$, $-OCD_3$, $-OCH(CH_3)_2$, $N(CH_3)_2$, $-OCHF_2$ or $-OCH_2F$. In some embodiments, the hydrogen atoms in Z are optionally replaced by 1 to 12, or 1 to 8, or 1 to 6, or 1 to 3 or 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 deuterium atoms with at least 52.5%, 60%, 70%, 75%, 80%, 90%, 95%, 99%, 99.5% or 99.9% deuterium incorporation for each deuterium. In certain embodiments, each hydrogen atom in Z is optionally replaced by a deuterium atom with at least 52.5%, 60%, 70%, 75%, 80%, 90%, 95%, 99%, 99.5% or 99.9% deuterium incorporation for each deuterium. All the other variables A, L, E and R^1 of formula (II) are as defined in any of the embodiments as described herein.

Subformulae of Formula I or II

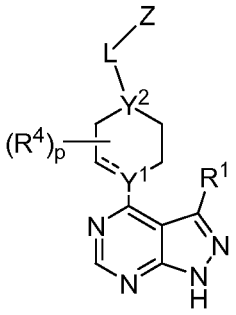
[0145] In one group of embodiments of the disclosure, compounds of formulas (I) or (II) have subformulas (IIa), (IIb) or (IIc):



IIa



IIb



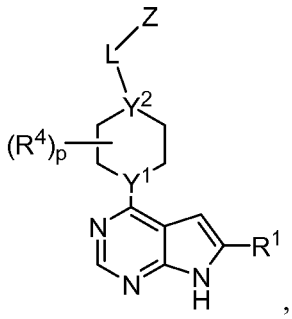
IIc

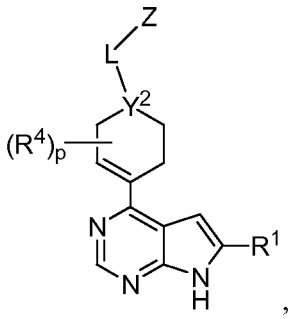
wherein:

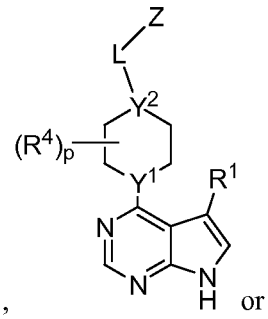
---- is a single bond or a double bond; Y^1 and Y^2 are each independently N, C or CH; each R^4 substituent is independently selected from –CN, C_{1-4} alkyl, C_{1-4} alkoxy, halogen, C_{1-4} haloalkyl or C_{1-4} haloalkoxy; or two R^4 substituents are taken together to form a $-(CH_2)_n-$ bridging linkage, which together with the atoms to which they are attached forms a 7- to 9-membered bicyclic ring, wherein n is 1, 2 or 3 and wherein the bicyclic ring is optionally substituted with from 1-2 substituents independently selected from C_{1-4} alkyl or halogen; the subscript p is 0, 1, 2, 3 or 4; the subscript m is 1 or 2; or optionally, two R^4

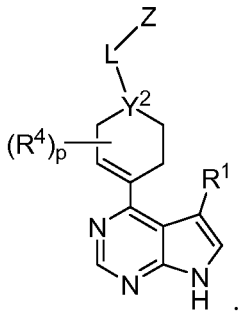
substituents, when attaching to the same carbon atom, are taken together with the atom to which they attach form a –C(=O)- linkage; and the substituents Z, L and R^1 are as defined in any of the embodiments disclosed herein. In some embodiments of compounds of formulas (IIa), (IIb) or (IIc), ---- is a single bond. The substituents Z, L and R^1 are as defined in any of the embodiments disclosed herein. In other embodiments, ---- is a double bond. In some embodiments of compounds of formulas (IIa), (IIb) or (IIc), the subscript p is zero. In certain embodiments of compounds of formulas (IIa), (IIb) or (IIc), the subscript p is 1, 2 or 3. In certain embodiments of compounds of formulas (IIa), (IIb) or (IIc), the subscript m is zero. In one embodiment of compounds of formulas (IIa), (IIb) or (IIc), the subscript m is 1. In another embodiment of compounds of formulas (IIa), (IIb) or (IIc), the subscript m is 2. In certain embodiments of compounds of formulas (IIa), (IIb) or (IIc), Y^1 and Y^2 are N. In certain embodiments of compounds of formulas (IIa), (IIb) or (IIc), Y^1 and Y^2 are CH. In certain embodiments of compounds of formulas (IIa), (IIb) or (IIc), Y^1 is N and Y^2 is CH. In certain embodiments of compounds of formulas (IIa), (IIb) or (IIc), Y^1 is CH and Y^2 is N. In other embodiments of compounds of formulas (IIa), (IIb) or (IIc), Y^1 is C and Y^2 is N. In certain embodiments of compounds of formulas (IIa), (IIb) or (IIc), Y^1 is C and Y^2 is CH. In certain embodiments of compounds of formulas (IIa), (IIb) or (IIc), R^4 is C_{1-4} alkyl or halogen. In other embodiments of compounds of formulas (IIa), (IIb) or (IIc), R^4 is F, Cl, $-OCH_3$, CF_3, CN, $-OCF_3$, $-CHF_2$, $-CH_2F$, $-OCH_2F$ or $-OCHF_2$. In one instance, the disclosure provides compounds having formula (IIa). The variables Y^1, Y^2, R^4, p, m, Z, L and R^1 are as defined in any of the embodiments disclosed herein. In another instance, the disclosure provides compounds having formula (IIb). The variables Y^1, Y^2, R^4, p, m, Z, L and R^1 are as defined in any of the embodiments disclosed herein. In yet another instance, the disclosure provides compounds having formula (IIc). The variables Y^1, Y^2, R^4, p, m, Z, L and R^1 are as defined in any of the embodiments disclosed herein.

[0146] In a second group of embodiments of the disclosure, compounds of formulas (I), (II) or (IIa) have subformulas (IIa-1), (IIa-2), (IIa-3) or (IIa-4):


IIa-1


IIa-2

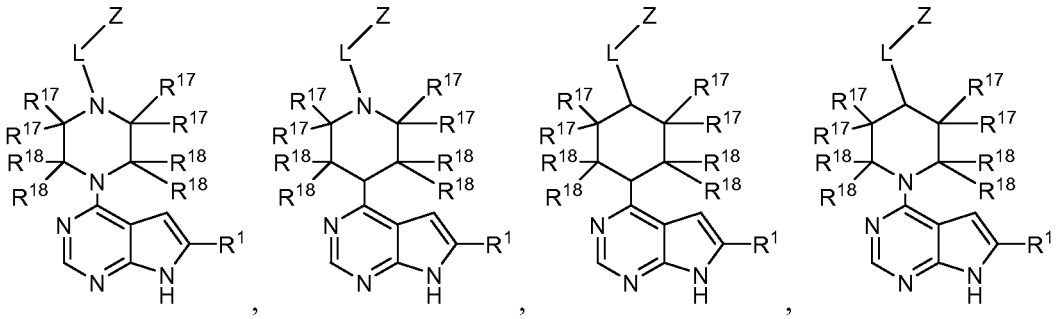

IIa-3 or


IIa-4

where the variables Y^1, Y^2, R^4, p, Z, L and R^1 are as defined in any of the embodiments disclosed herein. In one instance, the disclosure provides compounds having formula (IIa-1). In another instance, the

disclosure provides compounds having formula (IIa-2). In yet another instance, the disclosure provides compounds having formula (IIa-3). In still another instance, the disclosure provides compounds having formula (IIa-4). In some embodiments of compounds of formulas (IIa-1) or (IIa-3), Y^1 and Y^2 are CH. In other embodiments of compounds of formulas (IIa-1) or (IIa-3), Y^1 is CH and Y^2 is N. In other embodiments of compounds of formulas (IIa-1) or (IIa-3), Y^1 is N and Y^2 is CH. In some embodiments of compounds of formulas (IIa-1) or (IIa-3), Y^1 and Y^2 are N. In some embodiments of compounds of formulas (IIa-2) or (IIa-4), Y^2 is N. In other embodiments of compounds of formulas (IIa-2) or (IIa-4), Y^2 is CH. All the other variables R^4, p, Z, L and R^1 are as defined in any of the embodiments disclosed herein.

[0147] In a third group of embodiments of the disclosure, compounds of formulas (I), (II), (IIa) or (IIa-1) have subformulas (IIa-1a), (IIa-1b), (IIa-1c) or (IIa-1d):

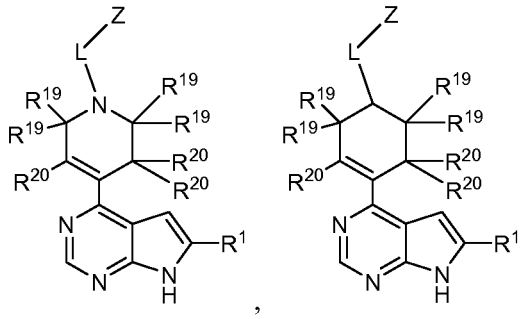


(IIa-1a) (IIa-1b) (IIa-1c) (IIa-1d)

where R^{17} and R^{18} are each independently selected from H, –CN, C_{1-4} alkyl, C_{1-4} alkoxy, halogen, C_{1-4} haloalkyl or C_{1-4} haloalkoxy; or two R^{17} substituents when attached to the same carbon atom are optionally taken together to form an oxo (i.e., =O) group; or two R^{18} substituents when attached to the same carbon atom are optionally taken together to form an oxo (i.e., =O) group, with the proviso that no more than two oxo groups are formed per ring. In some embodiments, each of R^{17} and R^{18} is H. In certain embodiments, R^{18} is H. In other embodiments, R^{17} is H. In some embodiments, R^{18} is H and each R^{17} is independently selected from H, –CN, C_{1-4} alkyl, C_{1-4} alkoxy, halogen, C_{1-4} haloalkyl or C_{1-4} haloalkoxy. In other embodiments, R^{18} is H and each R^{17} is independently selected from H, F, Cl, -OCH_3, CF_3, CN, -OCF_3, -CHF_2, -CH_2F, -OCH_2F or –$OCHF_2$. In some embodiments, 1 to 2 R^{18} substituents in any of formulas (IIa-1a), (IIa-1b), (IIa-1c) or (IIa-1d) are independently selected from F, Cl, -OCH_3, CF_3, CN, -OCF_3, -CHF_2, -CH_2F, -OCH_2F or –$OCHF_2$ and the other R^{18} substituents are H. In some embodiments, one set of R^{17} substituents attached to the same carbon atom are taken together to form an oxo group. In some embodiments, one set of R^{18} substituents attached to the same carbon atom are taken together to form an oxo group. In other embodiments, one set of R^{17} substituents attached to the same carbon atom

are taken together to form an oxo group and one set of R^{18} substituents attached to the same carbon atom are taken together to form an oxo group. In some embodiments, each of R^{17} and R^{18} in any of formulas (IIa-1a), (IIa-1b), (IIa-1c) or (IIa-1d) is D. All the other variables Z, L and R^1 are as defined in any of the embodiments disclosed herein.

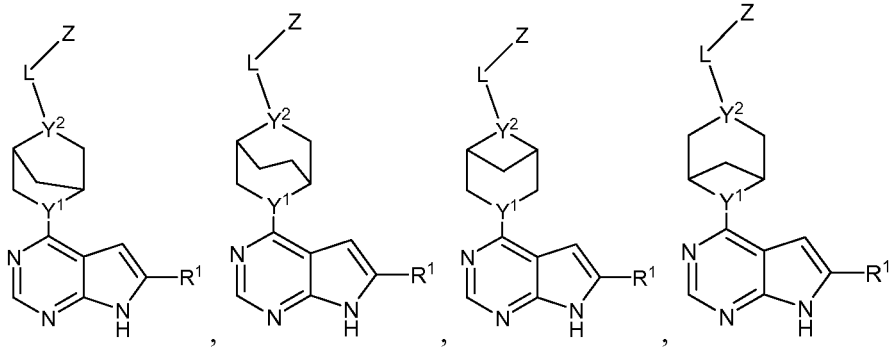
[0148] In a fourth group of embodiments of the disclosure, compounds of formulas (I), (II), (IIa) or (IIa-2) have subformulas (IIa-2a) or (IIa-2b):



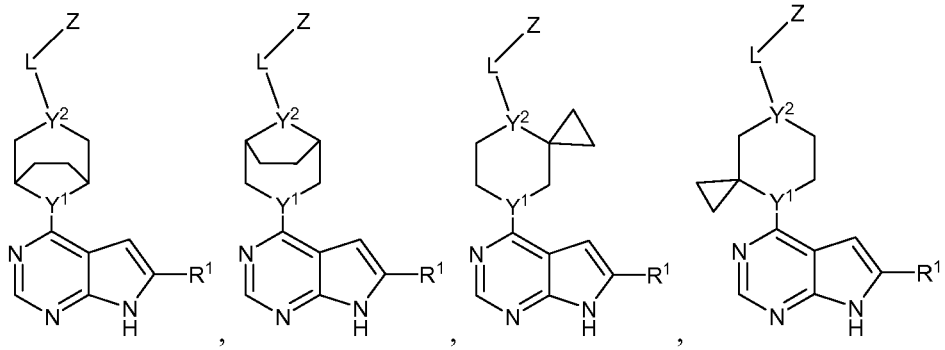
(IIa-2a) (IIa-2b)

where R^{19} and R^{20} are each independently H, –CN, C_{1-4} alkyl, C_{1-4} alkoxy, halogen, C_{1-4} haloalkyl or C_{1-4} haloalkoxy; or two R^{19} substituents when attached to the same carbon atom are optionally taken together to form an oxo (i.e., =O) group; or two R^{20} substituents when attached to the same carbon atom are optionally taken together to form an oxo (i.e., =O) group, with the proviso that no more than two oxo groups are formed per ring. In certain embodiments, R^{20} is H. In other embodiments, R^{19} is H. In one embodiment, each of R^{19} and R^{20} in any of formulas (IIa-2a) and (IIa-2b) is H. In some embodiments, R^{20} is H and each R^{19} is independently selected from H, –CN, C_{1-4} alkyl, C_{1-4} alkoxy, halogen, C_{1-4} haloalkyl or C_{1-4} haloalkoxy. In other embodiments, R^{20} is H and each R^{19} is independently selected from H, F, Cl, $-OCH_3$, CF_3, CN, $-OCF_3$, $-CHF_2$, $-CH_2F$, $-OCH_2F$ or $-OCHF_2$. In some embodiments, 1 or 2 R^{20} substituents in any of formulas (IIa-2a) or (IIa-2b) are independently selected from F, Cl, $-OCH_3$, CF_3, CN, $-OCF_3$, $-CHF_2$, $-CH_2F$, $-OCH_2F$ or $-OCHF_2$ and the other R^{20} substituents are H. In some embodiments, one set of R^{19} substituents attached to the same carbon atom are taken together to form an oxo group. In some embodiments, one set of R^{20} substituents attached to the same carbon atom are taken together to form an oxo group. In other embodiments, one set of R^{19} substituents attached to the same carbon atom are taken together to form an oxo group and one set of R^{20} substituents attached to the same carbon atom are taken together to form an oxo group. In some embodiments, each of R^{19} and R^{20} in any of formulas (IIa-2a) or (IIa-2b) is D. All the other variables Z, L and R^1 are as defined in any of the embodiments disclosed herein.

[0149] In a fifth group of embodiments of the disclosure, compounds of formulas (I), (II), (IIa) or (IIa-1) have subformulas (IIa-1e), (IIa-1f), (IIa-1g), (IIa-1h), (IIa-1i), (IIa-1j), (IIa-1k) or (IIa-1m):



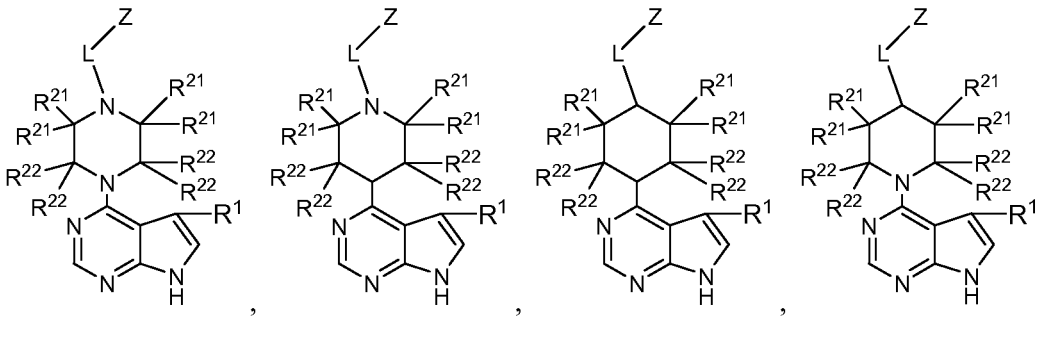
(IIa-1e) (IIa-1f) (IIa-1g) (IIa-1h)



(IIa-1i) (IIa-1j) (IIa-1k) (IIa-1m)

The variables Y^1, Y^2, L, Z and R^1 in any of formulas (IIa-1e), (IIa-1f), (IIa-1g), (IIa-1h), (IIa-1i), (IIa-1j), (IIa-1k) or (IIa-1m) are as defined in any of the embodiments disclosed herein. In some embodiments, Y^1 and Y^2 are CH. In other embodiments, Y^1 and Y^2 are CH. In yet other embodiments, Y^1 is N and Y^2 is CH. In other embodiments, Y^1 is CH and Y^2 is N.

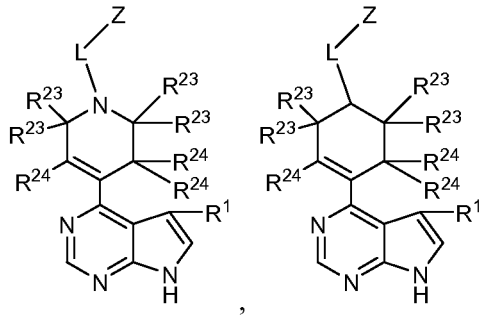
[0150] In a sixth group of embodiments of the disclosure, compounds of formulas (I), (II), (IIa) or (IIa-3) have subformulas (IIa-3a), (IIa-3b), (IIa-3c) or (IIa-3d):



(IIa-3a) (IIa-3b) (IIa-3c) (IIa-3d)

where R^{21} and R^{22} are each independently H, –CN, C_{1-4} alkyl, C_{1-4} alkoxy, halogen, C_{1-4} haloalkyl or C_{1-4} haloalkoxy; or two R^{21} substituents when attached to the same carbon atom are optionally taken together to form an oxo (i.e., =O) group; or two R^{22} substituents when attached to the same carbon atom are optionally taken together to form an oxo (i.e., =O) group, with the proviso that no more than two oxo groups are formed per ring. In some embodiments, each of R^{21} and R^{22} is H. In certain embodiments, R^{22} is H. In other embodiments, R^{21} is H. In some embodiments, R^{22} is H and each R^{21} is independently selected from H, –CN, C_{1-4} alkyl, C_{1-4} alkoxy, halogen, C_{1-4} haloalkyl or C_{1-4} haloalkoxy. In other embodiments, R^{22} is H and each R^{21} is independently selected from H, F, Cl, -OCH_3, CF_3, CN, -OCF_3, -CHF_2, -CH_2F, -OCH_2F or –$OCHF_2$. In some embodiments, 1 or 2 R^{22} substituents in any of formulas (IIa-1a), (IIa-1b), (IIa-1c) or (IIa-1d) are independently selected from F, Cl, -OCH_3, CF_3, CN, -OCF_3, -CHF_2, -CH_2F, -OCH_2F or –$OCHF_2$ and the other R^{22} substituents are H. In some embodiments, one set of R^{21} substituents attached to the same carbon atom are taken together to form an oxo group. In some embodiments, one set of R^{22} substituents attached to the same carbon atom are taken together to form an oxo group. In other embodiments, one set of R^{21} substituents attached to the same carbon atom are taken together to form an oxo group and one set of R^{22} substituents attached to the same carbon atom are taken together to form an oxo group. In some embodiments, each of R^{21} and R^{22} in any of formulas (IIa-1a), (IIa-1b), (IIa-1c) or (IIa-1d) is D. All the other variables Z, L and R^1 are as defined in any of the embodiments disclosed herein.

[0151] In a seventh group of embodiments of the disclosure, compounds of formulas (I), (II), (IIa) or (IIa-4) have subformulas (IIa-4a) or (IIa-4b):

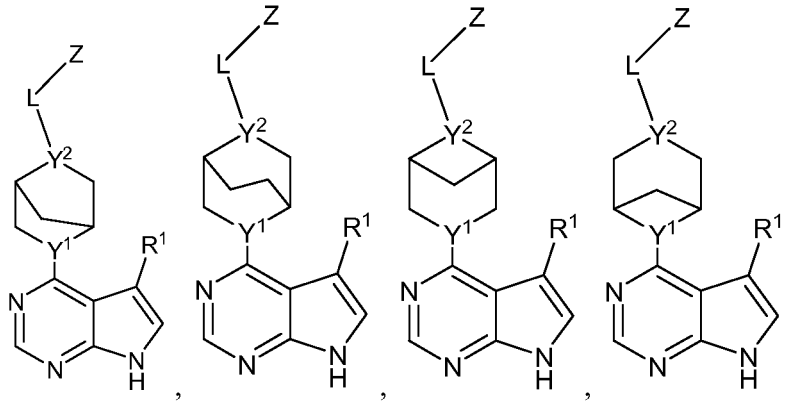


IIa-4a IIa-4b

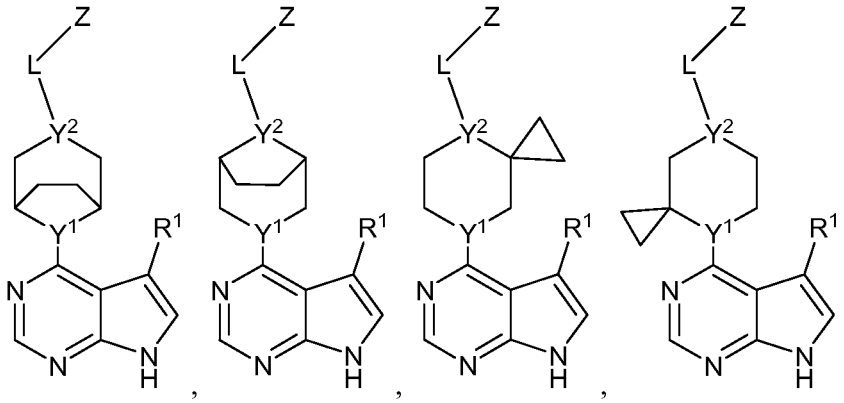
where R^{23} and R^{24} are each independently H, –CN, C_{1-4} alkyl, C_{1-4} alkoxy, halogen, C_{1-4} haloalkyl or C_{1-4} haloalkoxy; or two R^{23} substituents when attached to the same carbon atom are optionally taken together to form an oxo (i.e., =O) group; or two R^{24} substituents when attached to the same carbon atom are optionally taken together to form an oxo (i.e., =O) group, with the proviso that no more than two oxo groups are formed per ring. In some embodiments, each of R^{23} and R^{24} is H. In certain embodiments, R^{24} is H. In other embodiments, R^{23} is H. In some embodiments, R^{24} is H and each R^{23} is independently

selected from H, –CN, C_{1-4} alkyl, C_{1-4} alkoxy, halogen, C_{1-4} haloalkyl or C_{1-4} haloalkoxy. In other embodiments, R^{24} is H and each R^{23} is independently selected from H, F, Cl, -OCH_3, CF_3, CN, -OCF_3, -CHF_2, -CH_2F, -OCH_2F or –$OCHF_2$. In some embodiments, 1 to 2 R^{24} substituents in any of formulas (IIa-4a) or (IIa-4b) are independently selected from F, Cl, -OCH_3, CF_3, CN, -OCF_3, -CHF_2, -CH_2F, -OCH_2F or –$OCHF_2$ and the other R^{24} substituents are H. In some embodiments, one set of R^{23} substituents attached to the same carbon atom are taken together to form an oxo group. In some embodiments, one set of R^{24} substituents attached to the same carbon atom are taken together to form an oxo group. In other embodiments, one set of R^{23} substituents attached to the same carbon atom are taken together to form an oxo group and one set of R^{24} substituents attached to the same carbon atom are taken together to form an oxo group. In some embodiments, each of R^{23} and R^{24} in any of formulas (IIa-4a) or (IIa-4b) is D. All the other variables Z, L and R^1 are as defined in any of the embodiments disclosed herein.

[0152] In an eighth group of embodiments of the disclosure, compounds of formulas (I), (II), (IIa) or (IIa-3) have subformulas (IIa-3e), (IIa-3f), (IIa-3g), (IIa-3h), (IIa-3i), (IIa-3j), (IIa-3k) or (IIa-3m):



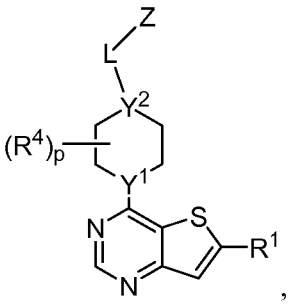
(IIa-3e) (IIa-3f) (IIa-3g) (IIa-3h),

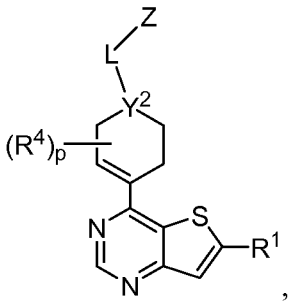


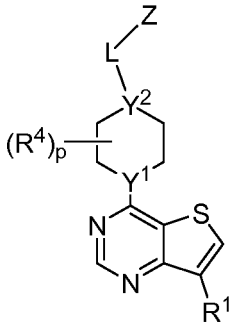
(IIa-3i) (IIa-3j) (IIa-3k) (IIa-3m)

The variables Y^1, Y^2, L, Z and R^1 in any of formulas (IIa-3e), (IIa-3f), (IIa-3g), (IIa-3h), (IIa-3i), (IIa-3j), (IIa-3k) or (IIa-3m) are as defined in any of the embodiments disclosed herein. In some embodiments, Y^1 and Y^2 are CH. In other embodiments, Y^1 and Y^2 are CH. In yet other embodiments, Y^1 is N and Y^2 is CH. In other embodiments, Y^1 is CH and Y^2 is N.

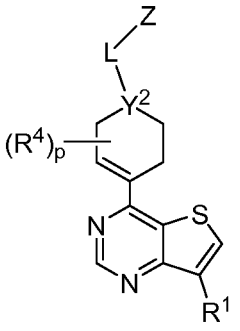
[0153] In an ninth group of embodiments of the disclosure, compounds of formulas (I), (II) or (IIb) have subformulas (IIb-1), (IIb-2), (IIb-3) or (IIb-4):


IIb-1


IIb-2

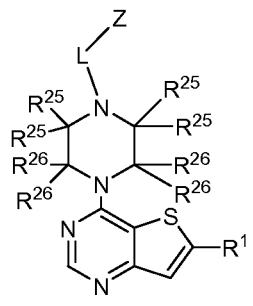

IIb-3

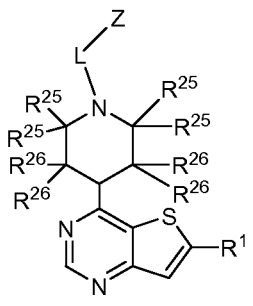
or

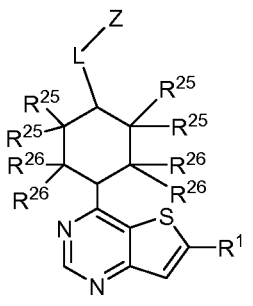

IIb-4

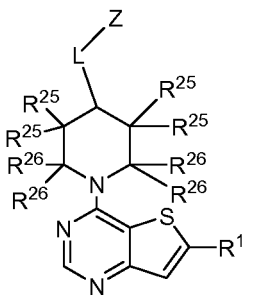
where the variables Y^1, Y^2, R^4, p, Z, L and R^1 are as defined in any of the embodiments disclosed herein. In one instance, the disclosure provides compounds having formula (IIb-1). In another instance, the disclosure provides compounds having formula (IIb-2). In yet another instance, the disclosure provides compounds having formula (IIb-3). In still another instance, the disclosure provides compounds having formula (IIb-4). In some embodiments of compounds of formulas (IIb-1) or (IIb-3), Y^1 and Y^2 are CH. In other embodiments of compounds of formulas (IIb-1) or (IIb-3), Y^1 is CH and Y^2 is N. In other embodiments of compounds of formulas (IIb-1) or (IIb-3), Y^1 and Y^2 are N. In some embodiments of compounds of formulas (IIb-1) or (IIb-3), Y^1 is N and Y^2 is CH. In other embodiments of compounds of formulas (IIb-2) or (II-4), Y^2 is N. In other embodiments of compounds of formulas (IIa-2) or (IIa-4), Y^2 is CH. All the other variables R^4, p, Z, L and R^1 are as defined in any of the embodiments disclosed herein.

[0154] In a tenth group of embodiments of the disclosure, compounds of formulas (I), (II), (IIb) or (IIb-1) have subformulas (IIb-1a), (IIb-1b), (IIb-1c) or (IIb-1d):


(IIb-1a)

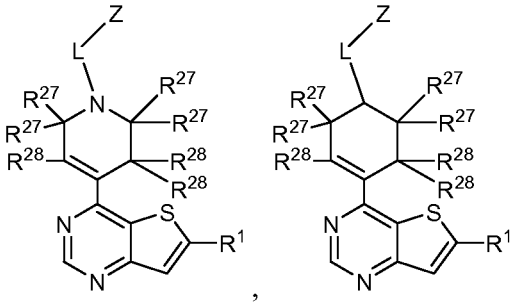

(IIb-1b)


(IIb-1c)


(IIb-1d)

where R^{25} and R^{26} are each independently H, –CN, C_{1-4} alkyl, C_{1-4} alkoxy, halogen, C_{1-4} haloalkyl or C_{1-4} haloalkoxy; or two R^{25} substituents when attached to the same carbon atom are optionally taken together to form an oxo (i.e., =O) group; or two R^{26} substituents when attached to the same carbon atom are optionally taken together to form an oxo (i.e., =O) group, with the proviso that no more than two oxo groups are formed per ring. In some embodiments, each of R^{25} and R^{26} is H. In certain embodiments, R^{26} is H. In other embodiments, R^{25} is H. In some embodiments, R^{26} is H and each R^{25} is independently selected from H, –CN, C_{1-4} alkyl, C_{1-4} alkoxy, halogen, C_{1-4} haloalkyl or C_{1-4} haloalkoxy. In other embodiments, R^{26} is H and each R^{25} is independently selected from H, F, Cl, -OCH_3, CF_3, CN, -OCF_3, -CHF_2, -CH_2F, -OCH_2F or –$OCHF_2$. In some embodiments, 1 to 2 R^{26} substituents in any of formulas (IIb-1a), (IIb-1b), (IIb-1c) or (IIb-1d) are independently selected from F, Cl, -OCH_3, CF_3, CN, -OCF_3, -CHF_2, -CH_2F, -OCH_2F or –$OCHF_2$ and the other R^{26} substituents are H. In some embodiments, one set of R^{25} substituents attached to the same carbon atom are taken together to form an oxo group. In some embodiments, one set of R^{26} substituents attached to the same carbon atom are taken together to form an oxo group. In other embodiments, one set of R^{25} substituents attached to the same carbon atom are taken together to form an oxo group and one set of R^{26} substituents attached to the same carbon atom are taken together to form an oxo group. In some embodiments, each of R^{25} and R^{26} in any of formulas (IIb-1a), (IIb-1b), (IIb-1c) or (IIb-1d) is D. All the other variables Z, L and R^1 are as defined in any of the embodiments disclosed herein.

[0155] In an eleventh group of embodiments of the disclosure, compounds of formulas (I), (II), (IIb) or (IIb-2) have subformulas (IIb-2a) or (IIb-2b):

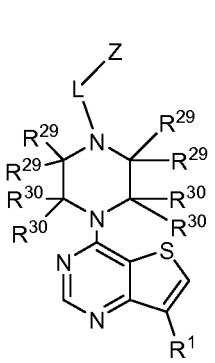


IIb-2a IIb-2b

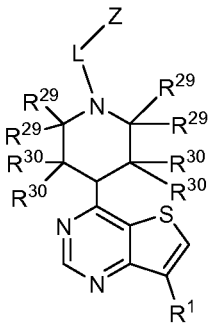
where R^{27} and R^{28} are each independently H, –CN, C_{1-4} alkyl, C_{1-4} alkoxy, halogen, C_{1-4} haloalkyl or C_{1-4} haloalkoxy; or two R^{27} substituents when attached to the same carbon atom are optionally taken together to form an oxo (i.e., =O) group; or two R^{28} substituents when attached to the same carbon atom are optionally taken together to form an oxo (i.e., =O) group, with the proviso that no more than two oxo groups are formed per ring. In some embodiments, each of R^{27} and R^{28} is H. In certain embodiments, R^{28} is H. In other embodiments, R^{27} is H. In some embodiments, R^{28} is H and each R^{27} is independently selected from H, –CN, C_{1-4} alkyl, C_{1-4} alkoxy, halogen, C_{1-4} haloalkyl or C_{1-4} haloalkoxy. In other embodiments, R^{28} is H and each R^{27} is independently selected from H, F, Cl, -OCH_3, CF_3, CN, -OCF_3, -

CHF_2, $-CH_2F$, $-OCH_2F$ or $-OCHF_2$. In some embodiments, 1 to 2 R^{28} substituents in any of formulas (IIb-2a) or (IIb-2b) are independently selected from F, Cl, $-OCH_3$, CF_3, CN, $-OCF_3$, $-CHF_2$, $-CH_2F$, $-OCH_2F$ or $-OCHF_2$ and the other R^{28} substituents are H. In some embodiments, one set of R^{27} substituents attached to the same carbon atom are taken together to form an oxo group. In some embodiments, one set of R^{28} substituents attached to the same carbon atom are taken together to form an oxo group. In other embodiments, one set of R^{27} substituents attached to the same carbon atom are taken together to form an oxo group and one set of R^{28} substituents attached to the same carbon atom are taken together to form an oxo group. In some embodiments, each of R^{27} and R^{28} in any of formulas (IIb-2a) or (IIb-2b) is D. All the other variables Z, L and R^1 are as defined in any of the embodiments disclosed herein.

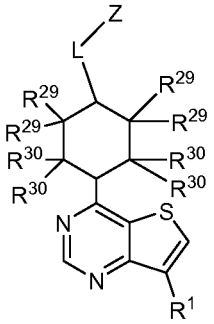
[0156] In a twelfth group of embodiments of the disclosure, compounds of formulas (I), (II), (IIb) or (IIb-3) have subformulas: (IIb-3a), (IIb-3b), (IIb-3c) or (IIb-3d):



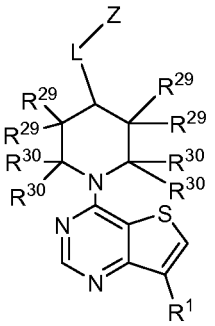
(IIb-3a)



(IIb-3b)



(IIb-3c)

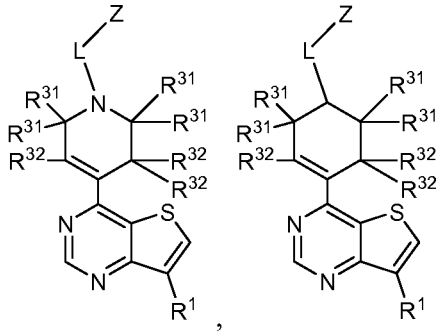


(IIb-3d):

where R^{29} and R^{30} are each independently H, –CN, C_{1-4} alkyl, C_{1-4} alkoxy, halogen, C_{1-4} haloalkyl or C_{1-4} haloalkoxy; or two R^{29} substituents when attached to the same carbon atom are optionally taken together to form an oxo (i.e., =O) group; or two R^{30} substituents when attached to the same carbon atom are optionally taken together to form an oxo (i.e., =O) group, with the proviso that no more than two oxo groups are formed per ring. In some embodiments, each of R^{29} and R^{30} is H. In certain embodiments, R^{30} is H. In other embodiments, R^{29} is H. In some embodiments, R^{30} is H and each R^{29} is independently selected from H, –CN, C_{1-4} alkyl, C_{1-4} alkoxy, halogen, C_{1-4} haloalkyl or C_{1-4} haloalkoxy. In other embodiments, R^{30} is H and each R^{29} is independently selected from H, F, Cl, $-OCH_3$, CF_3, CN, $-OCF_3$, $-CHF_2$, $-CH_2F$, $-OCH_2F$ or $-OCHF_2$. In some embodiments, 1 to 2 R^{30} substituents in any of formulas (IIb-3a), (IIb-3b), (IIb-3c) or (IIb-3d) are independently selected from F, Cl, $-OCH_3$, CF_3, CN, $-OCF_3$, $-CHF_2$, $-CH_2F$, $-OCH_2F$ or $-OCHF_2$ and the other R^{30} substituents are H. In some embodiments, one set of R^{29} substituents attached to the same carbon atom are taken together to form an oxo group. In some embodiments, one set of R^{30} substituents attached to the same carbon atom are taken together to form an oxo group. In other embodiments, one set of R^{29} substituents attached to the same carbon atom are taken

together to form an oxo group and one set of R^{30} substituents attached to the same carbon atom are taken together to form an oxo group. In some embodiments, each of R^{29} and R^{30} in any of formulas (IIb-3a), (IIb-3b), (IIb-3c) or (IIb-3d) is D. All the other variables Z, L and R^1 are as defined in any of the embodiments disclosed herein.

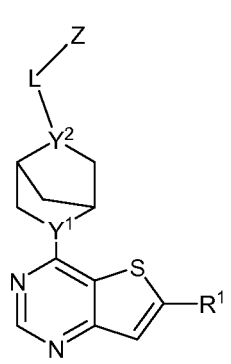
[0157] In a thirteenth group of embodiments of the disclosure, compounds of formulas (I), (II), (IIb) or (IIb-4) have subformulas: (IIb-4a) or (IIb-4b):

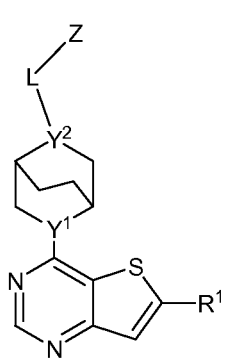


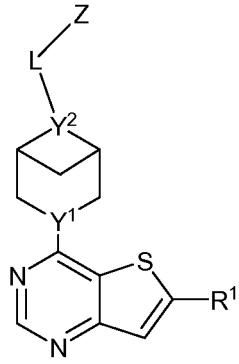
(IIb-4a) (IIb-4b)

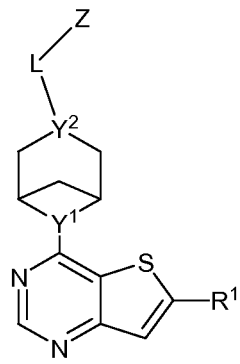
where R^{31} and R^{32} are each independently H, –CN, C_{1-4} alkyl, C_{1-4} alkoxy, halogen, C_{1-4} haloalkyl or C_{1-4} haloalkoxy; or two R^{31} substituents when attached to the same carbon atom are optionally taken together to form an oxo (i.e., =O) group; or two R^{32} substituents when attached to the same carbon atom are optionally taken together to form an oxo (i.e., =O) group, with the proviso that no more than two oxo groups are formed per ring. In some embodiments, each of R^{31} and R^{32} is H. In certain embodiments, R^{32} is H. In other embodiments, R^{31} is H. In some embodiments, R^{32} is H and each R^{31} is independently selected from H, –CN, C_{1-4} alkyl, C_{1-4} alkoxy, halogen, C_{1-4} haloalkyl or C_{1-4} haloalkoxy. In other embodiments, R^{32} is H and each R^{31} is independently selected from H, F, Cl, -OCH_3, CF_3, CN, -OCF_3, -CHF_2, -CH_2F, -OCH_2F or –$OCHF_2$. In some embodiments, 1 to 2 R^{32} substituents in any of formulas (IIb-4a) or (IIb-4b) are independently selected from F, Cl, -OCH_3, CF_3, CN, -OCF_3, -CHF_2, -CH_2F, -OCH_2F or –$OCHF_2$ and the other R^{32} substituents are H. In some embodiments, one set of R^{31} substituents attached to the same carbon atom are taken together to form an oxo group. In some embodiments, one set of R^{32} substituents attached to the same carbon atom are taken together to form an oxo group. In other embodiments, one set of R^{31} substituents attached to the same carbon atom are taken together to form an oxo group and one set of R^{32} substituents attached to the same carbon atom are taken together to form an oxo group. In some embodiments, each of R^{31} and R^{32} in any of formulas (IIb-4a) or (IIb-4b) is D. All the other variables Z, L and R^1 are as defined in any of the embodiments disclosed herein.

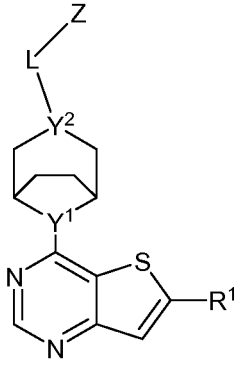
[0158] In a fourteenth group of embodiments of the disclosure, compounds of formulas (I), (II), (IIb), (IIb-1) or (IIb-3) have subformulas: (IIb-1e), (IIb-1f), (IIb-1g), (IIb-1h), (IIb-1i), (IIb-1j), (IIb-1k), (IIb-1m), (IIb-3e), (IIb-3f), (IIb-3g), (IIb-3h), (IIb-3i), (IIb-3j), (IIb-3k) or (IIb-3m):

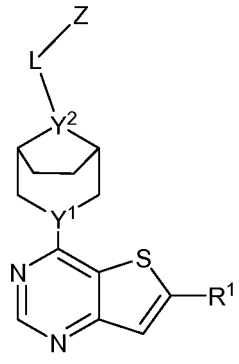

(IIb-1e),

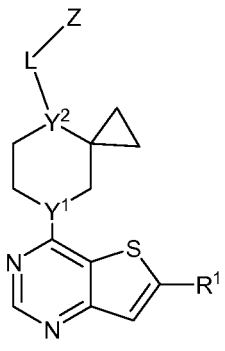

(IIb-1f),

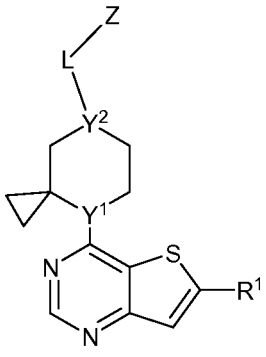

(IIb-1g),

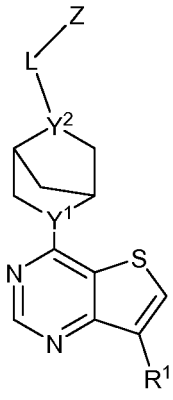

(IIb-1h),

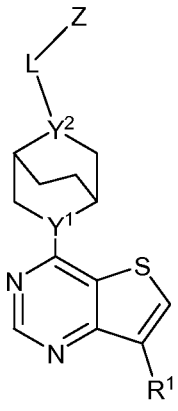

(IIb-1i),

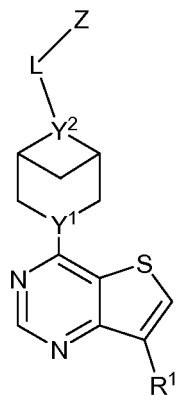

(IIb-1j),

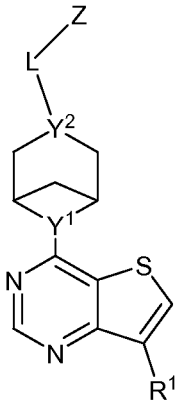

(IIb-1k),

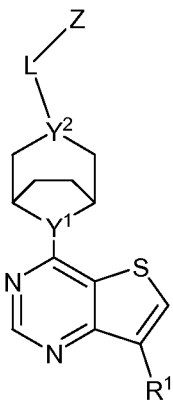

(IIb-1m),

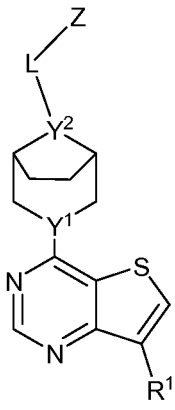

(IIb-3e),

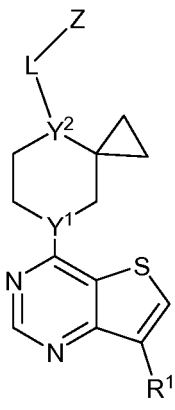

(IIb-3f),

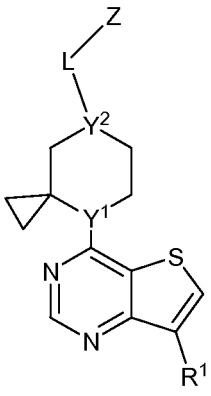

(IIb-3g),


(IIb-3h),


(IIb-3i),

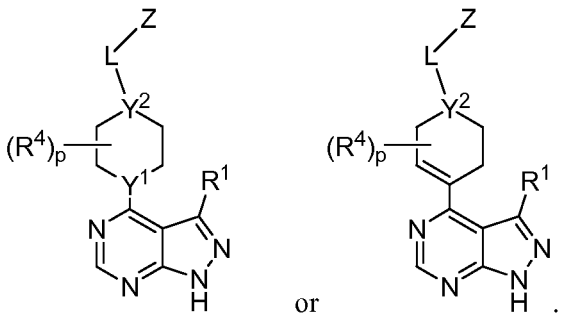

(IIb-3j),


(IIb-3k),


(IIb-3m):

The variables Y^1, Y^2, L, Z and R^1 in any of formulas (IIb-1e), (IIb-1f), (IIb-1g), (IIb-1h), (IIb-1i), (IIb-1j), (IIb-1k), (IIb-1m), (IIb-3e), (IIb-3f), (IIb-3g), (IIb-3h), (IIb-3i), (IIb-3j), (IIb-3k) or (IIb-3m) are as defined in any of the embodiments disclosed herein. In some embodiments, Y^1 and Y^2 are CH. In other embodiments, Y^1 and Y^2 are CH. In yet other embodiments, Y^1 is N and Y^2 is CH. In other embodiments, Y^1 is CH and Y^2 is N.

[0159] In a fifteenth group of embodiments of the disclosure, compounds of formulas (I), (II), (IIc) have subformulas (IIc-1) or (IIc-2):

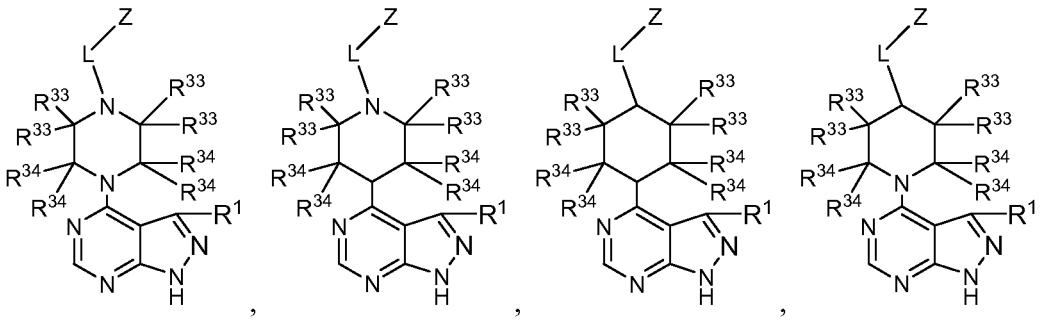


or

IIc-1 IIc-2

where the variables Y^1, Y^2, R^4, p, Z, L and R^1 are as defined in any of the embodiments disclosed herein. In one instance, the disclosure provides compounds having formula (IIc-1). In another instance, the disclosure provides compounds having formula (IIc-2). In some embodiments of compounds of formula (IIc-1), Y^1 and Y^2 are CH. In other embodiments of compounds of formula (IIc-1), Y^1 is CH and Y^2 is N. In other embodiments of compounds of formulas (IIc-1), Y^1 and Y^2 are N. In some embodiments of compounds of formulas (IIc-1), Y^1 is N and Y^2 is CH. In other embodiments of compounds of formulas (IIc-2), Y^2 is N. In other embodiments of compounds of formulas (IIc-2), Y^2 is CH. All the other variables R^4, p, Z, L and R^1 are as defined in any of the embodiments disclosed herein.

[0160] In a sixteenth group of embodiments of the disclosure, compounds of formulas (I), (II), (IIc) or (IIc-1) have subformulas (IIc-1a), (IIc-1b), (IIc-c) or (IIc-1d):

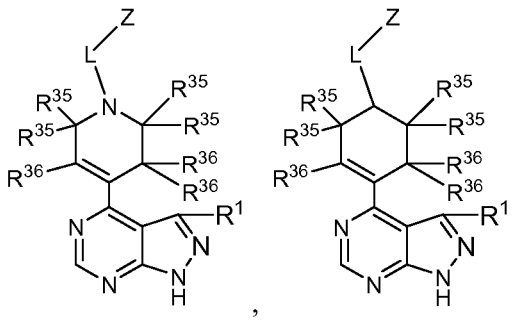


(IIc-1a) (IIc-1b) (IIc-1c) (IIc-1d):

where R^{33} and R^{34} are each independently H, –CN, C_{1-4} alkyl, C_{1-4} alkoxy, halogen, C_{1-4} haloalkyl or C_{1-4} haloalkoxy; or two R^{33} substituents when attached to the same carbon atom are optionally taken together to form an oxo (i.e., =O) group; or two R^{34} substituents when attached to the same carbon atom are optionally taken together to form an oxo (i.e., =O) group, with the proviso that no more than two oxo groups are formed per ring. In some embodiments, each of R^{33} and R^{34} is H. In certain embodiments, R^{34} is H. In other embodiments, R^{33} is H. In some embodiments, R^{34} is H and each R^{33} is independently selected from H, –CN, C_{1-4} alkyl, C_{1-4} alkoxy, halogen, C_{1-4} haloalkyl or C_{1-4} haloalkoxy. In other embodiments, R^{34} is H and each R^{33} is independently selected from H, F, Cl, -OCH_3, CF_3, CN, -OCF_3, -

CHF_2, $-CH_2F$, $-OCH_2F$ or $-OCHF_2$. In some embodiments, 1 to 2 R^{34} substituents in any of formulas (IIc-1a), (IIc-1b), (IIc-1c) or (IIc-1d) are independently selected from F, Cl, $-OCH_3$, CF_3, CN, $-OCF_3$, $-CHF_2$, $-CH_2F$, $-OCH_2F$ or $-OCHF_2$ and the other R^{34} substituents are H. In some embodiments, one set of R^{33} substituents attached to the same carbon atom are taken together to form an oxo group. In some embodiments, one set of R^{34} substituents attached to the same carbon atom are taken together to form an oxo group. In other embodiments, one set of R^{33} substituents attached to the same carbon atom are taken together to form an oxo group and one set of R^{34} substituents attached to the same carbon atom are taken together to form an oxo group. In some embodiments, each of R^{33} and R^{34} in any of formulas (IIc-1a), (IIc-1b), (IIc-1c) or (IIc-1d) is D. All the other variables Z, L and R^1 are as defined in any of the embodiments disclosed herein.

[0161] In a seventeenth group of embodiments of the disclosure, compounds of formulas (I), (II), (IIc) or (IIc-2) have subformulas (IIc-2a) or (IIc-2b):

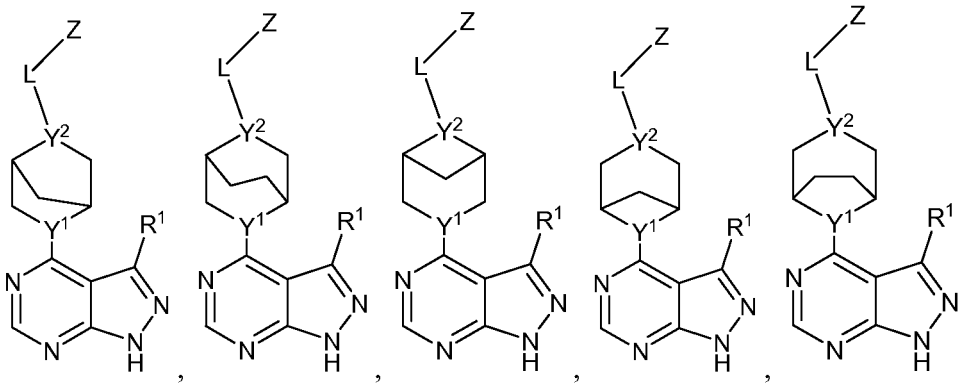


(IIc-2a) (IIc-2b)

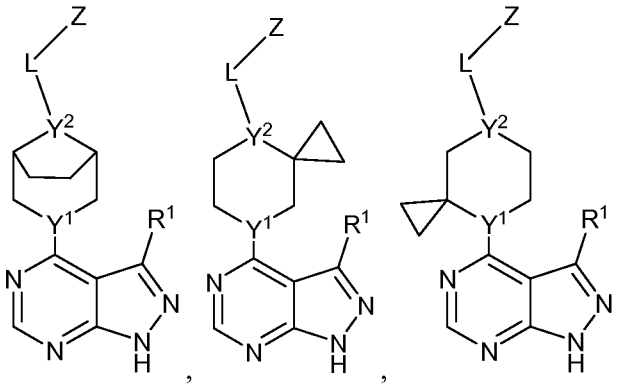
where R^{35} and R^{36} are each independently H, –CN, C_{1-4} alkyl, C_{1-4} alkoxy, halogen, C_{1-4} haloalkyl or C_{1-4} haloalkoxy; or two R^{35} substituents when attached to the same carbon atom are optionally taken together to form an oxo (i.e., =O) group; or two R^{36} substituents when attached to the same carbon atom are optionally taken together to form an oxo (i.e., =O) group, with the proviso that no more than two oxo groups are formed per ring. In some embodiments, each of R^{35} and R^{36} is H. In certain embodiments, R^{36} is H. In other embodiments, R^{35} is H. In some embodiments, R^{36} is H and each R^{35} is independently selected from H, –CN, C_{1-4} alkyl, C_{1-4} alkoxy, halogen, C_{1-4} haloalkyl or C_{1-4} haloalkoxy. In other embodiments, R^{36} is H and each R^{35} is independently selected from H, F, Cl, $-OCH_3$, CF_3, CN, $-OCF_3$, $-CHF_2$, $-CH_2F$, $-OCH_2F$ or $-OCHF_2$. In some embodiments, 1 to 2 R^{36} substituents in any of formulas (IIc-2a) or (IIc-2b) are independently selected from F, Cl, $-OCH_3$, CF_3, CN, $-OCF_3$, $-CHF_2$, $-CH_2F$, $-OCH_2F$ or $-OCHF_2$ and the other R^{36} substituents are H. In some embodiments, one set of R^{35} substituents attached to the same carbon atom are taken together to form an oxo group. In some embodiments, one set of R^{36} substituents attached to the same carbon atom are taken together to form an oxo group. In other embodiments, one set of R^{35} substituents attached to the same carbon atom are taken together to form an

oxo group and one set of R^{36} substituents attached to the same carbon atom are taken together to form an oxo group. In some embodiments, each of R^{35} and R^{36} in any of formulas (IIc-2a) or (IIc-2b is D. All the other variables Z, L and R^1 are as defined in any of the embodiments disclosed herein.

[0162] In an eighteenth group of embodiments of the disclosure, compounds of formulas (I), (II), (IIc) or (IIc-1) have subformulas (IIc-1e), (IIc-1f), (IIc-1g), (IIc-1h), (IIc-1i), (IIc-1j), (IIc-1k) or (IIc-1m):



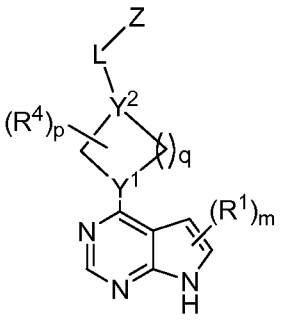
(IIc-1e), (IIc-1f), (IIc-1g), (IIc-1h), (IIc-1i),



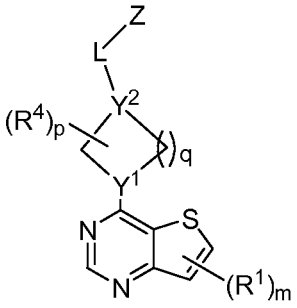
(IIc-1j), (IIc-1k), (IIc-1m):

The variables Y^1, Y^2, L, Z and R^1 in any of formulas (IIc-1e), (IIc-1f), (IIc-1g), (IIc-1h), (IIc-1i), (IIc-1j), (IIc-1k) or (IIc-1m) are as defined in any of the embodiments disclosed herein. In some embodiments, Y^1 and Y^2 are CH. In other embodiments, Y^1 and Y^2 are CH. In yet other embodiments, Y^1 is N and Y^2 is CH. In other embodiments, Y^1 is CH and Y^2 is N.

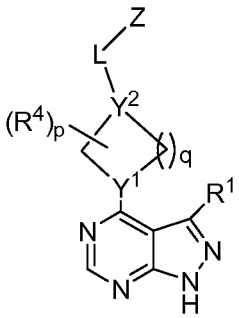
[0163] In a nineteenth group of embodiments of the disclosure, compounds of formulas (I) or (II) have subformulas (IId), (IIe) or (IIf):



IId



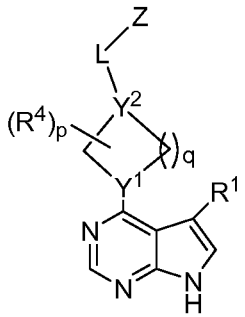
IIe



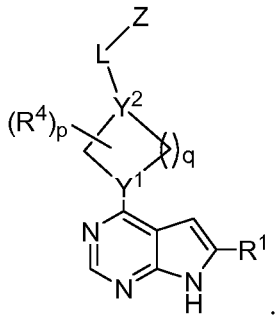
IIf

where the variables Z, L, Y^1, Y^2, R^4, R^1, p, q and m are as defined in any of the embodiments disclosed herein. In some embodiments, the variable q in any of formulas (IId), (IIe) or (IIf) is 1. In other embodiments, the variable q in any of formulas (IId), (IIe) or (IIf) is 2. The other variables are as defined in any of the embodiments disclosed herein. In some embodiments, the subscript p in any of formulas (IId), (IIe) or (IIf) is 0. In other embodiments, the subscript p in any of formulas (IId), (IIe) or (IIf) is 1, 2 or 3. In one embodiment, the disclosure provides compounds having formula (IId). In another embodiment, the disclosure provides compounds having formula (IIe). In another embodiment, the disclosure provides compounds having formula (IIf). In some embodiments of compounds of any of formulas (IId), (IIe) or (IIf), Y^1 and Y^2 are each independently N or CH; each R^4 substituent is independently selected from C_{1-4} alkyl or halogen or two R^4 substituents are taken together to form a $-(CH_2)_n-$ bridging linkage, which together with the atoms to which they are attached forms a 5- to 8-membered bicyclic ring, wherein n is 1, 2 or 3 and wherein the bicyclic ring is optionally substituted with from 1-2 substituents independently selected from C_{1-4} alkyl or halogen; or two R^4 substituents, when attached to the same carbon atom, are optionally taken together to form an oxo (i.e., =O) group; the subscript q is 1 or 2; the subscript p is 0, 1, 2, 3 or 4; and the subscript m is 1 or 2. In some instances, m is 1. In other instances, m is 2.

[0164] In a twentieth group of embodiments of the disclosure, compounds of formulas (I), (II) or (IId) have subformulas (IId-1) or (IId-2):



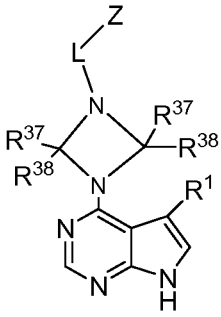
IId-1

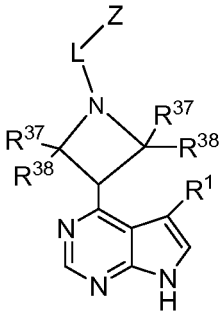


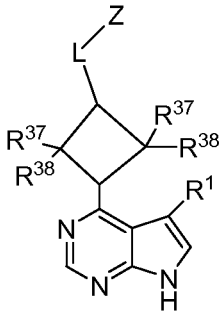
IId-2

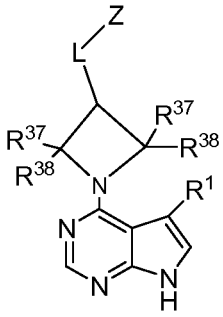
where the variables Y^1, Y^2, R^4, p, q, Z, L and R^1 are as defined in any of the embodiments disclosed herein. As indicated in the subformulas, $(R^4)_p$- means that one or more R^4 substituents, when present, covalently bond to any of the appropriate carbon atoms in the heterocyclic or carbocyclic ring containing Y^1 and Y^2 set forth in the subformulas. In one instance, the disclosure provides compounds having formula (IId-1). In another instance, the disclosure provides compounds having formula (IId-2). In some embodiments of compounds of formulas (IId-1) or (IId-2), Y^1 and Y^2 are CH. In other embodiments of compounds of formulas (IId-1) or (IId-2), Y^1 is CH and Y^2 is N. In other embodiments of compounds of formulas (IId-1) or (IId-2), Y^1 and Y^2 are N. In some embodiments of compounds of formulas (IId-1) or (IId-2), Y^1 is N and Y^2 is CH. In some embodiments of compounds of formulas (IId-1) or (IId-2) as described herein, q is 1. In other embodiments of compounds of formulas (IId-1) or (IId-2), q is 2. All the other variables R^4, p, Z, L and R^1 are as defined in any of the embodiments disclosed herein.

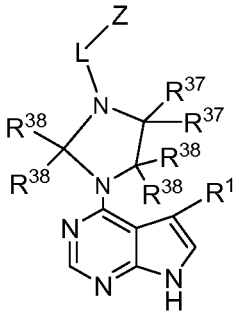
[0165] In a 21st group of embodiments of the disclosure, compounds of formulas (I), (II), (IId) or (IId-1) have subformulas (IId-1a), (IId-1b), (IId-1c), (IId-1d), (IId-1e), (IId-1f), (IId-1g), (IId-1h) or (IId-1i):

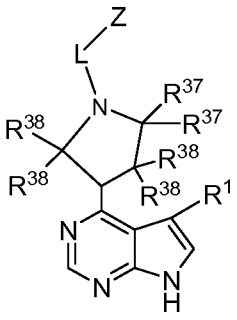

(IId-1a),

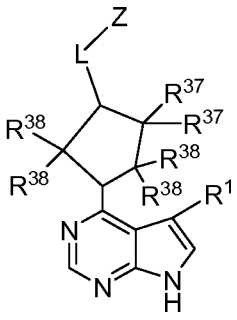

(IId-1b),

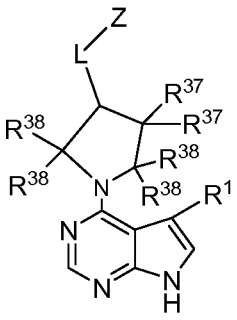

(IId-1c),

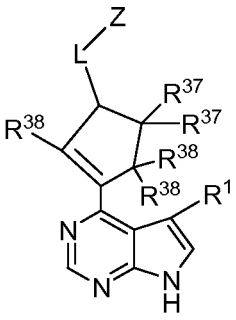

(IId-1d),


(IId-1e),


(IId-1f),


(IId-1g),

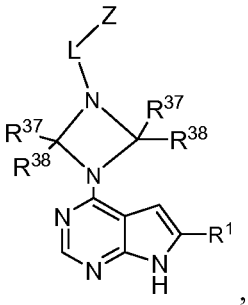

(IId-1h),


(IId-1i)

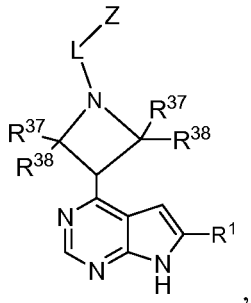
where R^{37} and R^{38} are each independently H, –CN, C_{1-4} alkyl, C_{1-4} alkoxy, halogen, C_{1-4} haloalkyl or C_{1-4} haloalkoxy; or two R^{37} substituents when attached to the same carbon atom are optionally taken together to form an oxo (i.e., =O) group; or two R^{38} substituents when attached to the same carbon atom are optionally taken together to form an oxo (i.e., =O) group; or two R^{37} and R^{38} substituents when attached to the same carbon atom are optionally taken together to form an oxo (i.e., =O) group, with the proviso that

no more than two oxo groups are formed per ring. In some embodiments, each of R^{37} and R^{38} is H. In certain embodiments, R^{38} is H. In other embodiments, R^{37} is H. In some embodiments, R^{38} is H and each R^{37} is independently selected from H, –CN, C_{1-4} alkyl, C_{1-4} alkoxy, halogen, C_{1-4} haloalkyl or C_{1-4} haloalkoxy. In other embodiments, R^{38} is H and each R^{37} is independently selected from H, F, Cl, -OCH_3, CF_3, CN, -OCF_3, -CHF_2, -CH_2F, -OCH_2F or –$OCHF_2$. In some embodiments, 1 to 2 R^{38} substituents in any of formulas (IId-1a), (IId-1b), (IId-1c), (IId-1d), (IId-1e), (IId-1f), (IId-1g), (IId-1h) or (IId-1i) are independently selected from F, Cl, -OCH_3, CF_3, CN, -OCF_3, -CHF_2, -CH_2F, -OCH_2F or –$OCHF_2$ and the other R^{38} substituents are H. In some embodiments, two R^{37} substituents attached to the same carbon atom are taken together to form an oxo group. In some embodiments, one set of R^{38} substituents attached to the same carbon atom are taken together to form an oxo group. In other embodiments, one set of R^{37} substituents attached to the same carbon atom are taken together to form an oxo group and one set of R^{38} substituents attached to the same carbon atom are taken together to form an oxo group. In yet other embodiments, one set of R^{37} and R^{38} substituents when attached to the same carbon atom are taken together to form an oxo group. In other embodiments, two sets of R^{38} substituents attached to the same carbon atom are taken together to form an oxo group. In some embodiments, each of R^{37} and R^{38} in any of formulas (IId-1a), (IId-1b), (IId-1c), (IId-1d), (IId-1e), (IId-1f), (IId-1g), (IId-1h) or (IId-1i) is D. All the other variables Z, L and R^1 are as defined in any of the embodiments disclosed herein.

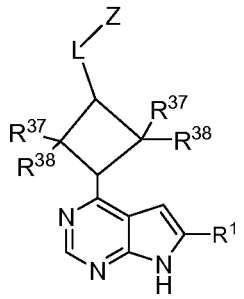
[0166] In a 22nd group of embodiments of the disclosure, compounds of formulas (I), (II), (IId) or (IId-2) have subformulas (IId-2a), (IId-2b), (IId-2c), (IId-2d), (IId-2e), (IId-2f), (IId-2g), (IId-2h) or (IId-2i):



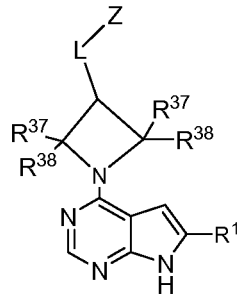
(IId-2a),



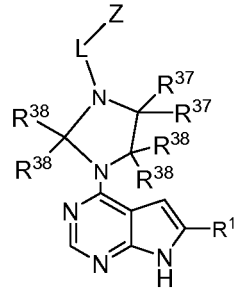
(IId-2b),



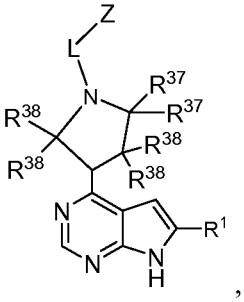
(IId-2c),



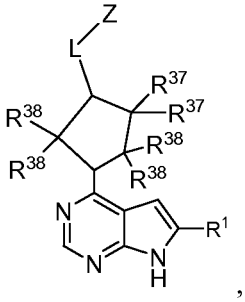
(IId-2d),



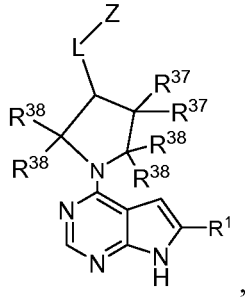
(IId-2e),



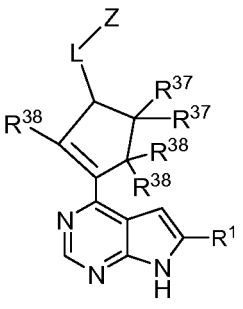
(IId-2f),



(IId-2g),



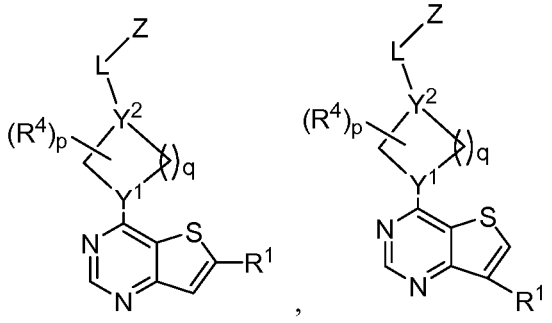
(IId-2h),



(IId-2i)

where R^{37} and R^{38} are each independently H, –CN, C_{1-4} alkyl, C_{1-4} alkoxy, halogen, C_{1-4} haloalkyl or C_{1-4} haloalkoxy; or two R^{37} substituents when attached to the same carbon atom are optionally taken together to form an oxo (i.e., =O) group; or two R^{38} substituents when attached to the same carbon atom are optionally taken together to form an oxo (i.e., =O) group; or two R^{37} and R^{38} substituents when attached to the same carbon atom are optionally taken together to form an oxo (i.e., =O) group, with the proviso that no more than two oxo groups are formed per ring. In some embodiments, each of R^{37} and R^{38} is H. In certain embodiments, R^{38} is H. In other embodiments, R^{37} is H. In some embodiments, R^{38} is H and each R^{37} is independently selected from H, –CN, C_{1-4} alkyl, C_{1-4} alkoxy, halogen, C_{1-4} haloalkyl or C_{1-4} haloalkoxy. In other embodiments, R^{38} is H and each R^{37} is independently selected from H, F, Cl, -OCH_3, CF_3, CN, -OCF_3, -CHF_2, -CH_2F, -OCH_2F or –$OCHF_2$. In some embodiments, 1 to 2 R^{38} substituents in any of formulas (IId-2a), (IId-2b), (IId-2c), (IId-2d), (IId-2e), (IId-2f), (IId-2g), (IId-2h) or (IId-2i) are independently selected from F, Cl, -OCH_3, CF_3, CN, -OCF_3, -CHF_2, -CH_2F, -OCH_2F or –$OCHF_2$ and the other R^{38} substituents are H. In some embodiments, two R^{37} substituents attached to the same carbon atom are taken together to form an oxo group. In some embodiments, one set of R^{38} substituents attached to the same carbon atom are taken together to form an oxo group. In other embodiments, one set of R^{37} substituents attached to the same carbon atom are taken together to form an oxo group and one set of R^{38} substituents attached to the same carbon atom are taken together to form an oxo group. In yet other embodiments, one set of R^{37} and R^{38} substituents when attached to the same carbon atom are taken together to form an oxo group. In other embodiments, two sets of R^{38} substituents attached to the same carbon atom are taken together to form an oxo group. In some embodiments, each of R^{37} and R^{38} in any of formulas (IId-2a), (IId-2b), (IId-2c), (IId-2d), (IId-2e), (IId-2f), (IId-2g), (IId-2h) or (IId-2i) is D. All the other variables Z, L and R^1 are as defined in any of the embodiments disclosed herein.

[0167] In a 23rd group of embodiments of the disclosure, compounds of formulas (I), (II) or (IIe) or have subformulas (IIe-1) or (IIe-2):

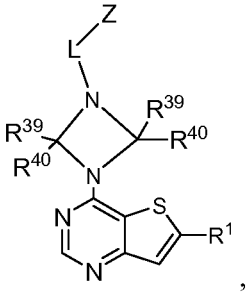


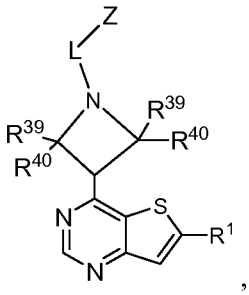
IIe-1 IIe-2

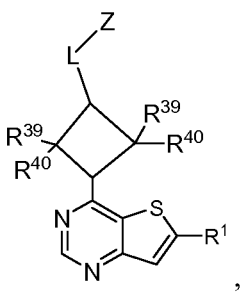
where the variables Y^1, Y^2, R^4, p, q, Z, L and R^1 are as defined in any of the embodiments disclosed herein. In some embodiments of compounds of formulas (IId-1) or (IId-2), Y^1 and Y^2 are CH. In other embodiments of compounds of formulas (IId-1) or (IId-2), Y^1 is CH and Y^2 is N. In other embodiments

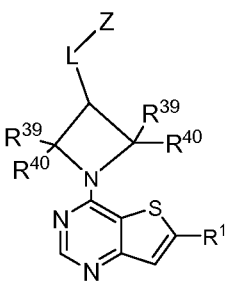
of compounds of any of formulas (IIe-1) or (IIe-2), Y^1 and Y^2 are N. In some embodiments of compounds of any of formulas (IIe-1) or (IIe-2), Y^1 is N and Y^2 is CH. In some embodiments of compounds of any of formulas (IIe-1) or (IIe-2) as described herein, q is 1. In other embodiments of compounds of any of formulas (IIe-1) or (IIe-2), q is 2. All the other variables R^4, p, Z, L and R^1 are as defined in any of the embodiments disclosed herein.

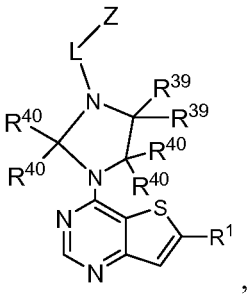
[0168] In a 24th group of embodiments of the disclosure, compounds of formulas (I), (II), (IIe) or (IIe-1) have subformulas (IIe-1a), (IIe-1b), (IIe-1c), (IIe-1d), (IIe-1e), (IIe-1f), (IIe-1g), (IIe-1h), (IIe-1i), (IIe-2a), (IIe-2b), (IIe-2c), (IIe-2d), (IIe-2e), (IIe-2f), (IIe-2g), (IIe-2h) or (IIe-2i):

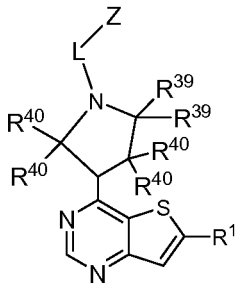

(IIe-1a),

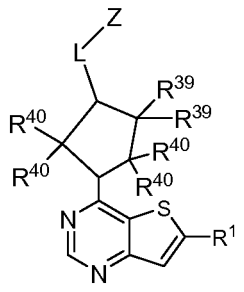

(IIe-1b),

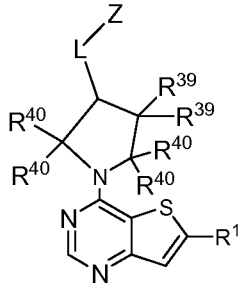

(IIe-1c),

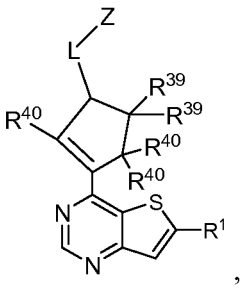

(IIe-1d)

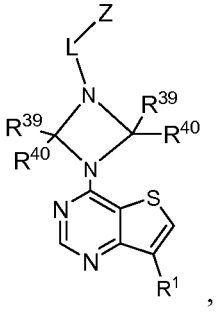

(IIe-1e),

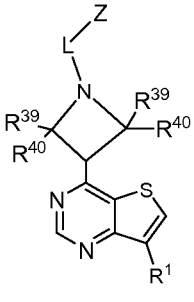

(IIe-1f),

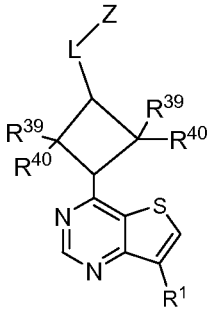

(IIe-1g),

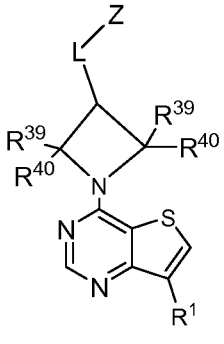

(IIe-1h),

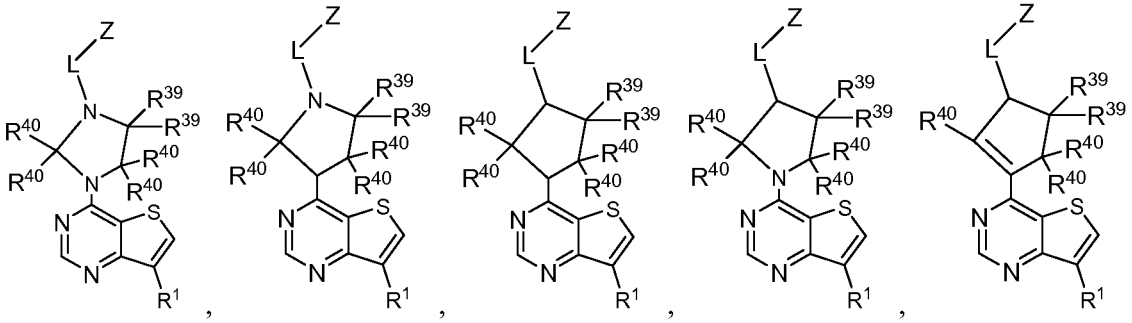

(IIe-1i),


(IIe-2a),


(IIe-2b),


(IIe-2c),

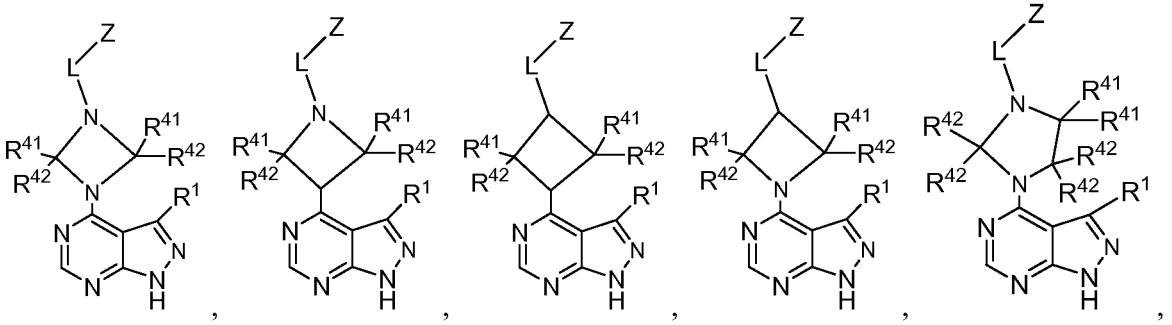

(IIe-2d),



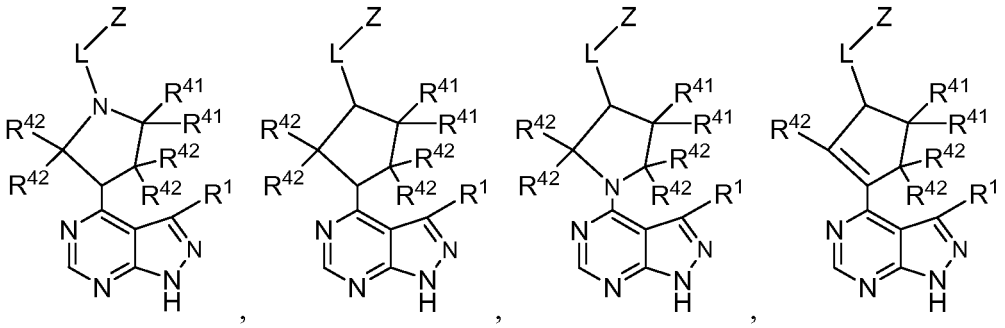
(IIe-2e) (IIe-2f) (IIe-2g) (IIe-2h) (IIe-2i)

where R^{39} and R^{40} are each independently H, –CN, C_{1-4} alkyl, C_{1-4} alkoxy, halogen, C_{1-4} haloalkyl or C_{1-4} haloalkoxy; or two R^{39} substituents when attached to the same carbon atom are optionally taken together to form an oxo (i.e., =O) group; or two R^{40} substituents when attached to the same carbon atom are optionally taken together to form an oxo (i.e., =O) group; or two R^{39} and R^{40} substituents when attached to the same carbon atom are optionally taken together to form an oxo (i.e., =O) group, with the proviso that no more than two oxo groups are formed per ring. . In some embodiments, each of R^{39} and R^{40} is H. In certain embodiments, R^{40} is H. In other embodiments, R^{39} is H. In some embodiments, R^{40} is H and each R^{37} is independently selected from H, –CN, C_{1-4} alkyl, C_{1-4} alkoxy, halogen, C_{1-4} haloalkyl or C_{1-4} haloalkoxy. In other embodiments, R^{40} is H and each R^{39} is independently selected from H, F, Cl, -OCH_3, CF_3, CN, -OCF_3, -CHF_2, -CH_2F, -OCH_2F or –$OCHF_2$. In some embodiments, 1 to 2 R^{40} substituents in any of formulas (IIe-1a), (IIe-1b), (IIe-1c), (IIe-1d), (IIe-1e), (IIe-1f), (IIe-1g), (IIe-1h), (IIe-1i), (IIe-2a), (IIe-2b), (IIe-2c), (IIe-2d), (IIe-2e), (IIe-2f), (IIe-2g), (IIe-2h) or (IIe-2i) are independently selected from F, Cl, -OCH_3, CF_3, CN, -OCF_3, -CHF_2, -CH_2F, -OCH_2F or –$OCHF_2$ and the other R^{40} substituents are H. In some embodiments, two R^{39} substituents attached to the same carbon atom are taken together to form an oxo group. In some embodiments, one set of R^{40} substituents attached to the same carbon atom are taken together to form an oxo group. In other embodiments, one set of R^{39} substituents attached to the same carbon atom are taken together to form an oxo group and one set of R^{40} substituents attached to the same carbon atom are taken together to form an oxo group. In yet other embodiments, one set of R^{39} and R^{40} substituents when attached to the same carbon atom are taken together to form an oxo group. In other embodiments, two sets of R^{40} substituents attached to the same carbon atom are taken together to form an oxo group. In some embodiments, each of R^{39} and R^{40} in any of formulas (IIe-1a), (IIe-1b), (IIe-1c), (IIe-1d), (IIe-1e), (IIe-1f), (IIe-1g), (IIe-1h), (IIe-1i), (IIe-2a), (IIe-2b), (IIe-2c), (IIe-2d), (IIe-2e), (IIe-2f), (IIe-2g), (IIe-2h) or (IIe-2i) is D. All the other variables Z, L and R^1 are as defined in any of the embodiments disclosed herein.

[0169] In a 25th group of embodiments of the disclosure, compounds of formulas (I), (II) or (IIf) have subformulas (IIf-1a), (IIf-1b), (IIf-1c), (IIf-1d), (IIf-1e), (IIf-1f), (IIf-1g), (IIf-1h) or (IIf-1i):



(IIf-1a) (IIf-1b) (IIf-1c) (IIf-1d) (IIf-1e),

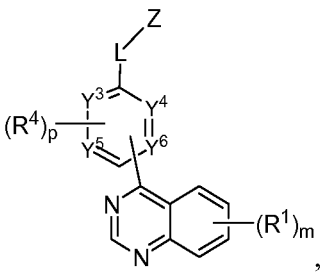


(IIf-1f) (IIf-1g) (IIf-1h) (IIf-1i)

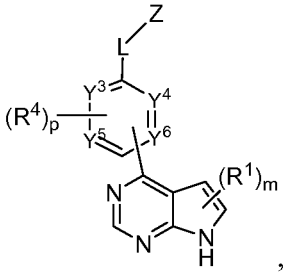
where R^{41} and R^{42} are each independently H, –CN, C_{1-4} alkyl, C_{1-4} alkoxy, halogen, C_{1-4} haloalkyl or C_{1-4} haloalkoxy; or two R^{41} substituents when attached to the same carbon atom are optionally taken together to form an oxo (i.e., =O) group; or two R^{42} substituents when attached to the same carbon atom are optionally taken together to form an oxo (i.e., =O) group; or two R^{41} and R^{42} substituents when attached to the same carbon atom are optionally taken together to form an oxo (i.e., =O) group, with the proviso that no more than two oxo groups are formed per ring. In some embodiments, each of R^{41} and R^{42} is H. In certain embodiments, R^{42} is H. In other embodiments, R^{41} is H. In some embodiments, R^{42} is H and each R^{41} is independently selected from H, –CN, C_{1-4} alkyl, C_{1-4} alkoxy, halogen, C_{1-4} haloalkyl or C_{1-4} haloalkoxy. In other embodiments, R^{42} is H and each R^{41} is independently selected from H, F, Cl, -OCH_3, CF_3, CN, -OCF_3, -CHF_2, -CH_2F, -OCH_2F or –$OCHF_2$. In some embodiments, 1 to 2 R^{42} substituents in any of formulas (IIf-1a), (IIf-1b), (IIf-1c), (IIf-1d), (IIf-1e), (IIf-1f), (IIf-1g), (IIf-1h) or (IIf-1i) are independently selected from F, Cl, -OCH_3, CF_3, CN, -OCF_3, -CHF_2, -CH_2F, -OCH_2F or –$OCHF_2$ and the other R^{42} substituents are H. In some embodiments, two R^{41} substituents attached to the same carbon atom are taken together to form an oxo group. In some embodiments, one set of R^{42} substituents attached to the same carbon atom are taken together to form an oxo group. In other embodiments, one set of R^{41} substituents attached to the same carbon atom are taken together to form an oxo group and one set of R^{42} substituents attached to the same carbon atom are taken together to form an oxo group. In yet other embodiments, one set of R^{41} and R^{42} substituents when attached to the same carbon atom are taken

together to form an oxo group. In other embodiments, two sets of R^{40} substituents attached to the same carbon atom are taken together to form an oxo group. In some embodiments, each of R^{41} and R^{42} in any of formulas (IIf-1a), (IIf-1b), (IIf-1c), (IIf-1d), (IIf-1e), (IIf-1f), (IIf-1g), (IIf-1h) or (IIf-1i) is D. All the other variables Z, L and R^1 are as defined in any of the embodiments disclosed herein.

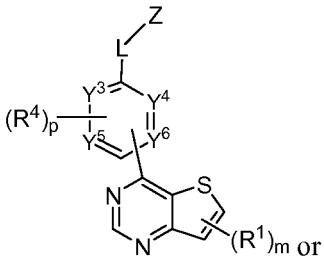
[0170] In a 26th group of embodiments of the disclosure, compounds of formulas (I) or (II) have subformulas (IIg), (IIh), (IIj) or (IIk):



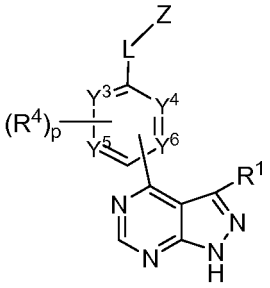
IIg



IIh



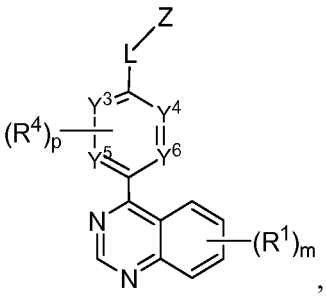
IIj

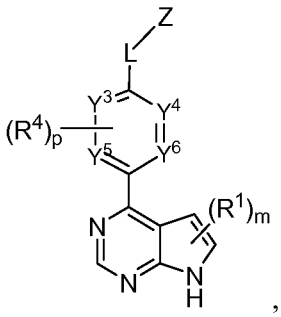


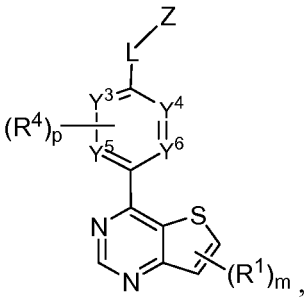
IIk

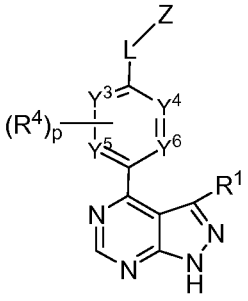
where in any of the subformulas, Y^3, Y^4, Y^5 and Y^6 are each independently CH or N with the proviso that Y^3, Y^4, Y^5 and Y^6 are not simultaneously N. As indicated in the subformulas, $(R^4)_p$- means that one or more R^4 groups, when present, covalently bond to any of the appropriate carbon atoms in the six-membered ring containing Y^3, Y^4, Y^5 and Y^6. All the other variables Z, L, R^4, p, m and R^1 are as defined in any of the embodiments disclosed herein. In some embodiments of compounds of any of the subformulas, Y^3, Y^4, Y^5 and Y^6 are CH. In other embodiments, Y^3 is N and Y^4, Y^5 and Y^6. In other embodiments, Y^5 is N and Y^3, Y^4 and Y^6 are CH. In other embodiments, Y^3 and Y^4 are N and Y^5 and Y^6 are CH. In other embodiments, Y^3 and Y^4 are CH and Y^5 and Y^6 are N. In other embodiments, Y^3 and Y^6 are N and Y^4 and Y^5 are CH. In other embodiments, Y^3 and Y^5 are N and Y^4 and Y^6 are CH. In some embodiments, R^4 substituent is independently selected from C_{1-4} alkyl or halogen. In some embodiments, the subscript p is 0, 1, 2, 3 or 4. In other embodiments, the subscript m is 1 or 2. The variables Z, L and R^1 are as defined in any of the embodiments disclosed herein.

[0171] In a 27th group of embodiments of the disclosure, compounds of formulas (I), (II), (IIg), (IIh), (IIj) or (IIk) have subformulas (IIg-1), (IIh-1), (IIj-1) or (IIk-1):


IIg-1

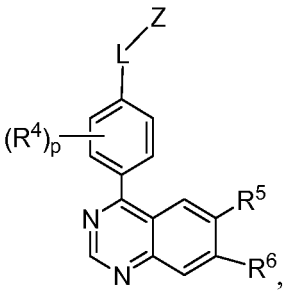

IIh-1

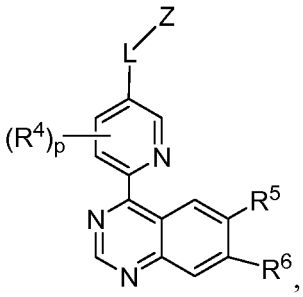

IIj-1

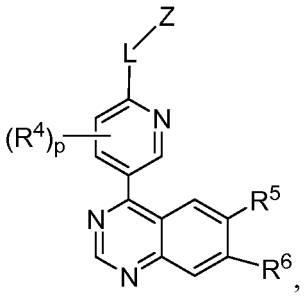

IIk-1

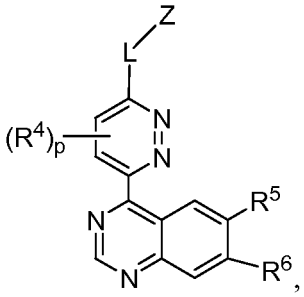
In any of the subformulas, all the variables are as defined in any of the embodiments disclosed herein. In some embodiments of the compounds of any of subformulas (IIg-1), (IIh-1), (IIj-1) or (IIk-1), Y^3, Y^4, Y^5 and Y^6 are each independently CH or N with the proviso that Y^3, Y^4, Y^5 and Y^6 are not simultaneously N; each R^4 substituent is independently selected from C_{1-4} alkyl or halogen; the subscript p is 0, 1, 2, 3 or 4; and the subscript m is 1 or 2. In some embodiments of the compounds of any of subformulas (IIg-1), (IIh-1), (IIj-1) or (IIk-1), the subscript p is 0.

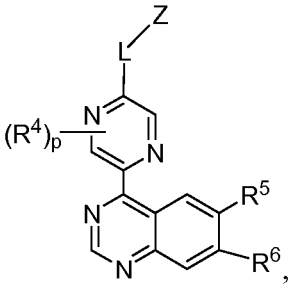
[0172] In a 28th group of embodiments of the disclosure, compounds of formulas (I), (II), (IIg) or (IIg-1) have subformulas (IIg-1a), (IIg-1b), (IIg-1c), (IIg-1d), (IIg-1e), (IIg-1f) or (IIg-1g):

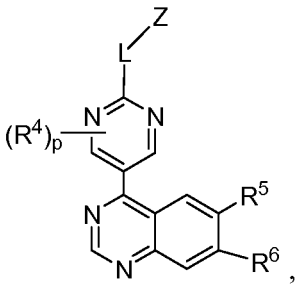

IIg-1a

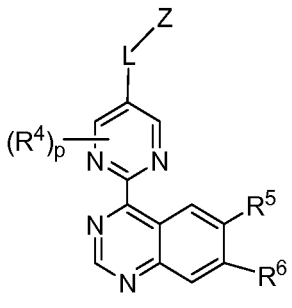

IIg-1b


IIg-1c


IIg-1d


IIg-1e

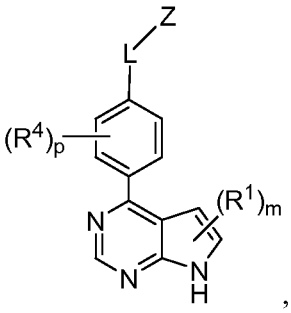

IIg-1f

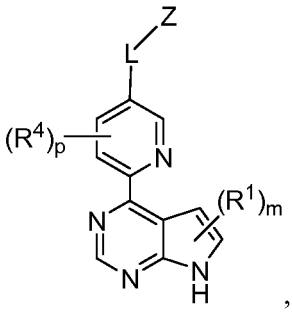

IIg-1g

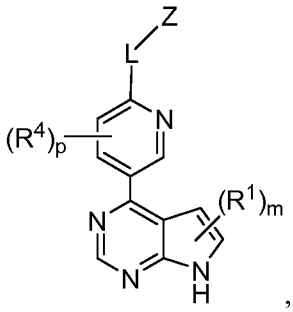
where R^5 and R^6 are each independently H or R^1 group, optionally substituted with 1-5 R^3 substituents; or R^5 and R^6 together with the atom to which they are attached form a 5- or -6-membered carbocyclic or heterocyclic ring. The substituents R^1 and R^3 are as defined in any of the embodiments disclosed herein. As indicated in the subformulas, $(R^4)_p$- means that one or more R^4 substituents, when present, covalently

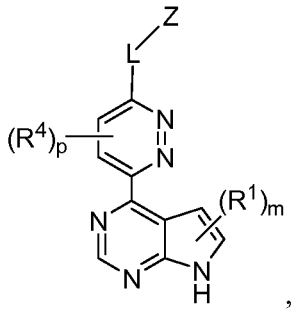
bond to any of the appropriate carbon atoms in phenylene, pyridine-2,5-diyl, pyrazin-2,5-diyl, pyridazin-3,6-diyl, or pyrimindin-2,5-diyl linkage set forth in the subformulas. In some instances of the compounds of any of formulas (IIg-1a), (IIg-1b), (IIg-1c), (IIg-1d), (IIg-1e), (IIg-1f) or (IIg-1g), R^5 is H and R^6 is optionally substituted R^1. In other instances of compounds of any formulas (IIg-1a), (IIg-1b), (IIg-1c), (IIg-1d), (IIg-1e), (IIg-1f) or (IIg-1g), R^5 is optionally substituted R^1 and R^6 is H. In other instances of compounds of any formulas (IIg-1a), (IIg-1b), (IIg-1c), (IIg-1d), (IIg-1e), (IIg-1f) or (IIg-1g), R^5 and R^6 are each independently optionally substituted R^1 group. The variables Z, L, R^4, p and R^1 are as defined in any of the embodiments disclosed herein. In some embodiments of the compounds of any of formulas (IIg-1a), (IIg-1b), (IIg-1c), (IIg-1d), (IIg-1e), (IIg-1f) or (IIg-1g), the subscript p is 0. In other embodiments of the compounds of any of formulas (IIg-1a), (IIg-1b), (IIg-1c), (IIg-1d), (IIg-1e), (IIg-1f) or (IIg-1g), the subscript p is 1 or 2 and R^4 is CH_3, F, Cl, -OCF_3, -CHF_2, CH_2F, CF_3, CN or –OCH_3.

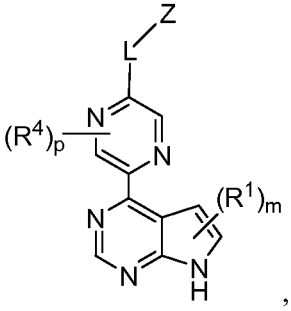
[0173] In a 29th group of embodiments of the disclosure, compounds of formulas (I), (II), (IIh) or (IIh-1) have subformulas (IIh-1a), (IIh-1b), (IIh-1c), (IIh-1d), (IIh-1e), (IIh-1f) or (IIh-1g):

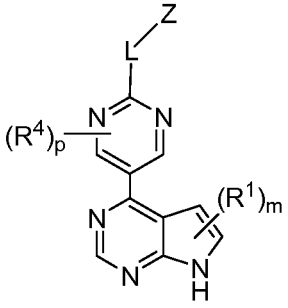

IIh-1a ,

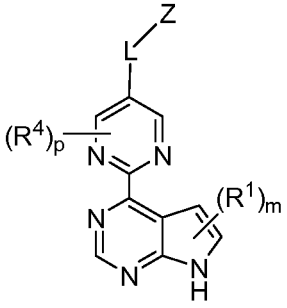

IIh-1b ,


IIh-1c ,

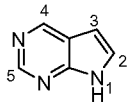

IIh-1d ,


IIh-1e ,

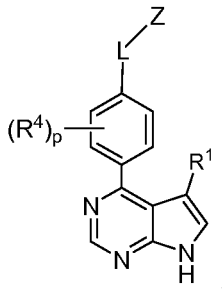

IIh-1f or

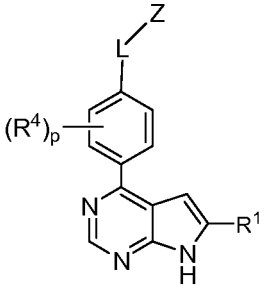

IIh-1g

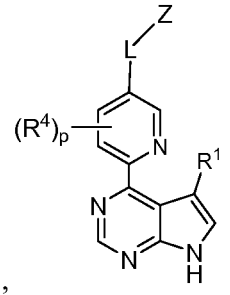
where in any of formulas (IIh-1a), (IIh-1b), (IIh-1c), (IIh-1d), (IIh-1e), (IIh-1f) or (IIh-1g), the variables Z, L, R^4, p, m and R^1 are as defined in any of the embodiments disclosed herein. As indicated in the subformulas, $(R^4)_p$- means that one or more R^4 substituents, when present, covalently bond to any of the appropriate carbon atoms in phenylene, pyridine-2,5-diyl, pyrazin-2,5-diyl, pyridazin-3,6-diyl, or pyrimindin-2,5-diyl linkage set forth in the subformulas. In one example, the pyrrol[2,3-d]pyrimidine

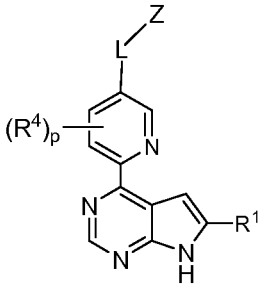

ring; has the indicated numbering notations. In some embodiments of compounds of any of formulas (IIh-1a), (IIh-1b), (IIh-1c), (IIh-1d), (IIh-1e), (IIh-1f) or (IIh-1g), the subscript m is 1 and R^1 is covalently attached to the carbon atom at the 2-position of the pyrrol[2,3-d]pyrimidine ring. In other embodiments of compounds of any of formulas (IIh-1a), (IIh-1b), (IIh-1c), (IIh-1d), (IIh-1e), (IIh-1f) or (IIh-1g), the subscript m is 1 and R^1 is covalently bonded to the carbon atom at the 3-position of the pyrrol[2,3-d]pyrimidine ring. In other embodiments of compounds of any of formulas (IIh-1a), (IIh-1b), (IIh-1c), (IIh-1d), (IIh-1e), (IIh-1f) or (IIh-1g), the subscript m is 2. In some embodiments of compounds of any of formulas (IIh-1a), (IIh-1b), (IIh-1c), (IIh-1d), (IIh-1e), (IIh-1f) or (IIh-1g), the subscript p is 0. In other embodiments of compounds of any of formulas (IIh-1a), (IIh-1b), (IIh-1c), (IIh-1d), (IIh-1e), (IIh-1f) or (IIh-1g), the subscript p is 1 or 2 and R^4 is CH_3, F, Cl, $-OCF_3$, $-CHF_2$, CH_2F, CF_3, CN or $-OCH_3$.

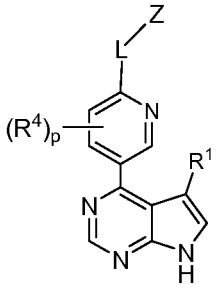
[0174] In a 30th group of embodiments of the disclosure, compounds of formulas (I), (II), (IIh), (IIh-1) or (IIh-1a) to (IIh-1g) have subformulas (IIh-1a-1), (IIh-1a-2), (IIh-1b-1), (IIh-1b-2), (IIh-1c-1), (IIh-1c-2), (IIh-1d-1), (IIh-1d-2), (IIh-1e-1), (IIh-1e-2), (IIh-1f-1), (IIh-1f-2), (IIh-1g) or (IIh-1g-2):

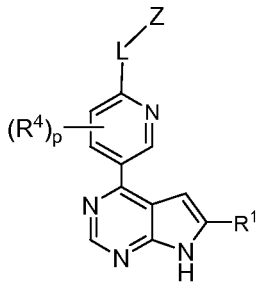

(IIh-1a-1)

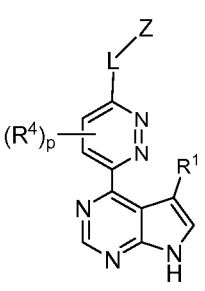

(IIh-1a-2)

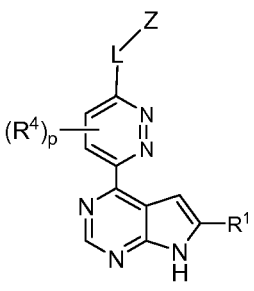

(IIh-1b-1)

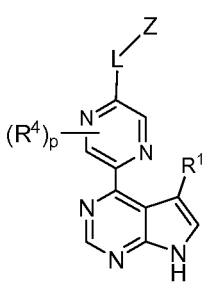

(IIh-1b-2)

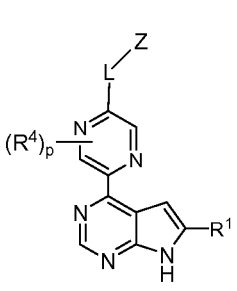

(IIh-1c-1)

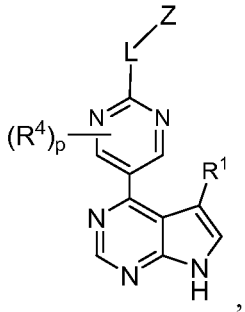

(IIh-1c-2)

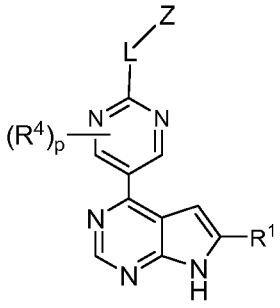

(IIh-1d-1)

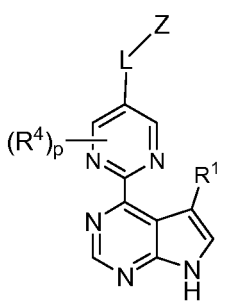

(IIh-1d-2)

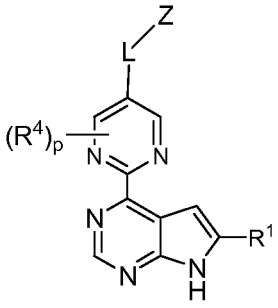

(IIh-1e-1)


(IIh-1e-2)


(IIh-1f-1)

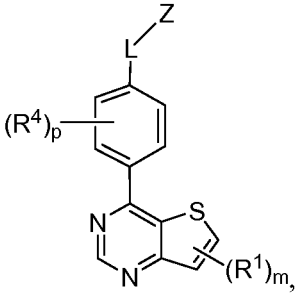

(IIh-1f-2)

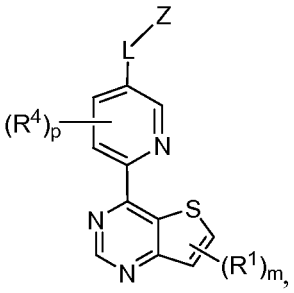

(IIh-1g)

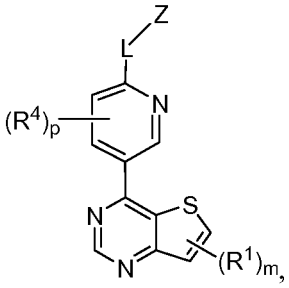

(IIh-1g-2)

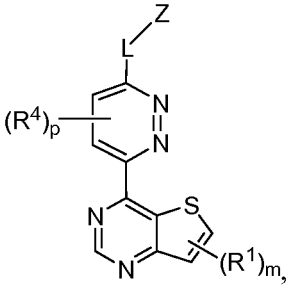
In any of formulas (IIh-1a-1), (IIh-1a-2), (IIh-1b-1), (IIh-1b-2), (IIh-1c-1), (IIh-1c-2), (IIh-1d-1), (IIh-1d-2), (IIh-1e-1), (IIh-1e-2), (IIh-1f-1), (IIh-1f-2), (IIh-1g) or (IIh-1g-2), the variables Z, L, R^4, p and R^1 are as defined in any of the embodiments disclosed herein.

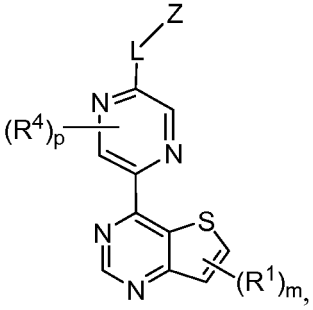
[0175] In a 31st group of embodiments of the disclosure, compounds of formulas (I), (II), (IIj) or (IIj-1) have subformulas (IIj-1a), (IIj-1b), (IIj-1c), (IIj-1d), (IIj-1e), (IIj-1f) or (IIj-1g):

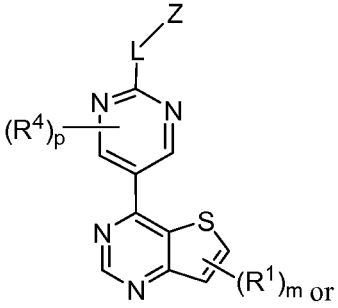

IIj-1a

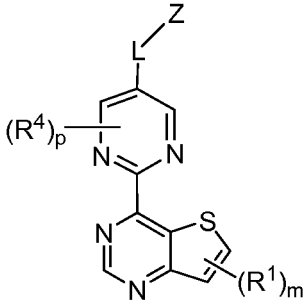

IIj-1b


IIj-1c


IIj-1d


IIj-1e

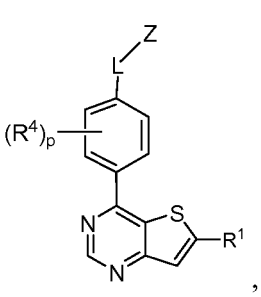

IIj-1f


IIj-1g

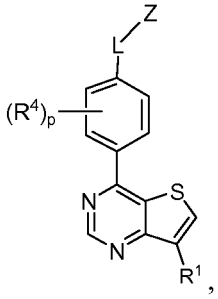
where in any of formulas (IIj-1a), (IIj-1b), (IIj-1c), (IIj-1d), (IIj-1e), (IIj-1f) or (IIj-1g), the variables Z, L, R^4, p, m and R^1 are as defined in any of the embodiments disclosed herein. In some embodiments of compounds of any of formulas (IIj-1a), (IIj-1b), (IIj-1c), (IIj-1d), (IIj-1e), (IIj-1f) or (IIj-1g), the subscript m is 1. In other embodiments of compounds of any of formulas (IIj-1a), (IIj-1b), (IIj-1c), (IIj-1d), (IIj-1e), (IIj-1f) or (IIj-1g), the subscript m is 2. In some embodiments of compounds of any of formulas (IIj-

1a), (IIj-1b), (IIj-1c), (IIj-1d), (IIj-1e), (IIj-1f) or (IIj-1g), the subscript p is 0. In other embodiments of compounds of any of formulas (IIj-1a), (IIj-1b), (IIj-1c), (IIj-1d), (IIj-1e), (IIj-1f) or (IIj-1g), the subscript p is 1 or 2 and R^4 is CH_3, F, Cl, $-OCF_3$, $-CHF_2$, CH_2F, CF_3, CN or $-OCH_3$.

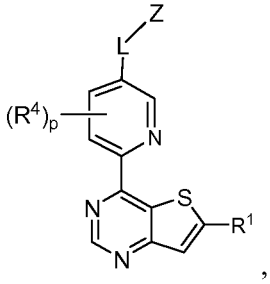
[0176] In a 32nd group of embodiments of the disclosure, compounds of formulas (I), (II), (IIj), (IIj-1), (IIj-1a), (IIj-1b), (IIj-1c), (IIj-1d), (IIj-1e), (IIj-1f) or (IIj-1g) have subformulas (IIj-1a-1), (IIj-1a-2), (IIj-1b-1), (IIj-1b-2), (IIj-1c-1), (IIj-1c-2), (IIj-1d-1), (IIj-1d-2), (IIj-1e-1), (IIj-1e-2), (IIj-1f-1), (IIj-1f-2), (IIj-1g) or (IIj-1g-2):



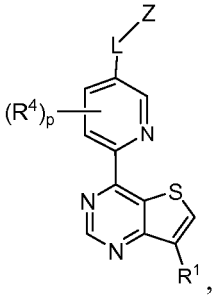
(IIj-1a-1)



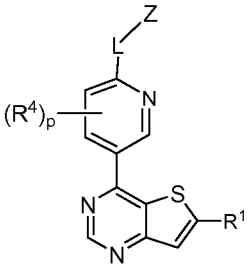
(IIj-1a-2)



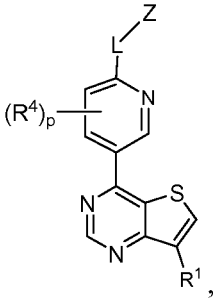
(IIj-1b-1)



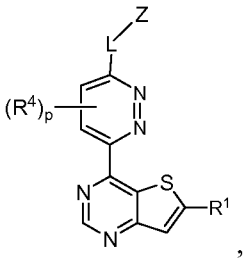
(IIj-1b-2)



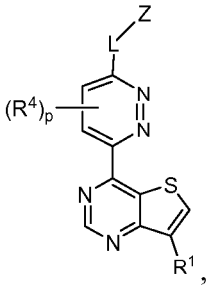
(IIj-1c-1)



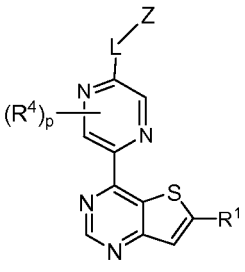
(IIj-1c-2)



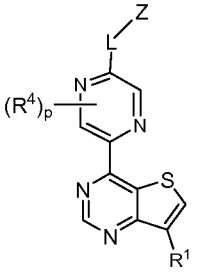
(IIj-1d-1)



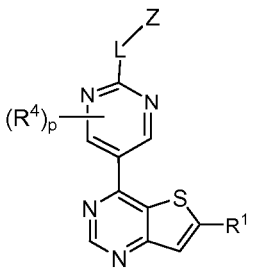
(IIj-1d-2)



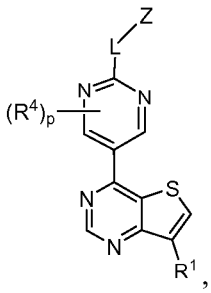
(IIj-1e-1)



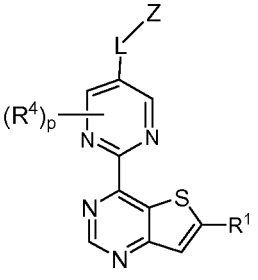
(IIj-1e-2)



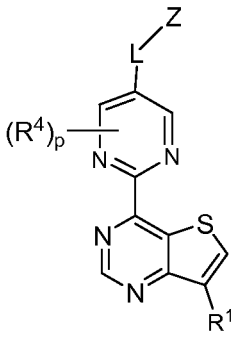
(IIj-1f-1)



(IIj-1f-2)



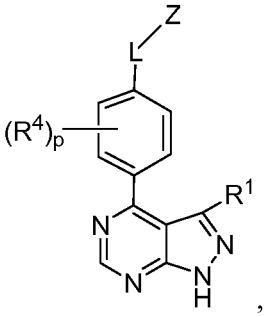
(IIj-1g)



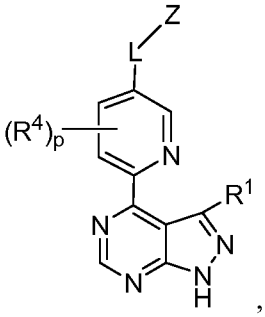
(IIj-1g-2)

In any of formulas (IIj-1a-1), (IIj-1a-2), (IIj-1b-1), (IIj-1b-2), (IIj-1c-1), (IIj-1c-2), (IIj-1d-1), (IIj-1d-2), (IIj-1e-1), (IIj-1e-2), (IIj-1f-1), (IIj-1f-2), (IIj-1g) or (IIj-1g-2), the variables Z, L, R^4, p and R^1 are as defined in any of the embodiments disclosed herein.

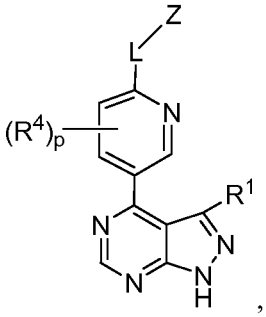
[0177] In a 33rd group of embodiments of the disclosure, compounds of formulas (I), (II), (IIk) or (IIk-1) have subformulas (IIk-1a), (IIk-1b), (IIk-1c), (IIk-1d), (IIk-1e), (IIk-1f) or (IIk-1g):



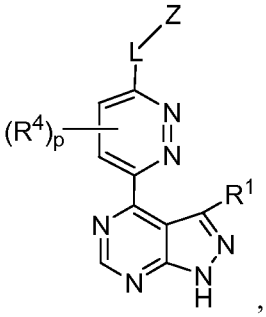
IIk-1a



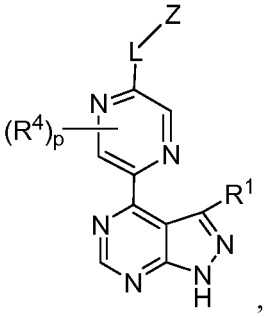
IIk-1b



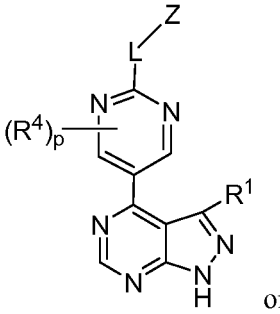
IIk-1c



IIk-1d

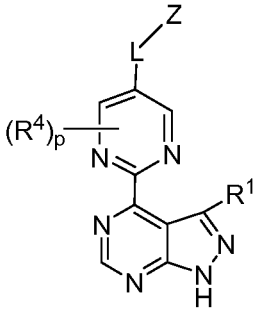


IIk-1e



IIk-1f

or



IIk-1g

In any of formulas (IIk-1a), (IIk-1b), (IIk-1c), (IIk-1d), (IIk-1e), (IIk-1f) or (IIk-1g), the variables Z, L, R^4, p and R^1 are as defined in any of the embodiments disclosed herein.

[0178] In some embodiments of compounds of any of formulas (IIg), (IIh, (IIj), (IIk), (IIg-1), (IIh-1), (IIj-1) or (IIk-1), Y^3, Y^4, Y^5 and Y^6 are CH. In other embodiments of compounds of any of formulas (IIg), (IIh, (IIj), (IIk), (IIg-1), (IIh-1), (IIj-1) or (IIk-1), Y^3, Y^4 and Y^5 are CH and Y^6 is N. In other embodiments of compounds of any of formulas (IIg), (IIh, (IIj), (IIk), (IIg-1), (IIh-1), (IIj-1) or (IIk-1), Y^3, Y^5 and Y^6 are CH and Y^4 is N. In other embodiments of compounds of any of formulas (IIg), (IIh, (IIj), (IIk), (IIg-1), (IIh-1), (IIj-1) or (IIk-1), Y^3 and Y^5 are CH and Y^4 and Y^6 are N. In other embodiments of compounds of any of formulas (IIg), (IIh, (IIj), (IIk), (IIg-1), (IIh-1), (IIj-1) or (IIk-1), Y^3 and Y^6 are N and Y^4 and Y^5 are CH. In other embodiments of compounds of any of formulas (IIg), (IIh, (IIj), (IIk), (IIg-1), (IIh-1), (IIj-1) or (IIk-1), Y^3 and Y^4 are N and Y^5 and Y^6 are CH. In other

embodiments of compounds of any of formulas (IIg), (IIh, (IIj), (IIk), (IIg-1), (IIh-1), (IIj-1) or (IIk-1), Y^3 and Y^4 are CH and Y^5 and Y^6 are N.

[0179] In some embodiments of compounds of any of formulas (IIg-1a), (IIg-1b), (IIg-1c), (IIg-1d), (IIg-1e), (IIg-1f), (IIg-1g), (IIh-1a), (IIh-1b), (IIh-1c), (IIh-1d), (IIh-1e), (IIh-1f), (IIh-1g), (IIj-1a), (IIj-1b), (IIj-1c), (IIj-1d), (IIj-1e), (IIj-1f), (IIj-1g), (IIk-1a), (IIk-1b), (IIk-1c), (IIk-1d), (IIk-1e), (IIk-1f), (IIk-1g), (IIg-1a-1), (IIg-1a-2), (IIg-1b-1), (IIg-1b-2), (IIg-1c-1), (IIg-1c-2), (IIg-1d-1), (IIg-1d-2), (IIg-1e-1), (IIg-1e-2), (IIg-1f-1), (IIg-1f-2), (IIg-1g), (IIg-1g-2), (IIh-1a-1), (IIh-1a-2), (IIh-1b-1), (IIh-1b-2), (IIh-1c-1), (IIh-1c-2), (IIh-1d-1), (IIh-1d-2), (IIh-1e-1), (IIh-1e-2), (IIh-1f-1), (IIh-1f-2), (IIh-1g), (IIh-1g-2), (IIj-1a-1), (IIj-1a-2), (IIj-1b-1), (IIj-1b-2), (IIj-1c-1), (IIj-1c-2), (IIj-1d-1), (IIj-1d-2), (IIj-1e-1), (IIj-1e-2), (IIj-1f-1), (IIj-1f-2), (IIj-1g) or (IIj-1g-2), the subscript p is 0 or 1. In certain instances, p is 1 or 2 and R^4 is $C_{1\text{-}4}$alkyl or halogen. In other instances, P is 1 or 2 and R^4 is F, Cl, $-OCH_3$, CF_3, CN, $-OCF_3$, $-CHF_2$, $-CH_2F$, $-OCH_2F$ or –OCHF.

[0180] In some embodiments, the disclosure provides any of the compounds set forth in Table 1, Table 2, Table 3, Table 4, Table 5 and Table 6, or pharmaceutically acceptable salts, hydrates, solvates, tautomers or isomers thereof. In certain embodiments, the disclosure provides the above selected compounds and pharmaceutically acceptable salts thereof. In certain embodiments, the disclosure provides any of compounds P-0001 to P-0731 as described herein or pharmaceutically acceptable salts, hydrates, solvates, tautomers or isomers thereof. In certain embodiments, the disclosure provides any of the compounds described in formulas (I), (II), or any of the subformulas as described herein, any of the compounds described in the examples and any of the compounds described herein, or pharmaceutically acceptable salts, hydrates, solvates, tautomers or isomers thereof.

[0181] In some embodiments, the disclosure provides compounds of any of formulas (I), (II), (IIa), (IIb), (IIc), (IIa-1), (IIa-2), (IIa-3), (IIa-4), (IIa-1a), (IIa-1b), (IIa-1c), (IIa-1d), (IIa-1e), (IIa-1f), (IIa-1g), (IIa-1h), (IIa-1i), (IIa-1j), (IIa-1k), (IIa-1m), (IIa-2a), (IIa-2b), (IIa-3a), (IIa-3b), (IIa-3c), (IIa-3d), (IIa-3e), (IIa-3f), (IIa-3g), (IIa-3h), (IIa-3i), (IIa-3j), (IIa-3k), (IIa-3m), (IIb-1), (IIb-2), (IIb-3), (IIb-4), (IIb-1a), (IIb-1b), (IIb-1c), (IIb-1d), (IIb-1e), (IIb-1f), (IIb-1g), (IIb-1h), (IIb-1i), (IIb-1j), (IIb-1k), (IIb-1m), (IIb-2a), (IIb-2b), (IIb-3a), (IIb-3b), (IIb-3c), (IIb-3d), (IIb-3e), (IIb-3f), (IIb-3g), (IIb-3h), (IIb-3i), (IIb-3j), (IIb-3k), (IIb-3m), (IIb-4a), (IIb-4b), (IIc-1), (IIc-2), (IIc-1a), (IIc-1b), (IIc-1c), (IIc-1d), (IIc-1e), (IIc-1f), (IIc-1g), (IIc-1h), (IIc-1i), (IIc-1j), (IIc-1k), (IIc-1m), (IIc-2a), (IIc-2b), (IId), (IIe), (IIf), (IId-1), (IId-2), (IId-1a), (IId-1b), (IId-1c), (IId-1d), (IId-1e), (IId-1f), (IId-1g), (IId-1h), (IId-1i), (IId-2a), (IId-2b), (IId-2c), (IId-2d), (IId-2e), (IId-2f), (IId-2g), (IId-2h), (IId-2i), (IIe-1), (IIe-2), (IIe-1a), (IIe-1b), (IIe-1c), (IIe-1d), (IIe-1e), (IIe-1f), (IIe-1g), (IIe-1h), (IIe-1i), (IIe-2a), (IIe-2b), (IIe-2c), (IIe-2d), (IIe-2e), (IIe-2f), (IIe-2g), (IIe-2h), (IIe-2i), (IIf-1a), (IIf-1b), (IIf-1c), (IIf-1d), (IIf-1e), (IIf-1f), (IIf-1g), (IIf-1h), (IIf-1i), (IIg), (IIh), (IIj), (IIk), (IIg-1), (IIh-1), (IIj-1), (IIk-1), (IIg-1a), (IIg-1b), (IIg-1c), (IIg-1d), (IIg-1e), (IIg-

1f), (IIg-1g), (IIh-1a), (IIh-1b), (IIh-1c), (IIh-1d), (IIh-1e), (IIh-1f), (IIh-1g), (IIj-1a), (IIj-1b), (IIj-1c), (IIj-1d), (IIj-1e), (IIj-1f), (IIj-1g), (IIk-1a), (IIk-1b), (IIk-1c), (IIk-1d), (IIk-1e), (IIk-1f), (IIk-1g), (IIg-1a-1), (IIg-1a-2), (IIg-1b-1), (IIg-1b-2), (IIg-1c-1), (IIg-1c-2), (IIg-1d-1), (IIg-1d-2), (IIg-1e-1), (IIg-1e-2), (IIg-1f-1), (IIg-1f-2), (IIg-1g), (IIg-1g-2), (IIh-1a-1), (IIh-1a-2), (IIh-1b-1), (IIh-1b-2), (IIh-1c-1), (IIh-1c-2), (IIh-1d-1), (IIh-1d-2), (IIh-1e-1), (IIh-1e-2), (IIh-1f-1), (IIh-1f-2), (IIh-1g), (IIh-1g-2), (IIj-1a-1), (IIj-1a-2), (IIj-1b-1), (IIj-1b-2), (IIj-1c-1), (IIj-1c-2), (IIj-1d-1), (IIj-1d-2), (IIj-1e-1), (IIj-1e-2), (IIj-1f-1), (IIj-1f-2), (IIj-1g), (IIj-1g-2), (IIk-1a), (IIk-1b), (IIk-1c), (IIk-1d), (IIk-1e), (IIk-1f), or (IIk-1g), or pharmaceutically acceptable salts, hydrates, solvates, tautomers or isomers thereof.

[0182] In some embodiments, the disclosure provides any of compounds selected from P-0001 to 0731, i.e., compounds 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-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, P-0100, 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-0125, P-0126, P-0127, P-0128, P-0129, P-0130, P-0131, P-0132, P-0134, P-0135, P-0136, P-0137, P-0138, P-0139, P-0140, P-0141, P-0142, P-0143, P-0144, P-0145, P-0146, P-0147, P-0148, P-0149, P-0150, P-0151, P-0152, P-0153, P-0154, P-0156, P-0157, P-0158, P-0159, P-0160, P-0161, P-0163, P-0164, P-0165, P-0167, P-0168, P-0169, P-0170, P-0171, P-0172, P-0173, P-0174, P-0175, P-0176, P-0179, P-0180, P-0181, P-0182, P-0183, 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, P-0212, P-0213, P-0214, P-0215, P-0216, P-0217, P-0218, P-0219, P-0220, P-0221, P-0222, P-0223, P-0224, P-0225, P-0226, P-0227, P-0228, P-0229, P-0230, P-0231, P-0232, P-0233, P-0234, P-0235, P-0236, P-0237, P-0238, P-0239, P-0240, P-0241, P-0242, P-0243, P-0244, P-0245, P-0247, P-0248, P-0249, P-0250, P-0251, P-0252, P-0253, P-0254, P-0255, P-0256, P-0257, P-0258, P-0259, P-0260, P-0261, P-0262, P-0263, P-0264, P-0265, P-0266, P-0267, P-0268, P-0269, P-0270, P-0271, P-0272, P-0273, P-0274, P-0275, P-0276, P-0277, P-0278, P-0279, P-0280, P-0281, P-0282, P-0283, P-0284, P-0285, P-0286, P-0287, P-0288, P-0289, P-0290, P-0291, P-0292, P-0293, P-0294, P-0295, P-0296, P-0297, P-0298, P-0299, P-0300, P-0301, P-0302, P-0303, P-0304, P-0305, P-0306, P-0307, P-0308, P-0309, P-0310, P-0311, P-0312, P-0313, P-0314, P-0315, P-0316, P-0317, P-0318, P-0319, P-0320, P-0321,

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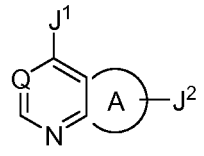
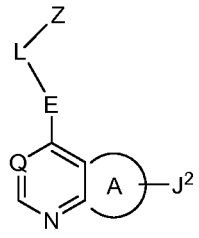
Method of preparation

[0183] In another aspect, the present disclosure provides a method for preparing a compound of formula (I), (II) or any of the subformula as described herein. The method includes contacting a compound having formula III or any of subformula thereof :



III

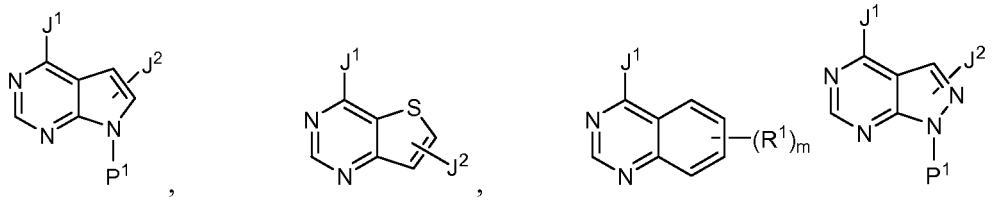
with an agent having formula: G^1-E-L-Z under conditions sufficient to form a compound having formula IIIa:



IIIa

and reacting a compound of formula IIIa with an agent having formula: G^2-$(R^1)_m$ under conditions sufficient to form a compound of formula I or II, where J^1 and J^2 are each independently halogen, tosylate, mesylate or triflate; Q is N or CH; G^1 and G^2 are each independently NH, $-B(OR^{50})_2$ or $-Sn(Bu)_3$, wherein R^{50} is –OH, alkyl or two $-OR^{50}$ substituents together with the boron atom to which they are attached to form an optionally substituted 5 or 6-membered ring; and the variables Z, L, E and A are as defined in any of the embodiments and formula and subformula as disclosed herein. In some embodiments, A is a fused pyrrole ring together with the aromatic ring to which it is fused forms a pyrrolo[2,3-b]pyridine or pyrrolo[2,3-d]pyrimidine moiety. In other embodiments, A is a fused thiophene ring together with the aromatic ring to which it is fused forms a thieno[3,2-b]pyridine or thieno[2,3-d]pyrimidine moiety. In yet other embodiments, A is a fused pyrazole ring together with the aromatic ring to which it is fused forms a pyrazolo[3,4-b]pyridine or pyrrolo[3,4-d]pyrimidine moiety. In other embodiments, A is a fused benzene ring together with the aromatic ring to which it is fused forms a quinoline or quinazoline moiety. In one embodiment, Q is N. In another embodiment, J^1 is Cl or Br and J^2 is I. In yet another embodiment, J^2 is I, Cl or Br and J^1 is Cl, Br, I. In some embodiments, R^{50} is H. In some embodiments, G^1-E-L-Z is reacted with a compound of formula III in the presence of a palladium complex. In other embodiments, G^2-$(R^1)_m$ is reacted with a compound of formula (IIIa) in the presence of a palladium complex. In certain instances, the palladium complexes include, but are not limited to,

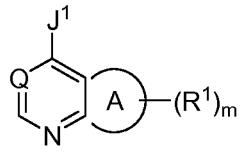
$Pd(PPh_3)_4$, palladium acetate, bis(diphenylphosphino)ferrocene]dichloropalladium and the like. In certain embodiments, compounds of formula III have subformulas (III-1) or (III-2):



(III-1) (III-2) (III-3) (III-4)

where P^1 is H or an amino protecting group and J^1 and J^2 are as defined in any of the embodiments and formulas disclosed herein. In certain embodiments, P^1 is 9-fluorenylmethoxycarbonyl, t-butoxycarbonyl, trimethylsilyl, t-butyldiphenylsilyl, phenylsulfonyl, 4-methylphenylsulfonyl or 2,6-dichlorophenylcarbonyl.

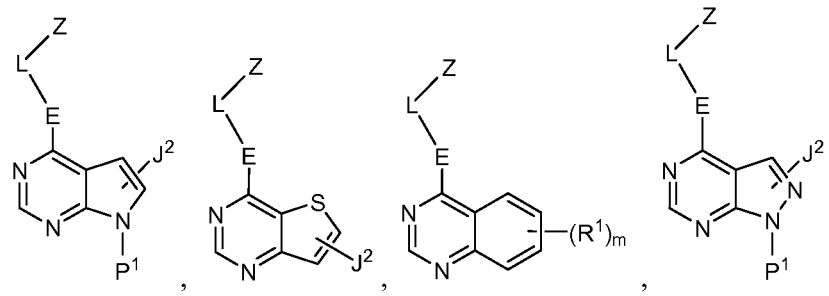
[0184] In some embodiments, the method includes contacting a compound of formulas III with an agent G^2-$(R^1)_m$ or under conditions sufficient to form a compound of formula IIIb:



IIIb

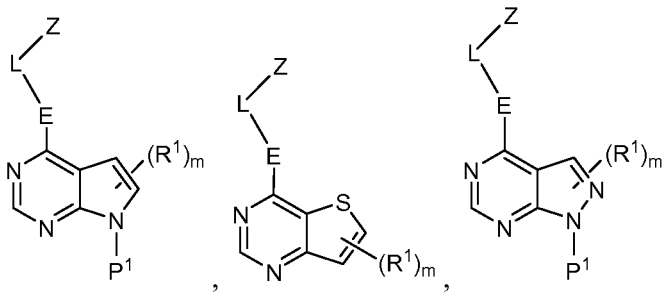
and followed by reacting compound IIIb with an agent having formula: G^1-E-L-Z under conditions sufficient to form a compound of formula III. In certain instances, the agent G^2-$(R^1)_m$ is reacted under a basic condition, e.g. in the presence of triethylamine or at a temperature greater than 100 °C.

[0185] In some embodiments, the method includes (i) contacting a compound of any of formulas (III-1), (III-2), (III-3) or (III-4) with an agent having formula: G^1-E-L-Z under conditions sufficient to form a compound having formulas (III-1a), (III-2a), (III-3a) or (III-4a):



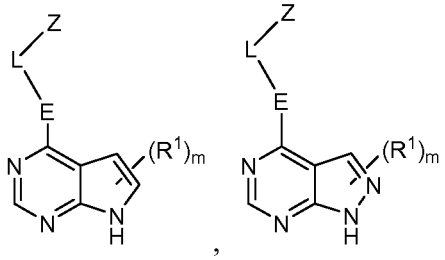
(III-1a) (III-2a) (III-3a) (III-4a)

(ii) reacting a compound of any of formulas (III-1a), (III-3a) or (III-4a) with an agent having formula:G^2-$(R^1)_m$ under conditions sufficient to form a compound having formulas (III-1b), (III-2b) or (III-4b), respectively:



(III-1b) (III-2b) (III-4b)

when P^1 is an amine protecting group, the method includes the step of removing the protecting group P^1 in the compounds of formulas (III-1b) or (III-4b) under conditions sufficient to form a compound of formulas (III-1c) or (III-4c), respectively:



(III-1c) (III-4c)

In one embodiment, the removing reaction is carried out under a basic condition, e.g., in the presence of KOH. In certain instances, the method also includes preparing compounds of formula (III-1c), (III-2b) , (III-4c) by carrying out steps (i) and (ii) above in reverse order, e.g., first reacting a compound of any of formulas (III-1), (III-2) or (III-3) with G^2-$(R^1)_m$ and followed by reacting with G^1-E-L-Z. The variables Z, L, E, m, R^1 and P^1 in subformulas (III-1b), (III-2b), (III-4b) are as defined in any of the embodiments and formulas and subformulas as disclosed herein. In some instances, m is 1.

[0186] In one embodiment, G^1 is $-B(OH)_2$. In another embodiment, G^1 is 2-hydroxy-1,3,2-benzodioxaborole or 2-hydroxy-4,4,5,5-tetramethyl-1,3,2-benzodioxaboro. In another embodiment, G^1 is $-Sn(Bu)_3$.

Organic Synthetic Techniques

[0187] A wide array of organic synthetic techniques exist in the art to facilitate the construction of potential modulators. Many of these organic synthetic methods are described in detail in standard

reference sources utilized by those skilled in the art. One example of such a reference is March, 1994, Advanced Organic Chemistry; Reactions, Mechanisms and Structure, New York, McGraw Hill. Thus, the techniques useful to synthesize a potential modulator of kinase function are readily available to those skilled in the art of organic chemical synthesis.

Alternative Compound Forms or Derivatives

[0188] Compounds contemplated herein are described with reference to both generic formulae and specific compounds. In addition, disclosure compounds may exist in a number of different forms or derivatives, all within the scope of the present disclosure. Alternative forms or derivatives, include, for example, (a) prodrugs, and active metabolites (b) tautomers, isomers (including stereoisomers and regioisomers), and racemic mixtures (c) pharmaceutically acceptable salts and (d) solid forms, including different crystal forms, polymorphic or amorphous solids, including hydrates and solvates thereof, and other forms.

(a) *Prodrugs and Metabolites*

[0189] 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.

[0190] 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 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. Esters include, for example, esters of a carboxylic acid group, or S-acyl or O-acyl derivatives of thiol, alcohol, or phenol groups. In this context, a common example is an alkyl ester of a carboxylic acid. Prodrugs may also include variants wherein an -NH group of the compound has undergone acylation, such as the 1-position of the 1H-pyrrolo[2,3-b]pyridine ring, or the nitrogen of the sulfonamide group of compounds as described herein, where cleavage of the acyl group provides the free -NH group of the active drug. Some prodrugs are activated enzymatically to yield the active compound, or a compound may undergo further chemical reaction to yield the active compound. 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.

[0191] 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 following types:

[0192] Oxidative reactions: Oxidative reactions are exemplified without limitation by 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.

[0193] Reductive reactions: Reductive reactions are exemplified without limitation by 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.

[0194] Reactions without change in the oxidation state: Reactions without change in the state of oxidation are exemplified without limitation by 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.

[0195] 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. 20040077595, App. No. 10/656,838, incorporated herein by reference.) Such carrier prodrugs are often advantageous for orally administered drugs. In some instances, the transport moiety provides targeted delivery of the drug, for example the drug may be conjugated to an antibody or antibody fragment. 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*.

[0196] 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 processes 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. For example, in some compounds, one or more alkoxy groups can be metabolized to hydroxyl groups while retaining pharmacologic activity and/or carboxyl groups can be esterified, e.g., glucuronidation. In some cases, there can be more than one metabolite, where an intermediate metabolite(s) is further metabolized to provide an active metabolite. For example, in some cases a derivative compound resulting from metabolic glucuronidation may be inactive or of low activity, and can be further metabolized to provide an active metabolite.

[0197] Metabolites of a compound may be identified using routine techniques known in the art, and their activities determined using tests such as those described herein. 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*.

(b) *Tautomers, Stereoisomers, and Regioisomers*

[0198] 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.

[0199] 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 stereoisomeric forms are included within the formulae provided herein.

[0200] 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, such optically pure form being prepared and/or isolated by methods known in the art (e.g. by recrystallization techniques, chiral synthetic techniques (including synthesis from optically pure starting materials), and chromatographic separation using a chiral column.

(c) *Pharmaceutically acceptable salts*

[0201] Unless specified to the contrary, specification of a compound herein includes pharmaceutically acceptable salts of such compound. Thus, compounds described herein and recited in any of the claims can be in the form of pharmaceutically acceptable salts, or can be formulated as 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. A compound of the disclosure may possess a sufficiently acidic, a sufficiently basic, or both functional groups, and accordingly can react with any of a number of inorganic or organic bases, and inorganic and organic acids, to form a pharmaceutically acceptable salt.

[0202] Pharmaceutically acceptable salts include acid addition salts such as those containing chloride, bromide, iodide, hydrochloride, acetate, phenylacetate, acrylate, ascorbate, aspartate, benzoate, 2-phenoxybenzoate, 2-acetoxybenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, methylbenzoate, bicarbonate, butyne-1,4 dioate, hexyne-1,6-dioate, caproate, caprylate, chlorobenzoate, cinnamate, citrate, decanoate, formate, fumarate, glycolate, gluconate, glucarate, glucuronate, glucose-6-

phosphate, glutamate, heptanoate, hexanoate, isethionate, isobutyrate, gamma-hydroxybutyrate, phenylbutyrate, lactate, malate, maleate, hydroxymaleate, methylmaleate, malonate, mandelate, nicotinate, nitrate, isonicotinate, octanoate, oleate, oxalate, pamoate, phosphate, monohydrogenphosphate, dihydrogenphosphate, orthophosphate, metaphosphate, pyrophosphate, 2-phosphoglycerate, 3-phosphoglycerate, phthalate, propionate, phenylpropionate, propiolate, pyruvate, quinate, salicylate, 4-aminosalicylate, sebacate, stearate, suberate, succinate, sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, sulfamate, sulfonate, benzenesulfonate (i.e. besylate), ethanesulfonate (i.e. esylate), ethane-1,2-disulfonate, 2-hydroxyethanesulfonate (i.e. isethionate), methanesulfonate (i.e. mesylate), naphthalene-1-sulfonate, naphthalene-2-sulfonate (i.e. napsylate), propanesulfonate, *p*-toluenesulfonate (i.e. tosylate), xylenesulfonates, cyclohexylsulfamate, tartrate, and trifluoroacetate. These pharmaceutically acceptable acid addition salts can be prepared using the appropriate corresponding acid.

[0203] When acidic functional groups, such as carboxylic acid or phenol are present, pharmaceutically acceptable salts also include basic addition salts such as those containing benzathine, chloroprocaine, choline, ethanolamine, diethanolamine, triethanolamine, t-butylamine, dicyclohexylamine, ethylenediamine, N,N'-dibenzylethylenediamine, meglumine, hydroxyethylpyrrolidine, piperidine, morpholine, piperazine, procaine, aluminum, calcium, copper, iron, lithium, magnesium, manganese, potassium, sodium, zinc, ammonium, and mono-, di-, or tri-alkylamines (e.g. diethylamine), or salts derived from amino acids such as L-histidine, L-glycine, L-lysine, and L-arginine. For example, see *Remington's Pharmaceutical Sciences*, 19th ed., Mack Publishing Co., Easton, PA, Vol. 2, p. 1457, 1995. These pharmaceutically acceptable base addition salts can be prepared using the appropriate corresponding base.

[0204] 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. 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 appropriate inorganic or organic base.

(d) *Other compound forms*

[0205] 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.

[0206] 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 preferably 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.

[0207] 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.

IV. Formulations and Administration

[0208] In another aspect, the present disclosure provides pharmaceutical compositions comprising/including a pharmaceutically acceptable carrier or excipient and a compound of the disclosure described herein or a pharmaceutically acceptable salt or solvate thereof. In an exemplary embodiment, the present disclosure provides a pharmaceutical formulation comprising/including a compound as described herein. In one embodiment, the pharmaceutical formulation or composition includes/comprises

a compound set forth in Tables 1-6. In another embodiment, the pharmaceutical formulation or composition includes/comprises a compound selected from any of compounds P-0001 to P-0731. In one embodiment, the compound has any of formulas I, and Ia to In.

[0209] 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. Compounds described herein can be administered by different routes, including injection (i.e. parenteral, including intravenous, intraperitoneal, subcutaneous, and intramuscular), oral, transdermal, transmucosal, rectal, or inhalant. 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 Remington: *The Science and Practice of Pharmacy*, 21st edition, Lippincott, Williams and Wilkins, Philadelphia, PA, 2005 (hereby incorporated by reference herein).

[0210] In some embodiments, compositions will comprise pharmaceutically acceptable carriers or excipients, such as fillers, binders, disintegrants, glidants, lubricants, complexing agents, solubilizers, and surfactants, which may be chosen to facilitate administration of the compound by a particular route. Examples of carriers include calcium carbonate, calcium phosphate, various sugars such as lactose, glucose, or sucrose, types of starch, cellulose derivatives, gelatin, lipids, liposomes, nanoparticles, and the like. Carriers also include physiologically compatible liquids as solvents or for suspensions, including, for example, sterile solutions of water for injection (WFI), saline solution, dextrose solution, Hank's solution, Ringer's solution, vegetable oils, mineral oils, animal oils, polyethylene glycols, liquid paraffin, and the like. Excipients may also include, for example, colloidal silicon dioxide, silica gel, talc, magnesium silicate, calcium silicate, sodium aluminosilicate, magnesium trisilicate, powdered cellulose, macrocrystalline cellulose, carboxymethyl cellulose, cross-linked sodium carboxymethylcellulose, sodium benzoate, calcium carbonate, magnesium carbonate, stearic acid, aluminum stearate, calcium stearate, magnesium stearate, zinc stearate, sodium stearyl fumarate, syloid, stearowet C, magnesium oxide, starch, sodium starch glycolate, glyceryl monostearate, glyceryl dibehenate, glyceryl palmitostearate, hydrogenated vegetable oil, hydrogenated cotton seed oil, castor seed oil mineral oil, polyethylene glycol (e.g. PEG 4000-8000), polyoxyethylene glycol, poloxamers, povidone, crospovidone, croscarmellose sodium, alginic acid, casein, methacrylic acid divinylbenzene copolymer, sodium docusate, cyclodextrins (e.g. 2-hydroxypropyl-.delta.-cyclodextrin), polysorbates (e.g. polysorbate 80), cetrimide, TPGS (d-alpha-tocopheryl polyethylene glycol 1000 succinate), magnesium lauryl sulfate, sodium lauryl sulfate, polyethylene glycol ethers, di-fatty acid ester of polyethylene glycols, or a polyoxyalkylene sorbitan fatty acid ester (e.g., polyoxyethylene sorbitan ester Tween®), polyoxyethylene sorbitan fatty acid esters, sorbitan fatty acid ester, e.g. a sorbitan fatty acid ester from a fatty acid such as

oleic, stearic or palmitic acid, mannitol, xylitol, sorbitol, maltose, lactose, lactose monohydrate or lactose spray dried, sucrose, fructose, calcium phosphate, dibasic calcium phosphate, tribasic calcium phosphate, calcium sulfate, dextrates, dextran, dextrin, dextrose, cellulose acetate, maltodextrin, simethicone, polydextrosem, chitosan, gelatin, HPMC (hydroxypropyl methyl celluloses), HPC (hydroxypropyl cellulose), hydroxyethyl cellulose, and the like.

[0211] Pharmaceutical formulations may be presented in unit dose forms containing a predetermined amount of active ingredient per unit dose. Such a unit may contain, for example, 0.5 mg to 1 g, preferably 1 mg to 700 mg, more preferably 5 mg to 100 mg of a compound of the disclosure (as a free-base, solvate (including hydrate) or salt, in any form), depending on the condition being treated, the route of administration, and the age, weight and condition of the patient. Preferred unit dosage formulations are those containing a daily dose, weekly dose, monthly dose, a sub-dose or an appropriate fraction thereof, of an active ingredient. Furthermore, such pharmaceutical formulations may be prepared by any of the methods well known in the pharmacy art.

[0212] Pharmaceutical formulations may be adapted for administration by any appropriate route, for example by the oral (including capsules, tablets, liquid-filled capsules, disintegrating tablets, immediate, delayed and controlled release tablets, oral strips, solutions, syrups, buccal and sublingual), rectal, nasal, inhalation, topical (including transdermal), vaginal or parenteral (including subcutaneous, intramuscular, intravenous or intradermal) route. Such formulations may be prepared by any method known in the art of pharmacy, for example by bringing into association the active ingredient with the carrier(s), excipient(s) or diluent. Generally, the carrier, excipient or diluent employed in the pharmaceutical formulation is "non-toxic," meaning that it/they is/are deemed safe for consumption in the amount delivered in the pharmaceutical composition, and "inert" meaning that it/they does/do not appreciably react with or result in an undesired effect on the therapeutic activity of the active ingredient.

[0213] In some embodiments, oral administration may be used. Pharmaceutical preparations for oral use can be formulated into conventional oral dosage forms such as discrete units capsules, tablets, and liquid preparations such as syrups, elixirs, and concentrated drops. Compounds described herein may be combined with solid excipients, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain, for example, tablets, coated tablets, hard capsules, soft capsules, solutions (e.g. aqueous, alcoholic, or oily solutions) and the like. Suitable excipients are, in particular, fillers such as sugars, including lactose, glucose, sucrose, mannitol, or sorbitol; cellulose preparations, for example, corn starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose (CMC), and/or polyvinylpyrrolidone (PVP: povidone); oily excipients, including vegetable and animal oils, such as sunflower oil, olive oil, or cod liver oil. The oral dosage formulations may also contain

disintegrating agents, such as the cross-linked polyvinylpyrrolidone, agar, or alginic acid, or a salt thereof such as sodium alginate; a lubricant, such as talc or magnesium stearate; a plasticizer, such as glycerol or sorbitol; a sweetening such as sucrose, fructose, lactose, or aspartame; a natural or artificial flavoring agent, such as peppermint, oil of wintergreen, or cherry flavoring; or dye-stuffs or pigments, which may be used for identification or characterization of different doses or combinations, such as unit dosages. Also provided are dragee cores 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, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Oral fluids such as solutions, syrups and elixirs can be prepared in dosage unit form so that a given quantity contains a predetermined amount of the compound.

[0214] 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.

[0215] In some embodiments, injection (parenteral administration) may be used, *e.g.*, intramuscular, intravenous, intraperitoneal, and/or subcutaneous. Compounds described herein for injection may be formulated in sterile liquid solutions, preferably in physiologically compatible buffers or solutions, such as saline solution, Hank's solution, or Ringer's solution. Dispersions may also be prepared in non-aqueous solutions, such as glycerol, propylene glycol, ethanol, liquid polyethylene glycols, triacetin, and vegetable oils. Solutions may also contain a preservative, such as methylparaben, propylparaben, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In addition, the compounds may be formulated in solid form, including, for example, lyophilized forms, and redissolved or suspended prior to use. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injection, immediately prior to use.

[0216] In some embodiments, transmucosal, topical or transdermal administration may be used. In such formulations of compounds described herein, penetrants appropriate to the barrier to be permeated are used. 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). Compositions of compounds described herein for topical administration may be 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 some embodiments, carriers are selected such that 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 preferably formulated from a mixture of mineral oil, self-emulsifying beeswax and water in which mixture the active ingredient, dissolved in a small amount of 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 be continuous rather than intermittent throughout the dosage regimen.

[0217] In some embodiments, compounds are administered as inhalants. Compounds described herein 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 described herein may also be used in combination with other inhaled therapies, for example corticosteroids such as fluticasone proprionate, beclomethasone dipropionate, triamcinolone acetonide, budesonide, and mometasone furoate; beta agonists such as albuterol, salmeterol, and formoterol; anticholinergic agents such as ipratroprium 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.

[0218] The amounts of various compounds to be administered can be determined by standard procedures taking into account factors such as the compound activity (*in vitro*, e.g. the compound IC_{50} vs. target, or *in vivo* activity in animal efficacy models), pharmacokinetic results in animal models (e.g. biological half-life or bioavailability), the age, size, and weight of the subject, and the disorder associated with the subject. The importance of these and other factors are well known to those of ordinary skill in the art. Generally, a dose will be in the range of about 0.01 to 50 mg/kg, also about 0.1 to 20 mg/kg of the subject being treated. Multiple doses may be used.

[0219] The compounds described herein 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.

[0220] 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 described herein, or at the same time as a compound described herein. 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 described herein 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 a compound described herein 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 a compound described herein 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 aspect, the other drug therapy may be co-administered with a compound described herein. 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 a compound described herein 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.

V. Disease indications and modulations of c-kit kinase

Exemplary Diseases Associated with c-Kit or mutant form of c-Kit

[0221] The compounds of formulas (I), (II) or any of the subformulas and compounds as described herein are useful for treating disorders related to c-kit e.g., diseases related to unregulated kinase signal

transduction, including cell proliferative disorders, fibrotic disorders and metabolic disorders, among others. As described in more detail below and in Lipson et al., U.S. 20040002534 (U.S. application 10/600, 868, filed June 23, 2003) which is incorporated herein by reference in its entirety, cell proliferative disorders which can be treated by the present disclosure include cancers, and mast cell proliferative disorders.

[0222] The presence of c-kit or mutant c-kit has also been associated with a number of different types of cancers, diseases and conditions, as described below. In addition, the association between abnormalities in c-kit and disease are not restricted to cancer. As such, c-kit has been associated with malignancies, including mast cell tumors, small cell lung cancer, testicular cancer, gastrointestinal stromal tumors (GISTs), metastatic GISTs, glioblastoma, astrocytoma, neuroblastoma, carcinomas of the female genital tract, sarcomas of neuroectodermal origin, colorectal carcinoma, carcinoma in situ, Schwann cell neoplasia associated with neurofibromatosis, acute myelocytic leukemia, acute lymphocytic leukemia, chronic myelogenous leukemia, mastocytosis, melanoma, and canine mast cell tumors, and inflammatory diseases, including asthma, rheumatoid arthritis, allergic rhinitis, multiple sclerosis, inflammatory bowel syndrome, transplant rejection, hypereosinophilia, urticaria pigmentosa (UP), telangiectasia macularis eruptiva perstans (TMEP), systemic mastocytosis, indolent systemic, smoldering systemic, aggressive systemic, mast cell leukemia and mast cell sarcoma. The presence of mutant forms of c-kit has been associated with diseases or conditions, for example, gastrointestinal stromal tumors (GISTs), mast cell leukemia, germ-cell tumor, t-cell lymphoma, mastocytosis, acute lymphocytic leukemia and seminama.

Exemplary malignant diseases associated with c-kit

[0223] Aberrant expression and/or activation of c-kit and/or mutant form of c-kit has been implicated in a variety of cancers (Roskoski, 2005, Biochemical and biophysical Research Comm. 338: 1307-1315). Evidence for a contribution of c-kit to neoplastic pathology includes its association with leukemias and mast cell tumors, small cell lung cancer, testicular cancer, and some cancers of the gastrointestinal tract and central nervous system. In addition, c-kit has been implicated in playing a role in carcinogenesis of the female genital tract (Inoue, et al., 1994, Cancer Res. 54(11):3049-3053), sarcomas of neuroectodermal origin (Ricotti, et al., 1998, Blood 91:2397-2405), and Schwann cell neoplasia associated with neurofibromatosis (Ryan, et al., 1994, J. Neuro. Res. 37:415-432). It was found that mast cells are involved in modifying the tumor microenvironment and enhancing tumor growth (Yang et al., 2003, J Clin Invest. 112:1851-1861; Viskochil, 2003, J Clin Invest. 112:1791-1793). Thus, c-kit is a useful target in treating neurofibromatosis as well as malignant tumors.

[0224] Small cell lung carcinoma: c-kit kinase receptor has been found to be aberrantly expressed in many cases of small cell lung carcinoma (SCLC) cells (Hibi, et al., 1991, Oncogene 6:2291-2296). Thus,

as an example, inhibition of c-kit kinase can be beneficial in treatment of SCLC, e.g., to improve the long term survival of patients with SCLC.

[0225] Leukemias: SCF binding to the c-kit protects hematopoietic stem and progenitor cells from apoptosis (Lee, et al., 1997, J. Immunol. 159:3211-3219), thereby contributing to colony formation and hematopoiesis. Expression of c-kit is frequently observed in acute myelocytic leukemia (AML), and in some cases of acute lymphocytic leukemia (ALL) (for reviews, see Sperling, et al., 1997, Haemat 82:617-621; Escribano, et al., 1998, Leuk. Lymph. 30:459-466). Although c-kit is expressed in the majority of AML cells, its expression does not appear to be prognostic of disease progression (Sperling, et al, 1997, Haemat 82:617-621). However, SCF protected AML cells from apoptosis induced by chemotherapeutic agents (Hassan, et al., 1996, Acta. Hem. 95:257-262). Inhibition of c-kit by the present disclosure will enhance the efficacy of these agents and can induce apoptosis of AML cells.

[0226] The clonal growth of cells from patients with myelodysplastic syndrome (Sawada, et al., 1996, Blood 88:319-327) or chronic myelogenous leukemia (CML) (Sawai, et al., 1996, Exp. Hem. 2:116-122) was found to be significantly enhanced by SCF in combination with other cytokines. CML is characterized by expansion of Philadelphia chromosome positive cells of the marrow (Verfaillie, et al., Leuk. 1998, 12:136-138), which appears to primarily result from inhibition of apoptotic death (Jones, Curr. Opin. Onc. 1997, 9:3-7). The product of the Philadelphia chromosome, $p210^{BCR-ABL}$, has been reported to mediate inhibition of apoptosis (Bedi, et al., Blood 1995, 86:1148-1158). Since $p210^{BCR-ABL}$ and c-kit both inhibit apoptosis and $p62^{dok}$ has been suggested as a substrate (Carpino, et al., Cell 1997, 88:197-204), clonal expansion mediated by these kinases may occur through a common signaling pathway. However, c-kit has also been reported to interact directly with $p210^{BCR-ABL}$ (Hallek, et al., Brit. J Haem. 1996, 94:5-16), which suggests that c-kit has a more causative role in CML pathology. Therefore, inhibition of c-kit will be useful in the treatment of the above disorders.

[0227] Gastrointestinal cancers: Normal colorectal mucosa does not express c-kit (Bellone, et al., 1997, J. Cell Physiol. 172:1-11). However, c-kit is frequently expressed in colorectal carcinoma (Bellone, et al., 1997, J. Cell Physiol. 172: 1-11), and autocrine loops of SCF and c-kit have been observed in several colon carcinoma cell lines (Toyota, et al., 1993, Turn Biol 14:295-302; Lahm, et al., 1995, Cell Growth &Differ 6:1111-1118; Bellone, et al., 1997, J. Cell Physiol. 172:1-11). Furthermore, disruption of the autocrine loop by the use of neutralizing antibodies (Lahm, et al., 1995, Cell Growth & Differ. 6:1111-1118) and down regulation of c-kit and/or SCF significantly inhibits cell proliferation (Lahm, et al., 1995, Cell Growth & Differ 6:1111-1118; Bellone, et al., 1997, J. Cell Physiol. 172:1-11).

[0228] SCF/c-kit autocrine loops have been observed in gastric carcinoma cell lines (Turner, et al., 1992, Blood 80:374-381; Hassan, et al., 1998, Digest. Dis. Science 43:8-14), and constitutive c-kit

activation also appears to be important for gastrointestinal stromal tumors (GISTs). GISTs are the most common mesenchymal tumor of the digestive system. More than 90% of GISTs express c-kit, which is consistent with the putative origin of these tumor cells from interstitial cells of Cajal (ICCs) (Hirota, et al., 1998, Science 279:577-580). ICCs are thought to regulate contraction of the gastrointestinal tract, and patients lacking c-kit in their ICCs exhibited a myopathic form of chronic idiopathic intestinal pseudo-obstruction (Isozaki, et al., 1997, Amer. J. of Gast. 9 332-334). The c-kit expressed in GISTs from several different patients was observed to have mutations in the intracellular juxtamembrane domain leading to constitutive activation of c-kit (Hirota, et al., 1998, Science 279:577-580). Hence, inhibition of c-kit kinase will be an efficacious means for the treatment of these cancers.

[0229] Overexpression or constitutive activation of Kit mutations have been implicated and associated in gastrointestinal stromal tumors (GISTs) and most GISTs contain oncogenic KIT receptor or PDGFRA receptor tyrosine kinase mutations (Miettinen, et al., 2006, Arch Pathol Lab Med, 130: 14661478; Fletcher, et al., 2007, Current Opinion in Genetics & Development, 17:3-7; and Frost, et al. 2002, Molecular Cancer Therapeutics, 1:1115-1124). Frost, et al, 2002 has shown that D816V KIT mutation is resistant to imatinib, such that additional types of c-kit inhibitors are useful. Many GISTs have activating mutations in the KIT justamembrane regions (Lux, et al., 2000, American Journal Pathology, 156:795). Constitutive activation of the Kit receptor tyrosine kinase is a central pathogenic event in most GISTs and generally results from oncogenic point mutations (Heinrich, et al. 2002, Human Pathology, 33:484-495). Inhibition of wild-type KIT and/or certain mutant KIT isoforms with a small molecule tyrosine kinase inhibitor has become standard of care for treating patient with metastatic GISTs (Schittenhelm, et al. 2006, Cancer Res., 66: 473-481). Therefore, inhibition of c-kit kinase and/or mutant c-kit kinase will be an efficacious means for the treatment of GISTs.

[0230] Testicular cancers: Male germ cell tumors have been histologically categorized into seminomas, which retain germ cell characteristics, and nonseminomas which can display characteristics of embryonal differentiation. Both seminomas and nonseminomas are thought to initiate from a preinvasive stage designated carcinoma in situ (CIS) (Murty, et al., 1998, Sem. Oncol. 25:133-144). Both c-kit and SCF have been reported to be essential for normal gonadal development during embryogenesis (Loveland, et al., 1997, J. Endocrinol 153:337-344). Loss of either the receptor or the ligand resulted in animals devoid of germ cells. In postnatal testes, c-kit has been found to be expressed in Leydig cells and spermatogonia, while SCF was expressed in Sertoli cells (Loveland, et al., 1997, J. Endocrinol 153:337-344). Testicular tumors develop from Leydig cells with high frequency in transgenic mice expressing human papilloma virus 16 (HPV16) E6 and E7 oncogenes (Kondoh, et al., 1991, J. Virol. 65:3335-3339; Kondoh, et al., 1994, J. Urol. 152:2151-2154). These tumors express both c-kit and SCF, and an autocrine loop may contribute to the tumorigenesis (Kondoh, et al., 1995, Oncogene 10:341-347) associated with cellular loss

of functional p53 and the retinoblastoma gene product by association with E6 and E7 (Dyson, et al., 1989, Science 243:934-937; Werness, et al., 1990, Science 248:76-79; Scheffner, et al., 1990, Cell 63:1129-1136). Defective signaling mutants of SCF (Kondoh, et al., 1995, Oncogene 10:341-347) or c-kit (Li, et al., 1996, Canc. Res. 56:4343-4346) inhibited formation of testicular tumors in mice expressing HPV16 E6 and E7. The c-kit kinase activation is pivotal to tumorigenesis in these animals and thus modulation of the c-kit kinase pathway by the present disclosure will prevent or treat such disorders.

[0231] Expression of c-kit in germ cell tumors shows that the receptor is expressed by the majority of carcinomas in situ and seminomas, but c-kit is expressed in only a minority of nonseminomas (Strohmeyer, et al., 1991, Canc. Res. 51:1811-1816; Rajpert-de Meyts, et al., 1994, Int. J. Androl. 17:85-92; Izquierdo, et al., 1995, J. Pathol. 177:253-258; Strohmeyer, et al., 1995, J. Urol. 153:511-515; Bokenmeyer, et al., 1996, J. Cancer Res. Clin. Oncol. 122:301-306; Sandlow, et al., 1996, J. Androl. 17:403-408). Therefore, inhibition of c-kit kinase provides a means for treating these disorders.

[0232] CNS cancers: SCF and c-kit are expressed throughout the CNS of developing rodents, and the pattern of expression indicates a role in growth, migration and differentiation of neuroectodermal cells. Expression of both receptor and ligand have also been reported in the adult brain (Hamel, et al., 1997, J. Neuro-Onc. 35:327-333). Expression of c-kit has also been observed in normal human brain tissue (Tada, et al. 1994, J. Neuro 80:1063-1073). Glioblastoma and astrocytoma, which define the majority of intracranial tumors, arise from neoplastic transformation of astrocytes (Levin, et al., 1997, Principles & Practice of Oncology:2022-2082). Expression of c-kit has been observed in glioblastoma cell lines and tissues (Berdel, et al., 1992, Canc. Res. 52:3498-3502; Tada, et al. 1994, J. Neuro 80:1063-1073; Stanulla, et al., 1995, Act Neuropath 89:158-165).

[0233] Cohen, et al., 1994, Blood 84:3465-3472 reported that all 14 neuroblastoma cell lines examined contained c-kit/SCF autocrine loops, and expression of both the receptor and ligand were observed in 45% of tumor samples examined. In two cell lines, anti-c-kit antibodies inhibited cell proliferation, suggesting that the SCF/c-kit autocrine loop contributed to growth (will Cohen, et al., 1994, Blood 84:3465-3472). Hence, c-kit kinase inhibitors can be used to treat these cancers.

Exemplary Mast Cell Diseases Involving c-kit

[0234] Excessive activation of c-kit is also associated with diseases resulting from an over-abundance of mast cells. Mastocytosis is the term used to describe a heterogeneous group of disorders characterized by excessive mast cell proliferation (Metcalfe, 1991, J. Invest. Derm 93:2S-4S; Golkar, et al., 1997, Lancet 349:1379-1385). Elevated c-kit expression was reported on mast cells from patients with aggressive mastocytosis (Nagata, et al., 1998, Leukemia 12:175-181).

[0235] Additionally, mast cells and eosinophils represent key cells involved in allergy, inflammation and asthma (Thomas, et al., 1996, Gen. Pharmacol 27:593-597; Metcalfe, et al., 1997, Physiol Rev 77:1033-1079; Naclerio, et al., 1997, JAMA 278:1842-1848; Costa, et al., 1997, JAMA 278:1815-1822). SCF, and hence c-kit, directly and indirectly regulates activation of both mast cells and eosinophils, thereby influencing the primary cells involved in allergy and asthma through multiple mechanisms. Because of this mutual regulation of mast cell and eosinophil function, and the role that SCF can play in this regulation, inhibition of c-kit can be used to treat allergy-associated chronic rhinitis, inflammation and asthma.

[0236] Mastocytosis: SCF (also known as mast cell growth factor) stimulation of c-kit has been reported to be essential for the growth and development of mast cells (Hamel, et al., 1997, J. Neuro-Onc. 35:327-333; Kitamura, et al., 1995, Int. Arch. Aller. Immunol. 107:54-56). Mice with mutations of c-kit that attenuate its signaling activity have exhibited significantly fewer mast cells in their skin (Tsujimura, 1996, Pathol Int 46:933-938). Excessive activation of c-kit can be associated with diseases resulting from an overabundance of mast cells.

[0237] Mastocytosis is limited to the skin in the majority of patients, but can involve other organs in 15-20% of patients (Valent, 1996, Wein/Klin Wochenschr 108:385-397; Golkar, et al., 1997, Lancet 349:1379-1385). Even among patients with systemic mastocytosis, the disease can range from having a relatively benign prognosis to aggressive mastocytosis and mast cell leukemia. (Valent, 1996, Wein/Klin Wochenschr 108:385-397; Golkar, et al., 1997, Lancet 349:1379-1385). c-kit has been observed on malignant mast cells from canine mast cell tumors (London, et al., 1996, J. Compar. Pathol. 115:399-414), as well as on mast cells from patients with aggressive systemic mastocytosis (Baghestanian, et al., 1996, Leuk.:116-122; Castells, et al., 1996, J. Aller. Clin. Immunol. 98:831-840).

[0238] SCF has been shown to be expressed on stromal cells as a membrane-bound protein, and its expression can be induced by fibrogenic growth factors such as PDGF. It has also been shown to be expressed on keratinocytes as a membrane-bound protein in normal skin. However, in the skin of patients with mastocytosis, an increased amount of soluble SCF has been observed (Longley, et al., 1993, New Engl. J. Med. 328:1302-1307).

[0239] Mast cell chymase has been reported to cleave membrane-associated SCF to a soluble and biologically active form. This mast cell-mediated process can generate a feedback loop to enhance mast cell proliferation and function (Longley, et al., 1997, Proc. Natl. Acad. Sci. 94:9017-9021), and may be important for the etiology of mastocytosis. Transgenic mice overexpressing a form of SCF that could not be proteolytically released from keratinocytes did not develop mastocytosis, while similar animals expressing normal SCF in keratinocytes exhibited a phenotype resembling human cutaneous mastocytosis

(Kunisada, et al., 1998, J. Exp. Med. 187:1565-1573). Formation of large amounts of soluble SCF can contribute to the pathology associated with mastocytosis in some patients and the present disclosure can treat or prevent such disorders by modulating the interaction between SCF and c-kit kinase. Several different mutations of c-kit that resulted in constitutive kinase activity have been found in human and rodent mast cell tumor cell lines (Furitsu, et al., 1993, J. Clin. Invest. 92:1736-1744; Tsujimura, et al., 1994, Blood 9:2619-2626; Tsujimura, et al., 1995, Int. Arch. Aller. Immunol 106:377-385; Tsujimura, 1996, Pathol Int 46:933-938). In addition, activating mutations of the c-kit gene have been observed in peripheral mononuclear cells isolated from patients with mastocytosis and associated hematologic disorders (Nagata, et al., 1998, Mastocytosis Leuk 12:175-181), and in mast cells from a patient with urticaria pigmentosa and aggressive mastocytosis (Longley, et al., 1996, Nat. Gen. 12:312-314). Inhibition of c-kit kinase will therefore prove to have an excellent therapeutic role in the treatment of these disorders.

[0240] In some patients, activating mutations of c-kit may be responsible for the pathogenesis of the disease and these patients can be treated, or their diseases prevented, by modulation of the SCF interaction with c-kit kinase. SCF activation of c-kit has been shown to prevent mast cell apoptosis which may be critical for maintaining cutaneous mast cell homeostasis (Iemura, et al., 1994, Amer. J. Pathol 144:321-328; Yee, et al., 1994, J. Exp. Med. 179:1777-1787; Mekori, et al., 1994, J. Immunol 153:2194-2203; Mekori, et al., 1995, Int. Arch. Allergy Immunol. 107:137-138). Inhibition of mast cell apoptosis can lead to the mast cell accumulation associated with mastocytosis. Thus, observation of c-kit activation resulting from overexpression of the receptor, excessive formation of soluble SCF, or mutations of the c-kit gene that constitutively activate its kinase, provides a rationale that inhibition of the kinase activity of c-kit will decrease the number of mast cells and provide benefit for patients with mastocytosis.

[0241] For cells with activating c-kit mutations, it was found that inhibitors of c-kit inhibit or even kill the cells (Ma et al., 2000, J Invest Dermatol. 114:392-394), particularly for mutations in the regulatory region (Ma et al., 2002, Blood 99:1741-1744). Ma et al., 2002, also showed that for mutations in the catalytic region, inhibitors STI571 (Gleevec) and SU9529 did not inhibit the cells, such that additional types of c-kit inhibitors are useful. Thus, c-kit inhibitors can be used against both wild-type c-kit as well as c-kit having mutations, e.g., activating mutations in the regulatory region and/or catalytic region.

[0242] It has been shown that mastocytosis is characterized by a pathologic increase of mast cells in tissues associated with mutations in KIT (Metcalfe, 2008, Blood, 112:946-956; and Ma, et al., 2002). D816 mutation of c-kit has been detected in patients with mastocytosis (Taylor, et al., 2001, Blood, 98:1195-1199; and Longley, et al. 1999, Proc. Natl. Acad. Sci. 96:1609-14). Inhibition of KIT oncogenic protein KIT^{D816V} with small molecule tyrosine kinase inhibitor is capable of treating patients with

systemic mastocytosis (Shah, et al., 2006, Blood, 108:286-291). Thus, c-kit inhibitors can be used in treating patients with mastocytosis.

[0243] Asthma & Allergy: Mast cells and eosinophils represent key cells in parasitic infection, allergy, inflammation, and asthma (Thomas, et al., 1996, Gen. Pharmacol 27:593-597; Metcalfe, et al., 1997, Physiol Rev 77:1033-1079; Holgate, 1997, CIBA Found. Symp.; Naclerio, et al, 1997, JAMA 278:1842-1848; Costa, et al., 1997, JAMA 778:1815-1822). SCF has been shown to be essential for mast cell development, survival and growth (Kitamura, et al., 1995, Int. Arch. Aller. Immunol. 107:54-56; Metcalfe, et al., 1997, Physiol Rev 77:1033-1079). In addition, SCF cooperates with the eosinophil-specific regulator, IL-5, to increase the development of eosinophil progenitors (Metcalf, et al., 1998, Proc. Natl. Acad. Sci., USA 95:6408-6412). SCF has also been reported to induce mast cells to secrete factors (Okayama, et al., 1997, Int. Arch. Aller. Immunol. 114:75-77; Okayama, et al., 1998, Eur. J. Immunol. 28:708-715) that promote the survival of eosinophils (Kay, et al., 1997, Int. Arch. Aller. Immunol. 113:196-199), which may contribute to chronic, eosinophil-mediated inflammation (Okayama, et al., 1997, Int. Arch. Aller. Immunol. 114:75-77; Okayama, et al., 1998, Eur. J. Immunol. 28:708-715). In this regard, SCF directly and indirectly regulates activation of both mast cells and eosinophils.

[0244] SCF induces mediator release from mast cells, as well as priming these cells for IgE-induced degranulation (Columbo, et al., 1992, J. Immunol 149:599-602) and sensitizing their responsiveness to eosinophil-derived granule major basic protein (Furuta, et al., 1998, Blood 92:1055-1061). Among the factors released by activated mast cells are IL-5, GM-CSF and TNF-α, which influence eosinophil protein secretion (Okayama, et al., 1997, Int. Arch. Aller. Immunol. 114:75-77; Okayama, et al., 1998, Eur. J. Immunol. 28:708-715). In addition to inducing histamine release from mast cells (Luckacs, et al., 1996, J. Immunol. 156:3945-3951; Hogaboam, et al., 1998, J. Immunol. 160:6166-6171), SCF promotes the mast cell production of the eosinophil chemotactic factor, eotaxin (Hogaboam, et al., 1998, J. Immunol. 160:6166-6171), and eosinophil infiltration (Luckacs, et al., 1996, J. Immunol. 156:3945-3951).

[0245] SCF also directly influences the adhesion of both mast cells (Dastych, et al., 1994, J. Immunol. 152:213-219; Kinashi, et al., 1994, Blood 83:1033-1038) and eosinophils (Yuan, et al., 1997, J. Exp. Med. 186:313-323), which in turn, regulates tissue infiltration. Thus, SCF can influence the primary cells involved in allergy and asthma through multiple mechanisms. Currently, corticosteroids are the most effective treatment for chronic rhinitis and inflammation associated with allergy (Naclerio, et al., 1997, JAMA 278:1842-1848; Meltzer, 1997, Aller. 52:33-40). These agents work through multiple mechanisms including reduction of circulating and infiltrating mast cells and eosinophils, and diminished survival of eosinophils associated with inhibition of cytokine production (Meltzer, 1997, Aller. 52:33-40). Steroids have also been reported to inhibit the expression of SCF by fibroblasts and resident connective tissue cells, which leads to diminished mast cell survival (Finotto, et al., 1997, J. Clin. Invest. 99 1721-1728).

Because of the mutual regulation of mast cell and eosinophil function, and the role that SCF can play in this regulation, inhibition of c-kit kinase will provide a means to treat allergy-associated chronic rhinitis, inflammation and asthma.

[0246] Inflammatory arthritis (e.g. rheumatoid arthritis): Due to the association of mast cells with the arthritic process (Lee et al., 2002, Science 297:1689-1692), c-kit provides a useful target for prevention, delay, and/or treatment of inflammatory arthritis, such as rheumatoid arthritis.

[0247] Multiple sclerosis: Mast cells have been shown to play an extensive role in autoimmune diseases, as demonstrated in the mouse model of multiple sclerosis (MS), experimental allergic encephalomyelitis (EAE). Mast cells were indicated to be required for full manifestation of the disease. Secor et al., 2000, J Exp Med 191:813-821. Thus, c-kit also provides a useful target for the prevention, delay, and/or treatment of multiple sclerosis.

Kinase Activity Assays

[0248] 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 describe assays that can be used.

[0249] In certain embodiments, compounds of formulas (I), (II) or any of the subformulas or compounds as disclosed herein are active in an assay measuring c-kit and/or mutant c-kit protein kinase activity. In some embodiments, a compound of formulas (I), (II) or any of the subformulas or a compound as described herein has an IC_{50} of less than 10,000 nM, 1,000 nM, less than 500 nM, less than 100 nM, less than 50 nM, less than 20 nM, less than 10 nM, less than 5 nM, or less than 1 nM as determined in a generally accepted c-kit and/or mutant c-kit kinase activity assay. In some embodiments, a compound as described herein has an IC_{50} of less than 10,000 nM, 1,000 nM, less than 500 nM, less than 100 nM, less than 50 nM, less than 20 nM, less than 10 nM, less than 5 nM, or less than 1 nM as determined in a generally accepted mutant c-kit kinase (such as D816F, D816H, D816N, D816Y, D816V, K642E, Y823D, Del 550-558, Del 557-561, N822K, V654A, N822H, Del 550-558+V654A, Del 557-561+V654A, Ins503AY, V560G, 558NP, Del 557-558, Del W559-560, F522C, Del 579, R634W, K642E, T801I, C809G, D820Y, N822K, N822H, Y823D, Y823C and T670I) activity assay. In some embodiments, the assay for measuring c-kit kinase activity and/or mutant c-kit kinase (such as D816F, D816H, D816N, D816Y, D816V, K642E, Y823D, Del 550-558, Del 557-561, N822K, V654A, N822H, Del 550-558+V654A, Del 557-561+V654A, Ins503AY, V560G, 558NP, Del 557-558, Del W559-560,

F522C, Del 579, R634W, K642E, T801I, C809G, D820Y, N822K, N822H, Y823D, Y823C and T670I) activity includes an assay (e.g., biochemical or cell-bases assays) such as described in Example 28 or an assay well known in the art similar to those described in Example 28.

[0250] In some embodiments, compounds of formulas (I), II), any of the subformulas as described herein or a compound as described herein are active in an assay measuring c-kit protein kinase activity and/or an assay for measuring mutant c-kit (such as D816V and/or V560G). In some embodiments a compound as described herein has an IC_{50} of less than 10,000 nM, 1,000 nM, less than 500 nM, less than 100 nM, less than 50 nM, less than 20 nM, less than 10 nM, less than 5 nM, or less than 1 nM as determined in a generally accepted c-kit kinase activity assay (including a mutant c-kit kinase activity assay). In some embodiments, a compound as described herein has an IC_{50} of less than 100 nM, less than 10 nM, or less than 1 nM in a D816V and/or V560G mutant c-kit activity assay.

Modulation of c-kit kinase

[0251] In another aspect, the disclosure provides a method for modulating or inhibiting a c-kit and/or mutant c-kit kinase. The method includes administering to a subject an effective amount of a compound of any of formulas (I), (II), (IIa), (IIb), (IIc), (IIa-1), (IIa-2), (IIa-3), (IIa-4), (IIa-1a), (IIa-1b), (IIa-1c), (IIa-1d), (IIa-1e), (IIa-1f), (IIa-1g), (IIa-1h), (IIa-1i), (IIa-1j), (IIa-1k), (IIa-1m), (IIa-2a), (IIa-2b), (IIa-3a), (IIa-3b), (IIa-3c), (IIa-3d), (IIa-3e), (IIa-3f), (IIa-3g), (IIa-3h), (IIa-3i), (IIa-3j), (IIa-3k), (IIa-3m), (IIb-1), (IIb-2), (IIb-3), (IIb-4), (IIb-1a), (IIb-1b), (IIb-1c), (IIb-1d), (IIb-1e), (IIb-1f), (IIb-1g), (IIb-1h), (IIb-1i), (IIb-1j), (IIb-1k), (IIb-1m), (IIb-2a), (IIb-2b), (IIb-3a), (IIb-3b), (IIb-3c), (IIb-3d), (IIb-3e), (IIb-3f), (IIb-3g), (IIb-3h), (IIb-3i), (IIb-3j), (IIb-3k), (IIb-3m), (IIb-4a), (IIb-4b), (IIc-1), (IIc-2), (IIc-1a), (IIc-1b), (IIc-1c), (IIc-1d), (IIc-1e), (IIc-1f), (IIc-1g), (IIc-1h), (IIc-1i), (IIc-1j), (IIc-1k), (IIc-1m), (IIc-2a), (IIc-2b), (IId), (IIe), (IIf), (IId-1), (IId-2), (IId-1a), (IId-1b), (IId-1c), (IId-1d), (IId-1e), (IId-1f), (IId-1g), (IId-1h), (IId-1i), (IId-2a), (IId-2b), (IId-2c), (IId-2d), (IId-2e), (IId-2f), (IId-2g), (IId-2h), (IId-2i), (IIe-1), (IIe-2), (IIe-1a), (IIe-1b), (IIe-1c), (IIe-1d), (IIe-1e), (IIe-1f), (IIe-1g), (IIe-1h), (IIe-1i), (IIe-2a), (IIe-2b), (IIe-2c), (IIe-2d), (IIe-2e), (IIe-2f), (IIe-2g), (IIe-2h), (IIe-2i), (IIf-1a), (IIf-1b), (IIf-1c), (IIf-1d), (IIf-1e), (IIf-1f), (IIf-1g), (IIf-1h), (IIf-1i), (IIg), (IIh), (IIj), (IIk), (IIg-1), (IIh-1), (IIj-1), (IIk-1), (IIg-1a), (IIg-1b), (IIg-1c), (IIg-1d), (IIg-1e), (IIg-1f), (IIg-1g), (IIh-1a), (IIh-1b), (IIh-1c), (IIh-1d), (IIh-1e), (IIh-1f), (IIh-1g), (IIj-1a), (IIj-1b), (IIj-1c), (IIj-1d), (IIj-1e), (IIj-1f), (IIj-1g), (IIk-1a), (IIk-1b), (IIk-1c), (IIk-1d), (IIk-1e), (IIk-1f), (IIk-1g), (IIg-1a-1), (IIg-1a-2), (IIg-1b-1), (IIg-1b-2), (IIg-1c-1), (IIg-1c-2), (IIg-1d-1), (IIg-1d-2), (IIg-1e-1), (IIg-1e-2), (IIg-1f-1), (IIg-1f-2), (IIg-1g), (IIg-1g-2), (IIh-1a-1), (IIh-1a-2), (IIh-1b-1), (IIh-1b-2), (IIh-1c-1), (IIh-1c-2), (IIh-1d-1), (IIh-1d-2), (IIh-1e-1), (IIh-1e-2), (IIh-1f-1), (IIh-1f-2), (IIh-1g), (IIh-1g-2), (IIj-1a-1), (IIj-1a-2), (IIj-1b-1), (IIj-1b-2), (IIj-1c-1), (IIj-1c-2), (IIj-1d-1), (IIj-1d-2), (IIj-1e-1), (IIj-1e-2), (IIj-1f-1), (IIj-1f-2), (IIj-1g), (IIj-1g-2), (IIk-1a), (IIk-1b), (IIk-1c), (IIk-1d), (IIk-1e), (IIk-1f), or (IIk-1g), or a compound set forth in Tables 1-6, or a compound of P-0001 to P-0731, or a

compound as described herein, or pharmaceutically acceptable salts, hydrates, solvates, tautomers or isomers thereof, or a composition comprising a compound of any of the formulas as described herein, thereby, modulating or inhibiting the c-kit and/or mutant c-kit kinase. In some embodiments, the c-kit is a wild type kit kinase. In other embodiments, the c-kit kinase is a mutant kit kinase having a mutation selected from D816F, D816H, D816N, D816Y, D816V, K642E, Y823D, Del 550-558, Del 557-561, N822K, V654A, N822H, Del 550-558+V654A, Del 557-561+V654A, Ins503AY, V560G, 558NP, Del 557-558, Del W559-560, F522C, Del 579, R634W, K642E, T801I, C809G, D820Y, N822K, N822H, Y823D, Y823C and T670I. In one embodiment, the mutant c-kit has an activating D816V and/or V560G mutation. In some embodiments, the method includes contacting a cell in vivo or in vitro with a compound of formulas (I), (II), or any of the subformulas as described herein, or a compound as disclosed herein, or pharmaceutically acceptable salts, hydrates, solvates, tautomers or isomers thereof, or a composition comprising a compound of any of the formulas as described herein. In other embodiments, the method includes contacting a mutant c-kit kinase in vivo or in vitro with a compound of formulas (I), (II), or any of the subformulas as described herein or a compound as disclosed herein or pharmaceutically acceptable salts, hydrates, solvates, tautomers or isomers thereof, or a composition comprising a compound of any of the formulas as described herein.

VI. Methods for Treating Conditions Mediated by c-Kit Kinase

[0252] In another aspect, the present disclosure provides a method for treating a subject suffering from or at risk of a c-kit and or a mutant c-kit protein kinase mediated diseases or conditions. The method includes administering to the subject an effective amount of a compound of any of formulas (I), (II), (IIa), (IIb), (IIc), (IIa-1), (IIa-2), (IIa-3), (IIa-4), (IIa-1a), (IIa-1b), (IIa-1c), (IIa-1d), (IIa-1e), (IIa-1f), (IIa-1g), (IIa-1h), (IIa-1i), (IIa-1j), (IIa-1k), (IIa-1m), (IIa-2a), (IIa-2b), (IIa-3a), (IIa-3b), (IIa-3c), (IIa-3d), (IIa-3e), (IIa-3f), (IIa-3g), (IIa-3h), (IIa-3i), (IIa-3j), (IIa-3k), (IIa-3m), (IIb-1), (IIb-2), (IIb-3), (IIb-4), (IIb-1a), (IIb-1b), (IIb-1c), (IIb-1d), (IIb-1e), (IIb-1f), (IIb-1g), (IIb-1h), (IIb-1i), (IIb-1j), (IIb-1k), (IIb-1m), (IIb-2a), (IIb-2b), (IIb-3a), (IIb-3b), (IIb-3c), (IIb-3d), (IIb-3e), (IIb-3f), (IIb-3g), (IIb-3h), (IIb-3i), (IIb-3j), (IIb-3k), (IIb-3m), (IIb-4a), (IIb-4b), (IIc-1), (IIc-2), (IIc-1a), (IIc-1b), (IIc-1c), (IIc-1d), (IIc-1e), (IIc-1f), (IIc-1g), (IIc-1h), (IIc-1i), (IIc-1j), (IIc-1k), (IIc-1m), (IIc-2a), (IIc-2b), (IId), (IIe), (IIf), (IId-1), (IId-2), (IId-1a), (IId-1b), (IId-1c), (IId-1d), (IId-1e), (IId-1f), (IId-1g), (IId-1h), (IId-1i), (IId-2a), (IId-2b), (IId-2c), (IId-2d), (IId-2e), (IId-2f), (IId-2g), (IId-2h), (IId-2i), (IIe-1), (IIe-2), (IIe-1a), (IIe-1b), (IIe-1c), (IIe-1d), (IIe-1e), (IIe-1f), (IIe-1g), (IIe-1h), (IIe-1i), (IIe-2a), (IIe-2b), (IIe-2c), (IIe-2d), (IIe-2e), (IIe-2f), (IIe-2g), (IIe-2h), (IIe-2i), (IIf-1a), (IIf-1b), (IIf-1c), (IIf-1d), (IIf-1e), (IIf-1f), (IIf-1g), (IIf-1h), (IIf-1i), (IIg), (IIh), (IIj), (IIk), (IIg-1), (IIh-1), (IIj-1), (IIk-1), (IIg-1a), (IIg-1b), (IIg-1c), (IIg-1d), (IIg-1e), (IIg-1f), (IIg-1g), (IIh-1a), (IIh-1b), (IIh-1c), (IIh-1d), (IIh-1e), (IIh-1f), (IIh-1g), (IIj-1a), (IIj-1b), (IIj-1c), (IIj-1d), (IIj-1e), (IIj-1f), (IIj-1g), (IIk-1a), (IIk-1b), (IIk-1c), (IIk-1d), (IIk-1e), (IIk-1f), (IIk-1g), (IIg-1a-1),

(IIg-1a-2), (IIg-1b-1), (IIg-1b-2), (IIg-1c-1), (IIg-1c-2), (IIg-1d-1), (IIg-1d-2), (IIg-1e-1), (IIg-1e-2), (IIg-1f-1), (IIg-1f-2), (IIg-1g), (IIg-1g-2), (IIh-1a-1), (IIh-1a-2), (IIh-1b-1), (IIh-1b-2), (IIh-1c-1), (IIh-1c-2), (IIh-1d-1), (IIh-1d-2), (IIh-1e-1), (IIh-1e-2), (IIh-1f-1), (IIh-1f-2), (IIh-1g), (IIh-1g-2), (IIj-1a-1), (IIj-1a-2), (IIj-1b-1), (IIj-1b-2), (IIj-1c-1), (IIj-1c-2), (IIj-1d-1), (IIj-1d-2), (IIj-1e-1), (IIj-1e-2), (IIj-1f-1), (IIj-1f-2), (IIj-1g), (IIj-1g-2), (IIk-1a), (IIk-1b), (IIk-1c), (IIk-1d), (IIk-1e), (IIk-1f) or (IIk-1g), or a compound disclosed in the Examples, a compound set forth in Tables 1-6, or a compound of P-0001 to P-0731, or a compound as described herein, or pharmaceutically acceptable salts, hydrates, solvates, tautomers or isomers thereof, or a composition comprising a compound of any of the formulas as described herein. In some embodiments, the mutant c-kit kinase has a mutation selected from D816F, D816H, D816N, D816Y, D816V, K642E, Y823D, Del 550-558, Del 557-561, N822K, V654A, N822H, Del 550-558+V654A, Del 557-561+V654A, Ins503AY, V560G, 558NP, Del 557-558, Del W559-560, F522C, Del 579, R634W, K642E, T801I, C809G, D820Y, N822K, N822H, Y823D, Y823C or T670I or combinations thereof. In one embodiment, the mutant c-kit has an activating D816 mutation. In one embodiment, the mutant c-kit has an activating D816V mutation. In another embodiment, the mutant c-kit has a V560G mutation. In yet another embodiment, the mutant c-kit has an activating D816V and V560G mutations. 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.

[0253] In some embodiments, the disclosure provides a method of suppressing undesired proliferation of tumor cells expressing a D816 (such as D816F, D816H, D816N, D816Y or D816V) and/or V560G mutant c-kit protein kinase. The method includes contacting tumor cells expressing D816 (such as D816F, D816H, D816N, D816Y or D816V) and/or V560G mutant c-kit protein kinase with an effective amount of a compound of any of formulas (I), (II), or any of the subformulas as described herein, or any compound as described herein, or pharmaceutically acceptable salts, hydrates, solvates, tautomers or isomers thereof, or a composition comprising a compound as described herein. In some instances, the tumor cells expressing D816V and/or V560G mutant c-kit kinase.

[0254] In certain embodiments, the disclosure provides a method of treating a c-kit protein kinase D816 (such as D816F, D816H, D816N, D816Y or D816V) and/or V560G mutation-positive patient. The method includes administering to the patient in need thereof an effective amount of a compound of any of formulas (I), (II), or any of the subformulas as described herein, or any compound as described herein, or pharmaceutically acceptable salts, hydrates, solvates, tautomers or isomers thereof, or a composition comprising a compound as described herein. In some embodiments, the patient is D816V mutation-positive. In other embodiments, the patient is V560G mutation-positive. In some embodiments, the

patient is D816V and V560G mutation-positive. In certain instances the patient is suffering from gastrointestinal stromal tumors (GISTs) and/or mastocytosis.

[0255] In some embodiments, the diseases or conditions treatable with the compounds of the present disclosure include, but are not limited to, multi-infarct dementia, head injury, spinal cord injury, Alzheimer's disease (AD), Parkinson's disease, seizures and epilepsy; neoplastic diseases including, but not limited to, melanoma, glioma, glioblastoma multiforme, pilocytic astrocytoma, sarcoma, carcinoma (e.g. gastrointestinal, liver, biliary tract, bile duct (cholangiocarcinoma), colorectal, lung, gallbladder, breast, pancreatic, thyroid, renal, ovarian, adrenocortical, prostate), lymphoma (e.g. histiocytic lymphoma) neurofibromatosis, gastrointestinal stromal tumors, acute myeloid leukemia, myelodysplastic syndrome, leukemia, tumor angiogenesis, neuroendocrine tumors such as medullary thyroid cancer, carcinoid, small cell lung cancer, Kaposi's sarcoma, and pheochromocytoma; pain of neuropathic or inflammatory origin, including, but not limited to, acute pain, chronic pain, cancer-related pain, and migraine; cardiovascular diseases including, but not limited to, heart failure, ischemic stroke, cardiac hypertrophy, thrombosis (e.g. thrombotic microangiopathy syndromes), atherosclerosis, and reperfusion injury; inflammation and/or proliferation including, but not limited to, psoriasis, eczema, arthritis and autoimmune diseases and conditions, osteoarthritis, endometriosis, scarring, vascular restenosis, fibrotic disorders, rheumatoid arthritis, inflammatory bowel disease (IBD); immunodeficiency diseases, including, but not limited to, organ transplant rejection, graft versus host disease, and Kaposi's sarcoma associated with HIV; renal, cystic, or prostatic diseases, including, but not limited to, diabetic nephropathy, polycystic kidney disease, nephrosclerosis, glomerulonephritis, prostate hyperplasia, polycystic liver disease, tuberous sclerosis, Von Hippel Lindau disease, medullary cystic kidney disease, nephronophthisis, and cystic fibrosis; metabolic disorders, including, but not limited to, obesity; infection, including, but not limited to *Helicobacter pylori, Hepatitis* and *Influenza* viruses, fever, HIV, and sepsis; pulmonary diseases including, but not limited to, chronic obstructive pulmonary disease (COPD) and acute respiratory distress syndrome (ARDS); genetic developmental diseases, including, but not limited to, Noonan's syndrome, Costello syndrome, (faciocutaneoskeletal syndrome), LEOPARD syndrome, cardio-faciocutaneous syndrome (CFC), and neural crest syndrome abnormalities causing cardiovascular, skeletal, intestinal, skin, hair and endocrine diseases; and diseases associated with muscle regeneration or degeneration, including, but not limited to, sarcopenia, muscular dystrophies (including, but not limited to, Duchenne, Becker, Emery-Dreifuss, Limb-Girdle, Facioscapulohumeral, Myotonic, Oculopharyngeal, Distal and Congenital Muscular Dystrophies), motor neuron diseases (including, but not limited to, amyotrophic lateral sclerosis, infantile progressive spinal muscular atrophy, intermediate spinal muscular atrophy, juvenile spinal muscular atrophy, spinal bulbar muscular atrophy, and adult spinal muscular atrophy), inflammatory myopathies (including, but not limited to, dermatomyositis, polymyositis, and inclusion body myositis), diseases of the neuromuscular junction (including, but not limited to,

myasthenia gravis, Lambert-Eaton syndrome, and congenital myasthenic syndrome), myopathies due to endocrine abnormalities (including, but not limited to, hyperthyroid myopathy and hypothyroid myopathy) diseases of peripheral nerve (including, but not limited to, Charcot-Marie-Tooth disease, Dejerine-Sottas disease, and Friedreich's ataxia), other myopathies (including, but not limited to, myotonia congenita, paramyotonia congenita, central core disease, nemaline myopathy, myotubular myopathy, and periodic paralysis), and metabolic diseases of muscle (including, but not limited to, phosphorylase deficiency, acid maltase deficiency, phosphofructokinase deficiency, debrancher enzyme deficiency, mitochondrial myopathy, carnitine deficiency, carnitine palmatyl transferase deficiency, phosphoglycerate kinase deficiency, phosphoglycerate mutase deficiency, lactate dehydrogenase deficiency, and myoadenylate deaminase deficiency). In one embodiment, the disease or condition is selected from the group consisting of melanoma, glioma, glioblastoma multiforme, pilocytic astrocytoma, sarcoma, liver cancer, biliary tract cancer, cholangiocarcinoma, colorectal cancer, lung cancer, gallbladder cancer, breast cancer, pancreatic cancer, thyroid cancer, renal cancer, ovarian cancer, adrenocortical cancer, prostate cancer, histiocytic lymphoma, neurofibromatosis, gastrointestinal stromal tumors, acute myeloid leukemia, myelodysplastic syndrome, leukemia, tumor angiogenesis, medullary thyroid cancer, carcinoid, small cell lung cancer, Kaposi's sarcoma, pheochromocytoma, acute pain, chronic pain, and polycystic kidney disease. In a preferred embodiment, the disease or condition is selected from the group consisting of melanoma, glioma, glioblastoma multiforme, pilocytic astrocytoma, colorectal cancer, thyroid cancer, lung cancer, ovarian cancer, prostate cancer, liver cancer, gallbladder cancer, gastrointestinal stromal tumors, biliary tract cancer, cholangiocarcinoma, acute pain, chronic pain, and polycystic kidney disease.

[0256] In other embodiments, the diseases or conditions treatable with the compounds of the present disclosure include, but are not limited to, ischemic stroke, cerebrovascular ischemia, multi-infarct dementia, head injury, spinal cord injury, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, dementia, senile chorea, Huntington's disease, neoplastic disease, complications with neoplastic disease, chemotherapy-induced hypoxia, gastrointestinal stromal tumors, prostate tumors, mast cell tumors, canine mast cell tumors, acute myeloid leukemia, acute lymphocytic leukemia, chronic myeloid leukemia, chronic lymphocytic leukemia, multiple myeloma, melanoma, mastocytosis, glioma, glioblastoma, astrocytoma, neuroblastoma, sarcomas, sarcomas of neuroectodermal origin, leiomyosarcoma, lung carcinoma, breast carcinoma, pancreatic carcinoma, colon carcinoma, hepatocellular carcinoma, renal carcinoma, carcinoma of the female genital tract, squamous cell carcinoma, carcinoma in situ, lymphoma, histiocytic lymphoma, non-Hodgkin's lymphoma, MEN2 syndromes, neurofibromatosis, Schwann cell neoplasia, myelodysplastic syndrome, leukemia, tumor angiogenesis, thyroid cancer, liver cancer, bone cancer, skin cancer, brain cancer, cancer of the central nervous system, pancreatic cancer, lung cancer, small cell lung cancer, non small cell lung cancer, breast

cancer, colon cancer, bladder cancer, prostate cancer, gastrointestinal tract cancer, cancer of the endometrium, fallopian tube cancer, testicular cancer, ovarian cancer, pain of neuropathic origin, pain of inflammatory origin, acute pain, chronic pain, migraine, cardiovascular disease, heart failure, cardiac hypertrophy, thrombosis, thrombotic microangiopathy syndromes, atherosclerosis, reperfusion injury, ischemia, cerebrovascular ischemia, liver ischemia, inflammation, polycystic kidney disease, age-related macular degeneration, rheumatoid arthritis, allergic rhinitis, inflammatory bowel disease, ulcerative colitis, Crohn's disease, systemic lupus erythematosis, Sjogren's Syndrome, Wegener's granulomatosis, psoriasis, scleroderma, chronic thyroiditis, Grave's disease, myasthenia gravis, multiple sclerosis, osteoarthritis, endometriosis, dermal scarring, tissue scarring, vascular restenosis, fibrotic disorders, hypereosinophilia, CNS inflammation, pancreatitis, nephritis, atopic dermatitis, hepatitis, immunodeficiency diseases, severe combined immunodeficiency, organ transplant rejection, graft versus host disease, renal disease, prostatic disease, diabetic nephropathy, nephrosclerosis, glomerulonephritis, interstitial nephritis, Lupus nephritis, prostate hyperplasia, chronic renal failure, tubular necrosis, diabetes-associated renal complication, associated renal hypertrophy, type 1 diabetes, type 2 diabetes, metabolic syndrome, obesity, hepatic steatosis, insulin resistance, hyperglycemia, lipolysis obesity, infection, *Helicobacter pylori* infection, *Influenza virus* infection, fever, sepsis, pulmonary diseases, chronic obstructive pulmonary disease, acute respiratory distress syndrome, asthma, allergy, bronchitis, emphysema, pulmonary fibrosis, genetic developmental diseases, Noonan's syndrome, Crouzon syndrome, acrocephalo-syndactyly type I, Pfeiffer's syndrome, Jackson-Weiss syndrome, Costello syndrome, faciocutaneoskeletal syndrome, leopard syndrome, cardio-faciocutaneous syndrome, neural crest syndrome abnormalities causing cardiovascular, skeletal, intestinal, skin, hair or endocrine diseases, disorders of bone structure or mineralization, osteoporosis, increased risk of fracture, hypercalcemia, bone metastases, Grave's disease, Hirschsprung's disease, lymphoedema, selective T-cell defect, X-linked agammaglobulinemia, diabetic retinopathy, alopecia, erectile dysfunction, and tuberous sclerosis

[0257] In some embodiments, the disease is selected from the group consisting of mast cell tumors, small cell lung cancer, testicular cancer, gastrointestinal stromal tumors (GISTs), metastatic GISTs, glioblastoma, astrocytoma, neuroblastoma, carcinomas of the female genital tract, sarcomas of neuroectodermal origin, colorectal carcinoma, carcinoma in situ, Schwann cell neoplasia associated with neurofibromatosis, acute myelocytic leukemia, acute lymphocytic leukemia, chronic myelogenous leukemia, mastocytosis, urticaria pigmentosa (UP), telangiectasia macularis eruptiva perstans (TMEP), systemic mastocytosis, indolent systemic, smoldering systemic, aggressive systemic, mast cell leukemia, mast cell sarcoma melanoma, and canine mast cell tumors, and inflammatory diseases, including asthma, rheumatoid arthritis, allergic rhinitis, multiple sclerosis, inflammatory bowel syndrome, transplant rejection, and hypereosinophilia. In certain instances, the disease is a c-kit and or c-kit mutant, such as D816F, D816H, D816N, D816Y, D816V, K642E, Y823D, Del 550-558, Del 557-561, N822K, V654A,

N822H, Del 550-558+V654A, Del 557-561+V654A, Ins503AY, V560G, 558NP, Del 557-558, Del W559-560, F522C, Del 579, R634W, K642E, T801I, C809G, D820Y, N822K, N822H, Y823D, Y823C or T670I mutant-mediated disease. In one embodiment, the disease is a D816 (such as D816F, D816H, D816N, D816Y or D816V) mutant mediated disease. In another embodiment, the disease is a D816V mutant mediated disease. In yet another embodiment, the disease is a V560G mutant mediated disease. In another embodiment, the disease is a D816V and V560G mutant mediated disease. In one embodiment, the disease is a cancer, preferably selected from the group consisting of melanoma, glioma, glioblastoma multiforme, pilocytic astrocytoma, colorectal cancer, thyroid cancer, lung cancer, ovarian cancer, prostate cancer, liver cancer, gallbladder cancer, gastrointestinal stromal tumors, biliary tract cancer, and cholangiocarcinoma. In one embodiment, the cancer is melanoma, colorectal cancer, thyroid cancer or lung cancer.

[0258] In some embodiments, the disclosure provides a method for treating a disease or condition selected from urticaria pigmentosa (UP), telangiectasia macularis eruptiva perstans (TMEP), systemic mastocytosis, indolent systemic, smoldering systemic, aggressive systemic, mast cell leukemia, mast cell sarcoma, GISTs and metastatic GISTs. The method involves administering to the subject in need thereof an effective amount of any one or more compound(s) as described herein, or pharmaceutically acceptable salts, hydrates, solvates, tautomers or isomers thereof, or a composition as described herein.

[0259] In some embodiments, the disclosure provides methods for treating any c-kit protein kinase mediated disease or condition, including any c-kit mutant kinase mediated disease or condition in an animal subject in need thereof, wherein the method involves administering to the subject an effective amount of any one or more compound(s) as described herein. 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.

[0260] In some embodiments, the disclosure provides methods for treating any c-kit D816F, D816H, D816N, D816Y, D816V, K642E, Y823D, Del 550-558, Del 557-561, N822K, V654A, N822H, Del 550-558+V654A, Del 557-561+V654A, Ins503AY, V560G, 558NP, Del 557-558, Del W559-560, F522C, Del 579, R634W, K642E, T801I, C809G, D820Y, N822K, N822H, Y823D, Y823C or T670I mutant protein kinase mediated disease or condition in an animal subject in need thereof, wherein the method involves administering to the subject an effective amount of any one or more compound(s) as described herein. 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. In some embodiments, the c-kit mutant protein kinase is c-kit D816 (such as D816F, D816H, D816N, D816Y or D816V) mutant kinase. In one embodiment, the c-kit mutant protein

kinase is c-kit D816V mutant. In another embodiment, the c-kit mutant protein kinase is c-kit V560G mutant. In another embodiment, the c-kit mutant protein kinase is c-kit D816V/V560G mutant.

[0261] In some embodiments, a compound of any of formulas (I), (II), or any of the subformulas as described herein, or a compound as described herein, or pharmaceutically acceptable salts, hydrates, solvates, tautomers or isomers thereof, or a composition comprising a compound as described herein is a c-kit and/or mutant c-kit kinase inhibitor and has an IC_{50} of less than 500 nM, less than 100 nM, less than 50 nM, less than 20 nM, less than 10 nM, less than 5 nM, or less than 1 nM as determined in a generally accepted c-kit kinase activity assay. In some embodiments, a compound as described herein will have an IC_{50} of less than 500 nM, less than 100 nM, less than 50 nM, less than 20 nM, less than 10 nM, less than 5 nM, or less than 1 nM with respect to c-kit, c-kit D816V mutant, c-kit V560G mutant or D816V/V560G mutant. In some embodiments, a compound as described herein will selectively inhibit one or more mutant c-kit kinases relative to one or more other mutant c-kit kinases.

[0262] In some embodiments, the disclosure provides a method for inhibiting a c-kit mutant protein kinase, such as D816V, V560G or D816V/V560G mutant protein kinase. The method includes contacting a compound of any of formulas (I), (II), or any of the subformulas as described herein, or a compound as described herein, or a composition comprising a compound as described herein, or pharmaceutically acceptable salts, hydrates, solvates, tautomers or isomers thereof with a cell or a c-kit mutant protein kinase either in vitro or in vivo.

[0263] In certain embodiments, the disclosure provides use of a compound of any of formulas (I), (II), or any of the subformulas as described herein, or a compound as described herein, or a composition comprising a compound as described herein, or pharmaceutically acceptable salts, hydrates, solvates, tautomers or isomers thereof in the manufacture of a medicament for the treatment of a disease or condition as described herein. In other embodiments, the disclosure provides a compound of any of formulas (I), (II), or any of the subformulas as described herein, or a compound as described herein, or a composition comprising a compound as described herein, or pharmaceutically acceptable salts, hydrates, solvates, tautomers or isomers thereof for use in treating a disease or condition as described herein.

Combination Therapy

[0264] 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.

[0265] In some embodiments, the disclosure provides methods for treating a c-kit and/or mutant c-kit protein kinase mediated disease or condition in an animal subject in need thereof, wherein the method involves administering to the subject an effective amount of any one or more compound(s) as described herein, or one or more compounds of any of formula (I), (II), or any of the subformulas as described herein, or pharmaceutically acceptable salts, solvates, tautomers or isomers thereof, or a composition comprising a compound as described herein in combination with one or more other therapeutic agent as described herein. In certain embodiments, the disclosure provides methods for treating a c-kit and/or mutant c-kit protein kinase mediated disease or condition in an animal subject in need thereof, wherein the method involves administering to the subject an effective amount of any one or more compound(s) as described herein, or one or more compounds of any of formula (I), (II), or any of the subformulas as described herein, or pharmaceutically acceptable salts, solvates, tautomers or isomers thereof, or a composition comprising a compound as described herein in combination with one or more other therapies for the disease or condition.

[0266] In some embodiments, the disclosure provides a composition comprising a compound of any of formulas (I), (II), (IIa), (IIb), (IIc), (IIa-1), (IIa-2), (IIa-3), (IIa-4), (IIa-1a), (IIa-1b), (IIa-1c), (IIa-1d), (IIa-1e), (IIa-1f), (IIa-1g), (IIa-1h), (IIa-1i), (IIa-1j), (IIa-1k), (IIa-1m), (IIa-2a), (IIa-2b), (IIa-3a), (IIa-3b), (IIa-3c), (IIa-3d), (IIa-3e), (IIa-3f), (IIa-3g), (IIa-3h), (IIa-3i), (IIa-3j), (IIa-3k), (IIa-3m), (IIb-1), (IIb-2), (IIb-3), (IIb-4), (IIb-1a), (IIb-1b), (IIb-1c), (IIb-1d), (IIb-1e), (IIb-1f), (IIb-1g), (IIb-1h), (IIb-1i), (IIb-1j), (IIb-1k), (IIb-1m), (IIb-2a), (IIb-2b), (IIb-3a), (IIb-3b), (IIb-3c), (IIb-3d), (IIb-3e), (IIb-3f), (IIb-3g), (IIb-3h), (IIb-3i), (IIb-3j), (IIb-3k), (IIb-3m), (IIb-4a), (IIb-4b), (IIc-1), (IIc-2), (IIc-1a), (IIc-1b), (IIc-1c), (IIc-1d), (IIc-1e), (IIc-1f), (IIc-1g), (IIc-1h), (IIc-1i), (IIc-1j), (IIc-1k), (IIc-1m), (IIc-2a), (IIc-2b), (IId), (IIe), (IIf), (IId-1), (IId-2), (IId-1a), (IId-1b), (IId-1c), (IId-1d), (IId-1e), (IId-1f), (IId-1g), (IId-1h), (IId-1i), (IId-2a), (IId-2b), (IId-2c), (IId-2d), (IId-2e), (IId-2f), (IId-2g), (IId-2h), (IId-2i), (IIe-1), (IIe-2), (IIe-1a), (IIe-1b), (IIe-1c), (IIe-1d), (IIe-1e), (IIe-1f), (IIe-1g), (IIe-1h), (IIe-1i), (IIe-2a), (IIe-2b), (IIe-2c), (IIe-2d), (IIe-2e), (IIe-2f), (IIe-2g), (IIe-2h), (IIe-2i), (IIf-1a), (IIf-1b), (IIf-1c), (IIf-1d), (IIf-1e), (IIf-1f), (IIf-1g), (IIf-1h), (IIf-1i), (IIg), (IIh), (IIj), (IIk), (IIg-1), (IIh-1), (IIj-1), (IIk-1), (IIg-1a), (IIg-1b), (IIg-1c), (IIg-1d), (IIg-1e), (IIg-1f), (IIg-1g), (IIh-1a), (IIh-1b), (IIh-1c), (IIh-1d), (IIh-1e), (IIh-1f), (IIh-1g), (IIj-1a), (IIj-1b), (IIj-1c), (IIj-1d), (IIj-1e), (IIj-1f), (IIj-1g), (IIk-1a), (IIk-1b), (IIk-1c), (IIk-1d), (IIk-1e), (IIk-1f), (IIk-1g), (IIg-1a-1), (IIg-1a-2), (IIg-1b-1), (IIg-1b-2), (IIg-1c-1), (IIg-1c-2), (IIg-1d-1), (IIg-1d-2), (IIg-1e-1), (IIg-1e-2), (IIg-1f-1), (IIg-1f-2), (IIg-1g), (IIg-1g-2), (IIh-1a-1), (IIh-1a-2), (IIh-1b-1), (IIh-1b-2), (IIh-1c-1), (IIh-1c-2), (IIh-1d-1), (IIh-1d-2), (IIh-1e-1), (IIh-1e-2), (IIh-1f-1), (IIh-1f-2), (IIh-1g), (IIh-1g-2), (IIj-1a-1), (IIj-1a-2), (IIj-1b-1), (IIj-1b-2), (IIj-1c-1), (IIj-1c-2), (IIj-1d-1), (IIj-1d-2), (IIj-1e-1), (IIj-

1e-2), (IIj-1f-1), (IIj-1f-2), (IIj-1g), (IIj-1g-2), (IIk-1a), (IIk-1b), (IIk-1c), (IIk-1d), (IIk-1e), (IIk-1f) or (IIk-1g), or a compound disclosed in the Examples, a compound set forth in Tables 1-6, or a compound of P-0001 to P-0731, or a compound as described herein, or pharmaceutically acceptable salts, hydrates, solvates, tautomers or isomers thereof and one or more other therapeutic agents. In some embodiments, the one or more other therapeutic agents are selected from an alkylating agent, including, but not limiting 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, ranimustine, satraplatin, semustine, streptozocin, temozolomide, thiotepa, treosulfan, triaziquone, triethylenemelamine, triplatin tetranitrate, trofosphamide, and uramustine; an antibiotic, including, but not limiting to, aclarubicin, amrubicin, bleomycin, dactinomycin, daunorubicin, doxorubicin, elsamitrucin, epirubicin, idarubicin, menogaril, mitomycin, neocarzinostatin, pentostatin, pirarubicin, plicamycin, valrubicin, and zorubicin; an antimetabolite, including, but not limiting to, aminopterin, azacitidine, azathioprine, capecitabine, cladribine, clofarabine, cytarabine, decitabine, floxuridine, fludarabine, 5-fluorouracil, gemcitabine, hydroxyurea, mercaptopurine, methotrexate, nelarabine, pemetrexed, raltitrexed, tegafur-uracil, thioguanine, trimethoprim, trimetrexate, and vidarabine; an immunotherapy, an antibody therapy, including, but not limiting to, alemtuzumab, bevacizumab, cetuximab, galiximab, gemtuzumab, panitumumab, pertuzumab, rituximab, brentuximab, tositumomab, trastuzumab, 90 Y ibritumomab tiuxetan, ipilimumab, tremelimumab and anti-CTLA-4 antibodies; a hormone or hormone antagonist, including, but not limiting to, anastrozole, androgens, buserelin, diethylstilbestrol, exemestane, flutamide, fulvestrant, goserelin, idoxifene, letrozole, leuprolide, magestrol, raloxifene, tamoxifen, and toremifene; a taxane, including, but not limiting to, DJ-927, docetaxel, TPI 287, larotaxel, ortataxel, paclitaxel, DHA-paclitaxel, and tesetaxel; a retinoid, including, but not limiting to, alitretinoin, bexarotene, fenretinide, isotretinoin, and tretinoin; an alkaloid, including, but not limiting to, demecolcine, homoharringtonine, vinblastine, vincristine, vindesine, vinflunine, and vinorelbine; an antiangiogenic agent, including, but not limiting to, AE-941 (GW786034, Neovastat), ABT-510, 2-methoxyestradiol, lenalidomide, and thalidomide; a topoisomerase inhibitor, including, but not limiting 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 liming 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), vemurafenib, dabrafenib, selumetinib, and vatalanib; a targeted signal transduction inhibitor including, but not limiting to bortezomib, geldanamycin, and rapamycin; a biological response modifier, including, but not limiting to, imiquimod,

interferon-α, and interleukin-2; and other chemotherapeutics, including, but not limiting 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. 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). In one embodiment, the method of treating a cancer involves administering to the subject an effective amount of a composition including any one or more compound(s) of Formulae (I), (II) or any of the subformulas as described herein or a compound as described herein in combination with a chemotherapeutic agent selected from capecitabine, 5-fluorouracil, carboplatin, dacarbazine, gefitinib, oxaliplatin, paclitaxel, SN-38, temozolomide, vinblastine, bevacizumab, cetuximab, interferon-α, interleukin-2, or erlotinib. In another embodiment, the chemotherapeutic agent is a Mek inhibitor. Exemplary Mek inhibitors include, but are not limited to, AS703026, AZD6244 (Selumetinib), AZD8330, BIX 02188, CI-1040 (PD184352), GSK1120212 (JTP-74057), PD0325901, PD318088, PD98059, RDEA119(BAY 869766), TAK-733 and U0126-EtOH. In another embodiment, the chemotherapeutic agent is a tyrosine kinase inhibitor. Exemplary tyrosine kinase inhibitors include, but are not limited to, AEE788, AG-1478 (Tyrphostin AG-1478), AG-490, Apatinib (YN968D1), AV-412, AV-951(Tivozanib), Axitinib, AZD8931, BIBF1120 (Vargatef), BIBW2992 (Afatinib), BMS794833, BMS-599626, Brivanib (BMS-540215), Brivanib alaninate(BMS-582664), Cediranib (AZD2171), Chrysophanic acid (Chrysophanol), Crenolanib (CP-868569), CUDC-101, CYC116, Dovitinib Dilactic acid (TKI258 Dilactic acid), E7080, Erlotinib Hydrochloride (Tarceva, CP-358774, OSI-774, NSC-718781), Foretinib (GSK1363089, XL880), Gefitinib (ZD-1839 or Iressa), Imatinib (Gleevec), Imatinib Mesylate, Ki8751, KRN 633, Lapatinib (Tykerb), Linifanib (ABT-869), Masitinib (Masivet, AB1010), MGCD-265, Motesanib (AMG-706), MP-470, Mubritinib(TAK 165), Neratinib (HKI-272), NVP-BHG712, OSI-420 (Desmethyl Erlotinib,CP-473420), OSI-930, Pazopanib HCl, PD-153035 HCl, PD173074, Pelitinib (EKB-569), PF299804, Ponatinib (AP24534), PP121, RAF265 (CHIR-265), Raf265 derivative, Regorafenib (BAY 73-4506), Sorafenib Tosylate (Nexavar), Sunitinib Malate (Sutent), Telatinib (BAY 57-9352), TSU-68 (SU6668), Vandetanib (Zactima), Vatalanib dihydrochloride (PTK787), WZ3146, WZ4002, WZ8040, XL-184 free base (Cabozantinib), XL647, EGFR siRNA, FLT4 siRNA, KDR siRNA, Antidiabetic agents such as metformin, PPAR agonists (rosiglitazone, pioglitazone, bezafibrate, ciprofibrate, clofibrate, gemfibrozil, fenofibrate, indeglitazar), and DPP4 inhibitors (sitagliptin, vildagliptin, saxagliptin, dutogliptin, gemigliptin, alogliptin). In another embodiment, the agent is an EGFR inhibitor. Exemplary EGFR inhibitors include, but are not limited to, AEE-788, AP-26113, BIBW-2992 (Tovok), CI-1033, GW-572016, Iressa, LY2874455, RO-5323441, Tarceva (Erlotinib, OSI-

774), CUDC-101 and WZ4002. In one embodiment, the method of treating a cancer involves administering to the subject an effective amount of a composition including any one or more compound(s) as described herein in combination with a chemotherapeutic agent selected from capecitabine, 5-fluorouracil, carboplatin, dacarbazine, gefitinib, oxaliplatin, paclitaxel, SN-38, temozolomide, vinblastine, bevacizumab, cetuximab, interferon-α, interleukin-2, or erlotinib. In some embodiments, a kit protein kinase modulator, particularly a compound of any of formula (I), (II), or any of the subformulas as described herein, or a compound described herein, or pharmaceutically acceptable salts, solvates, tautomers or isomers thereof, may be administered simultaneously, sequentially or separately in combination with one or more agents as described above.

[0267] In some embodiments, the disclosure provides methods for treating a disease or condition mediated by c-kit and/or mutant c-kit kinase, including any mutations thereof, by administering to a subject an effective amount of a composition as described herein, which includes any one or more compound(s) as described herein in combination with one or more other therapeutic agents as described herein. In other embodiments, , the disclosure provides methods for treating a disease or condition mediated by c-kit and/or mutant c-kit kinase, including any mutations thereof, by administering to a subject an effective amount of a composition as described herein, which includes any one or more compound(s) as described herein in combination with one or more other suitable therapies for treating the disease or condition.

[0268] In some embodiments, compositions are provided that include a therapeutically effective amount of any one or more compound(s) as described herein and at least one pharmaceutically acceptable carrier, excipient, and/or diluent, including combinations of any two or more compounds as described herein. The composition can further include a plurality of different pharmacologically active compounds, which can include a plurality of compounds as described herein. In certain embodiments, the composition can include any one or more compound(s) as described herein along with one or more compounds that are therapeutically effective for the same disease indication. In one aspect, 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. The compounds can be administered simultaneously or sequentially.

[0269] In one embodiment, the disclosure provides methods for treating a disease or condition mediated by c-kit mutant kinases, such as D816F, D816H, D816N, D816Y, D816V, K642E, Y823D, Del 550-558, Del 557-561, N822K, V654A, N822H, Del 550-558+V654A, Del 557-561+V654A, Ins503AY, V560G,

558NP, Del 557-558, Del W559-560, F522C, Del 579, R634W, K642E, T801I, C809G, D820Y, N822K, N822H, Y823D, Y823C or T670I mutant kinase, 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 as described herein for treating the disease. In one embodiment, the disclosure provides methods for treating a cancer mediated by c-kit mutant kinases, such as D816F, D816H, D816N, D816Y, D816V, K642E, Y823D, Del 550-558, Del 557-561, N822K, V654A, N822H, Del 550-558+V654A, Del 557-561+V654A, Ins503AY, V560G, 558NP, Del 557-558, Del W559-560, F522C, Del 579, R634W, K642E, T801I, C809G, D820Y, N822K, N822H, Y823D, Y823C or T670I mutant by administering to the subject an effective amount of a composition including any one or more compound(s) as described herein. In one embodiment, the disclosure provides methods for treating a cancer mediated by c-kit mutant kinases, such as D816F, D816H, D816N, D816Y, D816V, K642E, Y823D, Del 550-558, Del 557-561, N822K, V654A, N822H, Del 550-558+V654A, Del 557-561+V654A, Ins503AY, V560G, 558NP, Del 557-558, Del W559-560, F522C, Del 579, R634W, K642E, T801I, C809G, D820Y, N822K, N822H, Y823D, Y823C or T670I mutant 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 suitable anticancer therapies, such as one or more chemotherapeutic drugs or agents as described herein. In one instance, the c-kit mutant kinase is D816V mutant kinase. In another instance, the c-kit mutant kinase is V560G mutant kinase. In yet another instance, the c-kit mutant kinase has both D816V and V560G mutations.

[0270] In some embodiments, the disclosure provides a method of treating a cancer as described herein in a subject in need thereof by administering to the subject an effective amount of a compound or 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, γ-ray, or electron, proton, neutron, or α 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, motexafin lutetium), oncolytic viral or bacterial therapy, surgery, or bone marrow and stem cell transplantation. In certain embodiments, the disclosure provides a method of treating a cancer in a subject in need thereof by administering to the subject an effective amount of a compound as

described herein and applying a radiation treatment as described herein either separately or simultaneously. In one embodiment, the disclosure provides a method for treating a cancer in a subject in need thereof by administering an effective amount of a compound as described herein to the subject followed by a radiation treatment (e.g. x-ray, γ-ray, or electron, proton, neutron, or α particle beam). In another embodiment, the disclosure provides a method for treating a cancer in a subject in need thereof by applying a radiation treatment (e.g. x-ray, γ-ray, or electron, proton, neutron, or α particle beam) to the subject followed by administering an effective amount of a compound as described herein to the subject. In yet another embodiment, the disclosure provides a method for treating a cancer in a subject in need thereof by administering a compound as described herein and a radiation therapy (e.g. x-ray, γ-ray, or electron, proton, neutron, or α particle beam) to the subject simultaneously.

[0271] In another aspect, the disclosure provides kits or containers that include a compound of any of formula (I) to (In) or a compound as described herein or a composition thereof as described herein. 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 disclosure kit or container 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 c-kit 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.

VII. Examples

[0272] The following examples are offered to illustrate, but not to limit the claimed disclosure.

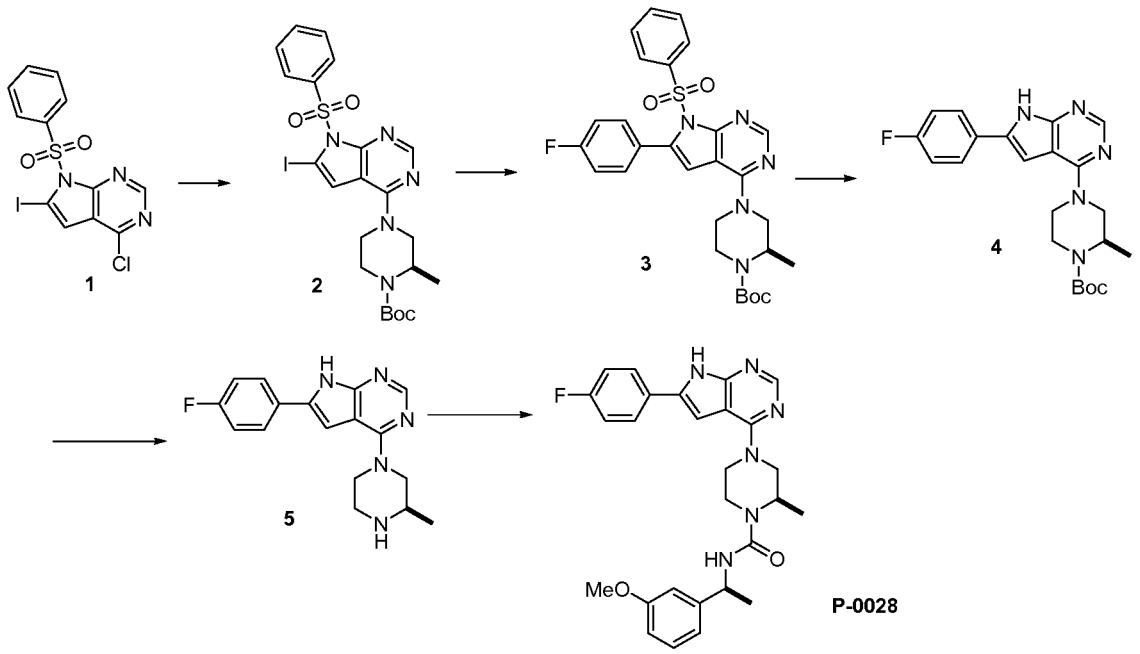
[0273] Compounds within the scope of this disclosure can be synthesized as described below, using a variety of reactions known to the skilled artisan. One skilled in the art will also recognize that alternative methods may be employed to synthesize the target compounds of this disclosure, and that the approaches described within the body of this document are not exhaustive, but do provide broadly applicable and practical routes to compounds of interest. In some examples, the mass spectrometry result indicated for a compound may have more than one value due to the isotope distribution of an atom in the molecule, such as a compound having a bromo or chloro substituent.

[0274] Certain molecules claimed in this patent can exist in different enantiomeric and diastereomeric forms or one or more hydrogen atoms of the molecules can be replaced by one or more deuterium atoms including perdeuterated analogs, all such variants of these compounds are claimed.

[0275] Those skilled in the art will also recognize that during standard work up procedures in organic chemistry, acids and bases are frequently used. Salts of the parent compounds are sometimes produced, if they possess the necessary intrinsic acidity or basicity, during the experimental procedures described within this patent.

Example 1: Preparation of (R)-4-[6-(4-Fluoro-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-2-methyl-piperazine-1-carboxylic acid [(S)-1-(3-methoxy-phenyl)-ethyl]-amide (P-0028)

Scheme 1.



[0276] **Step 1 - Synthesis of *tert*-butyl (2R)-4-[7-(benzenesulfonyl)-6-iodo-pyrrolo[2,3-d]pyrimidin-4-yl]-2-methyl-piperazine-1-carboxylate (2)**: To a microwave reaction vessel, 7-(benzenesulfonyl)-4-chloro-6-iodo-pyrrolo[2,3-d]pyrimidine (**1**), tert-butyl piperazine-1-carboxylate (1g, 2 mmol), acetonitrile (10.58 ml), and NEt_3 (0.673 ml, 2.02 equiv) were combined and heated at 90 °C for 60 minutes. The reaction was concentrated and attempted sonication with hexane to induce precipitate formation. The material was dissolved in dichloromethane (DCM) and concentrated. The product was isolated as a gummy solid, and taken forward without further purification.

[0277] **Step 2 – Synthesis of *tert*-butyl (2R)-4-[7-(benzenesulfonyl)-6-(4-fluorophenyl)pyrrolo[2,3-d]pyrimidin-4-yl]-2-methyl-piperazine-1-carboxylate (3):** To a microwave reaction vessel, *tert*-butyl (2R)-4-[7-(benzenesulfonyl)-6-iodo-pyrrolo[2,3-d]pyrimidin-4-yl]-2-methyl-piperazine-1-carboxylate (**2**) (1.6 g, 2 mmol), (4-fluorophenyl)boronic acid (0.307g, 2 mmol) , [1,1'-

bis(diphenylphosphino)ferrocene)dichloropalladium (II) (0.134 g, 0.18 mmol), acetonitrile (9.17 ml), and K_2CO_3 (aq, 1M) (6.58 ml) were combined, and heated at 100°C for 40 minutes. The reaction was diluted with water and extracted with EtOAc three times. The combined organic layers were washed with brine two times, dried over sodium sulfate and evaporated. The crude was absorbed onto silica and purified via flash chromatography, eluting with a gradient of 20-80% EtOAc in hexanes to afford the product as a light yellow oil. The oil was then taken on to the next step without further characterization.

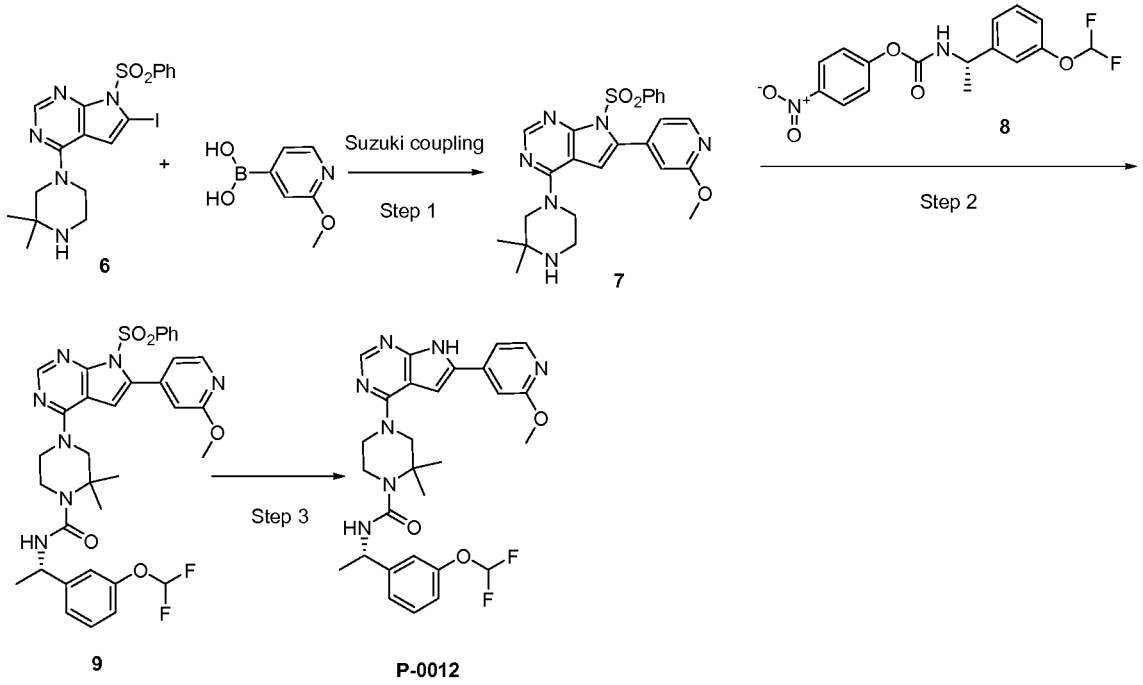
[0278] Step 3 – Synthesis of *tert*-butyl (2R)-4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-2-methyl-piperazine-1-carboxylate (4): To a reaction vial, *tert*-butyl (2R)-4-[7-(benzenesulfonyl)-6-(4-fluorophenyl)pyrrolo[2,3-d]pyrimidin-4-yl]-2-methyl-piperazine-1-carboxylate (**3**) (1.2 g, 2 mmol), MeOH (8.7 ml), and KOH (1M, aq) (5 ml) were combined and heated at 50 °C for 1 hour. The reaction was monitored by LC-MS to show that the 1-position was deprotected. The reaction was diluted with water, and extracted with EtOAc three times. The combined organic layers were washed with water, brine twice, and dried over sodium sulfate. After evaporation, LC-MS showed that the gummy solid was about 97% pure of the desired product. It was taken forward without further purification.

[0279] Step 4 – Synthesis of 6-(4-fluorophenyl)-4-[(3R)-3-methylpiperazin-1-yl]-7H-pyrrolo[2,3-d]pyrimidine (**5**): To a reaction vial, *tert*-butyl (2R)-4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-2-methyl-piperazine-1-carboxylate (**4**) (0.836g, 2mmol), was dissolved in DCM (12.37 ml) and TFA (5.95 ml), and stirred at 0 °C for 1 hour. The reaction was concentrated under reduced pressure. Diethyl ether was added to precipitate out the product. LC-MS showed ~ 97% pure product; MS (ESI) $(M+H^+)^+ = 312.15$; $(M-H)^- = 310.10$; product was isolated as an off-white powder. The data from the ^1H NMR spectrum was consistent with the structure of the compound.

[0280] Step 5 – Synthesis of (R)-4-[6-(4-Fluoro-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-2-methyl-piperazine-1-carboxylic acid [(S)-1-(3-methoxy-phenyl)-ethyl]-amide (P-0028): Into a scintillation vial were placed 6-(4-fluorophenyl)-4-[(3R)-3-methylpiperazin-1-yl]-7H-pyrrolo[2,3-d]pyrimidine (**5**) (80 mg, 0.26 mmol), 1-[(1S)-1-isocyanatoethyl]-3-methoxy-benzene (70 mg, 0.4 mmol) and DMF (3 mL). N,N-diisopropylethylamine (0.1 ml, 0.58 mmol) was added and the reaction was stirred at room temperature for 5 hours. The mixture was placed on silica and purified with silica gel chromatography eluting with a gradient of ethyl acetate: hexanes (40-100%). ^{1}HNMR and MS were consistent with the structure of the desired product. MS (ESI) $[M+H^+]^+ = 489.55$ $[M-H]^- = 487.1$.

Example 2: Preparation of N-[(1S)-1-[3-(difluoromethoxy)phenyl]ethyl]-4-[6-(2-methoxy-4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-2,2-dimethyl-piperazine-1-carboxamide (P-0012).

Scheme 2.



[0281] Step 1 – Synthesis of 7-(benzenesulfonyl)-4-(3,3-dimethylpiperazin-1-yl)-6-(2-methoxy-4-pyridyl)pyrrolo[2,3-d]pyrimidine (7): A mixture of 7-(benzenesulfonyl)-4-(3,3-dimethylpiperazin-1-yl)-6-iodo-pyrrolo[2,3-d]pyrimidine (**6**) (746.03 mg, 1.5 mmol, 1 eq), (2-methoxy-4-pyridyl)boronic acid (344.12 mg, 2.25 mmol, 1.2 eq) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (109.8 mg, 0.15 mmol, 0.1 eq) in acetonitrile (15 ml) was purged with N_2(g) then added 2.4 mL of 2.5M aqueous K_2CO_3 (4 eq). The reaction mixture was heated at 90 °C for 4 hrs. The resulting mixture was cooled & filtered through a pad of celite. The filtrate was dried over Na_2SO_4, collected & concentrated down. The obtained residue was purified by flash chromatography eluting with 10% methanol in CH_2Cl_2 to provide of 7-(benzenesulfonyl)-4-(3,3-dimethylpiperazin-1-yl)-6-(2-methoxy-4-pyridyl)pyrrolo[2,3-d]pyrimidine **(7)** 590 mg (82.2%) as a brown semi-solid. LC-MS ESI $[M+H^+]^+ = 479.25$. The data from the ^1H NMR spectrum were consistent with the structure of the compound.

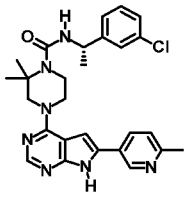
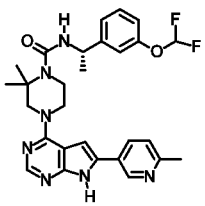
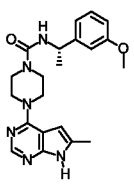
[0282] Step 2 – Synthesis of 4-[7-(benzenesulfonyl)-6-(2-methoxy-4-pyridyl)pyrrolo[2,3-d]pyrimidin-4-yl]-N-[(1S)-1-[3-(difluoromethoxy)phenyl]ethyl]-2,2-dimethyl-piperazine-1-carboxamide (9): To a mixture of compound **(7)** (71.8mg, 0.15 mmol, 1eq) and triethylamine (0.02 ml, 0.15 mmol, 1eq) in THF (1.5 ml) was added (4-nitrophenyl) N-[(1S)-1-[3-(difluoro methoxy)phenyl]ethyl] carbamate (**8**) (79.3 mg, 0.23 mmol, 1.5eq). The reaction mixture was stirred at 50 °C for 1 hr then concentrated down under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with 70% ethyl acetate/hexane to provide 4-[7-(benzenesulfonyl)-6-

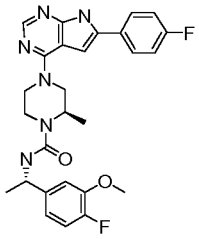
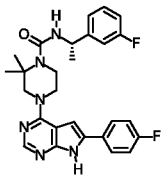
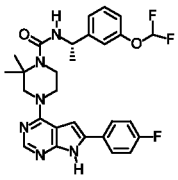
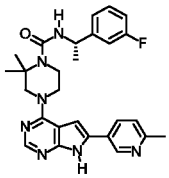
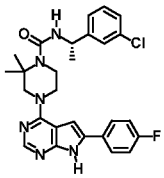
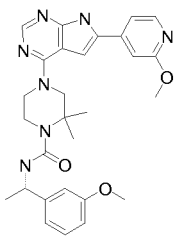
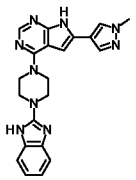
(2-methoxy-4-pyridyl)pyrrolo[2,3-d]pyrimidin-4-yl]-N-[(1S)-1-[3-(difluoromethoxy)phenyl]ethyl]-2,2-dimethyl-piperazine-1-carboxamide **(9)** (34 mg, 29.5 % yield) as a brittle foam. LC-MS (ESI) $[M+H^+]^+$ = 692.4. The data from the ^1H NMR spectrum were consistent with the structure of the compound.

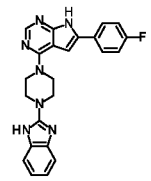
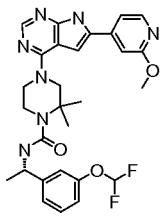
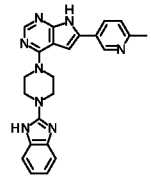
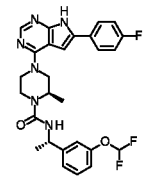
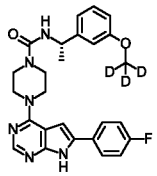
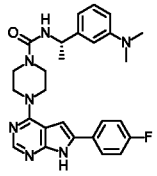
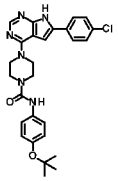
[0283] Step 3 – Synthesis of N-[(1S)-1-[3-(difluoromethoxy)phenyl]ethyl]-4-[6-(2-methoxy-4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-2,2-dimethyl-piperazine-1-carboxamide (P-0012): To a solution of **(9)** (34 mg, 0.05 mmol, 1 eq) in 0.5 mL of (1:1) THF/MeOH was added 0.1 mL of 1M aqueous KOH (2 eq). The reaction mixture was heated at 50 °C for 15 minutes. The reaction mixture was concentrated then re-diluted with dichloromethane. The dichloromethane solution was dried over Na_2SO_4 and concentrated. The sample was purified by flash chromatography on silica gel eluting with 5% MeOH in dichloromethane. The purified sample was recrystallized with ethyl acetate and hexane to provide N-[(1S)-1-[3-(difluoromethoxy)phenyl]ethyl]-4-[6-(2-methoxy-4-pyridyl)-7H-pyrrolo [2,3d] pyrimidin-4-yl]-2,2-dimethyl-piperazine-1-carboxamide **(P-0012)** (10 mg, 35.4% yield) as a white solid. LC-MS (ESI) $[M+H^+]^+$ = 552.40. The data from the ^1H NMR spectrum were consistent with the structure of the compound.

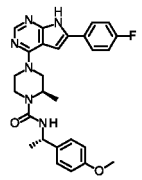
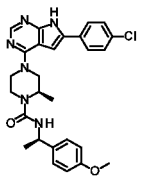
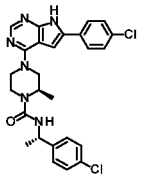
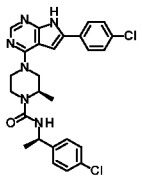
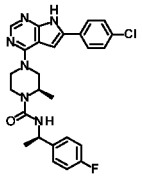
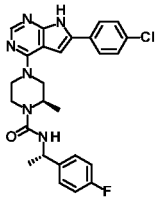
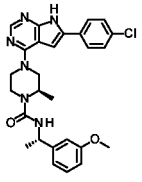
[0284] Compounds listed in Table 1 below, e.g., compounds P-0001 to P-0245 and P-0641 to P-0650 were prepared according to the protocols set forth in Examples 1 and 2 and Schemes 1 and 2. The ^1H NMR and mass spectroscopy data were consistent with the structures of the compounds.

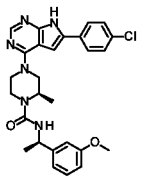
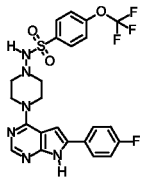
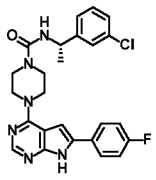
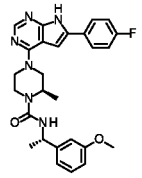
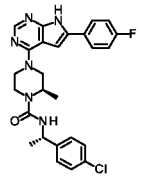
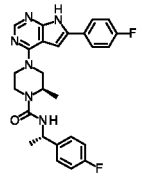
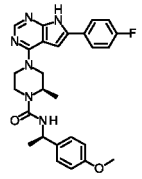
TABLE 1

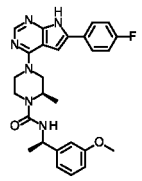
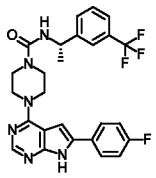
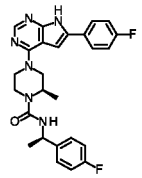
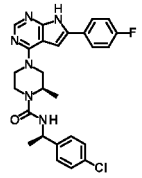
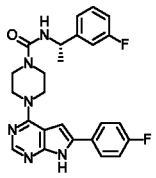
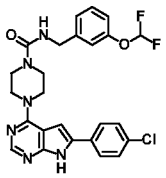
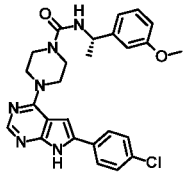
No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0001		N-[(1S)-1-(3-chlorophenyl)ethyl]-2,2-dimethyl-4-[6-(6-methyl-3-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	504.3
P-0002		N-[(1S)-1-[3-(difluoromethoxy)phenyl]ethyl]-2,2-dimethyl-4-[6-(6-methyl-3-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	536.5
P-0003		N-[(1S)-1-(3-methoxyphenyl)ethyl]-4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperazine-1-carboxamide	395.3

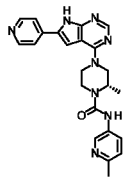
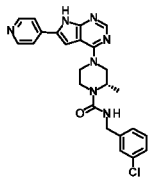
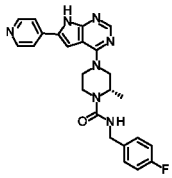
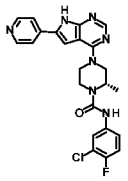
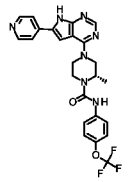
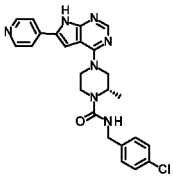
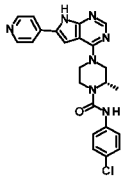
No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0004		(2R)-N-[(1S)-1-(4-fluoro-3-methoxy-phenyl)ethyl]-4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-2-methyl-piperazine-1-carboxamide	507.5
P-0005		N-[(1S)-1-(3-fluorophenyl)ethyl]-4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-2,2-dimethyl-piperazine-1-carboxamide	491.5
P-0006		N-[(1S)-1-[3-(difluoromethoxy)phenyl]ethyl]-4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-2,2-dimethyl-piperazine-1-carboxamide	539.5
P-0007		N-[(1S)-1-(3-fluorophenyl)ethyl]-2,2-dimethyl-4-[6-(6-methyl-3-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	488.5
P-0008		N-[(1S)-1-(3-chlorophenyl)ethyl]-4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-2,2-dimethyl-piperazine-1-carboxamide	507.0
P-0009		N-[(1S)-1-(3-methoxyphenyl)ethyl]-4-[6-(2-methoxy-4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-2,2-dimethyl-piperazine-1-carboxamide	516.5
P-0010		4-[4-(1H-benzimidazol-2-yl)piperazin-1-yl]-6-(1-methylpyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidine	399.9

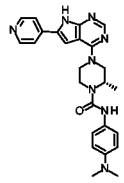
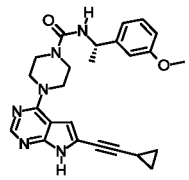
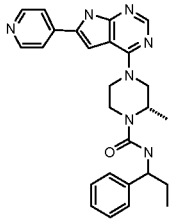
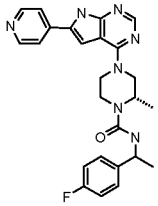
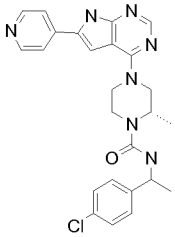
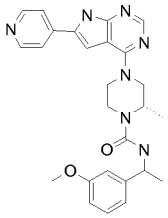
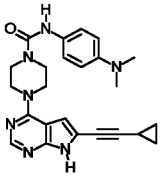
No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0011		4-[4-(1H-benzimidazol-2-yl)piperazin-1-yl]-6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidine	413.9
P-0012		N-[(1S)-1-[3-(difluoromethoxy)phenyl]ethyl]-4-[6-(2-methoxy-4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-2,2-dimethyl-piperazine-1-carboxamide	552.4
P-0013		4-[4-(1H-benzimidazol-2-yl)piperazin-1-yl]-6-(6-methyl-3-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine	410.9
P-0014		(2R)-N-[(1S)-1-[3-(difluoromethoxy)phenyl]ethyl]-4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-2-methyl-piperazine-1-carboxamide	525.5
P-0015		4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[(1S)-1-[3-(trideuteriomethoxy)phenyl]ethyl]piperazine-1-carboxamide	478.4
P-0016		N-[(1S)-1-[3-(dimethylamino)phenyl]ethyl]-4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	488.0
P-0017		N-(4-tert-butoxyphenyl)-4-[6-(4-chlorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	505.2

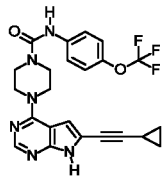
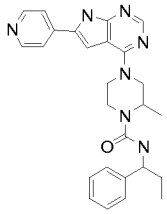
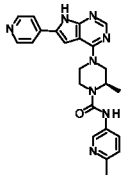
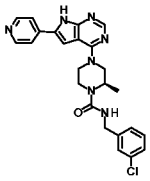
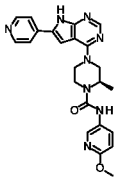
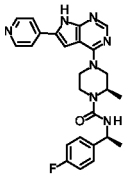
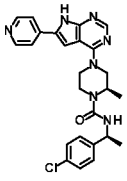
No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0018		(2R)-4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[(1S)-1-(4-methoxyphenyl)ethyl]-2-methyl-piperazine-1-carboxamide	
P-0019		(2R)-4-[6-(4-chlorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[(1R)-1-(4-methoxyphenyl)ethyl]-2-methyl-piperazine-1-carboxamide	505.0
P-0020		(2R)-N-[(1S)-1-(4-chlorophenyl)ethyl]-4-[6-(4-chlorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-2-methyl-piperazine-1-carboxamide	510.6
P-0021		(2R)-N-[(1R)-1-(4-chlorophenyl)ethyl]-4-[6-(4-chlorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-2-methyl-piperazine-1-carboxamide	508.9
P-0022		(2R)-4-[6-(4-chlorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[(1R)-1-(4-fluorophenyl)ethyl]-2-methyl-piperazine-1-carboxamide	493.0
P-0023		(2R)-4-[6-(4-chlorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[(1S)-1-(4-fluorophenyl)ethyl]-2-methyl-piperazine-1-carboxamide	493.0
P-0024		(2R)-4-[6-(4-chlorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[(1S)-1-(3-methoxyphenyl)ethyl]-2-methyl-piperazine-1-carboxamide	505.0

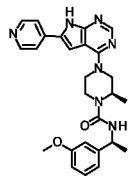
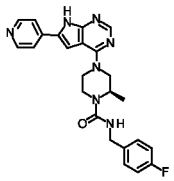
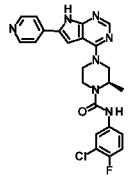
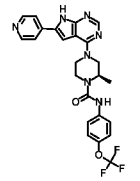
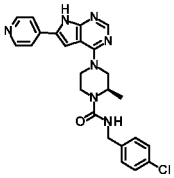
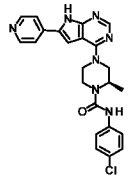
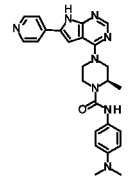
No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0025		(2R)-4-[6-(4-chlorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[(1R)-1-(3-methoxyphenyl)ethyl]-2-methyl-piperazine-1-carboxamide	505.0
P-0026		N-[4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazin-1-yl]-4-(trifluoromethoxy)benzenesulfonamide	536.9
P-0027		N-[(1S)-1-(3-chlorophenyl)ethyl]-4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	479.3
P-0028		(2R)-4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[(1S)-1-(3-methoxyphenyl)ethyl]-2-methyl-piperazine-1-carboxamide	489.4
P-0029		(2R)-N-[(1S)-1-(4-chlorophenyl)ethyl]-4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-2-methyl-piperazine-1-carboxamide	493.4
P-0030		(2R)-N-[(1S)-1-(4-fluorophenyl)ethyl]-4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-2-methyl-piperazine-1-carboxamide	477.6
P-0031		(2R)-4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[(1R)-1-(4-methoxyphenyl)ethyl]-2-methyl-piperazine-1-carboxamide	489.6

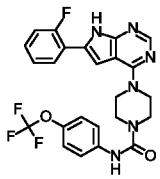
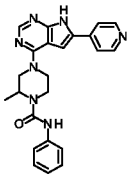
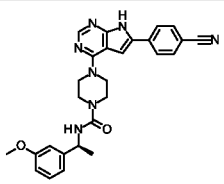
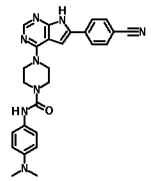
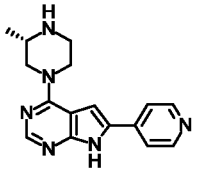
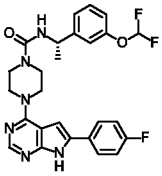
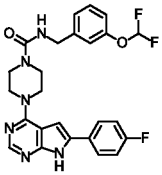
No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0032		(2R)-4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[(1R)-1-(3-methoxyphenyl)ethyl]-2-methyl-piperazine-1-carboxamide	489.0
P-0033		4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[(1S)-1-[3-(trifluoromethyl)phenyl]ethyl]piperazine-1-carboxamide	513.4
P-0034		(2R)-N-[(1R)-1-(4-fluorophenyl)ethyl]-4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-2-methyl-piperazine-1-carboxamide	477.5
P-0035		(2R)-N-[(1R)-1-(4-chlorophenyl)ethyl]-4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-2-methyl-piperazine-1-carboxamide	493.0
P-0036		N-[(1S)-1-(3-fluorophenyl)ethyl]-4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	463.5
P-0037		4-[6-(4-chlorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[[3-(difluoromethoxy)phenyl]methyl]piperazine-1-carboxamide	513.0
P-0038		4-[6-(4-chlorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[(1S)-1-(3-methoxyphenyl)ethyl]piperazine-1-carboxamide	491.0

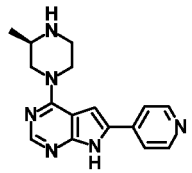
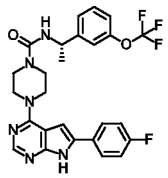
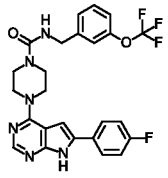
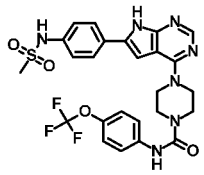
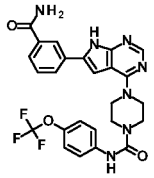
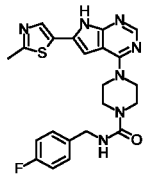
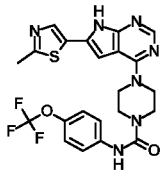
No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0039		(2S)-2-methyl-N-(6-methyl-3-pyridyl)-4-[6-(4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	428.2
P-0040		(2S)-N-[(3-chlorophenyl)methyl]-2-methyl-4-[6-(4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	462.4
P-0041		(2S)-N-[(4-fluorophenyl)methyl]-2-methyl-4-[6-(4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	446.2
P-0042		(2S)-N-(3-chloro-4-fluoro-phenyl)-2-methyl-4-[6-(4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	466.3
P-0043		(2S)-2-methyl-4-[6-(4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[4-(trifluoromethoxy)phenyl]piperazine-1-carboxamide	498.4
P-0044		(2S)-N-[(4-chlorophenyl)methyl]-2-methyl-4-[6-(4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	462.4
P-0045		(2S)-N-(4-chlorophenyl)-2-methyl-4-[6-(4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	448.3

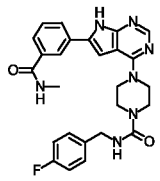
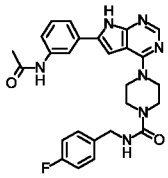
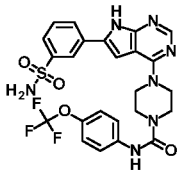
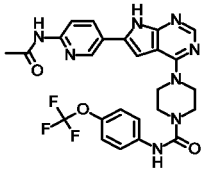
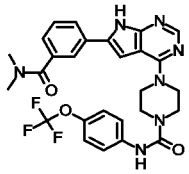
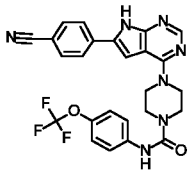
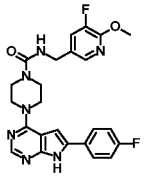
No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0046		(2S)-N-(4-dimethylaminophenyl)-2-methyl-4-[6-(4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	457.3
P-0047		4-[6-(2-cyclopropylethynyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[(1S)-1-(3-methoxyphenyl)ethyl]piperazine-1-carboxamide	445.1
P-0048		(2S)-2-methyl-N-[(1S)-1-phenylpropyl]-4-[6-(4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	456.4
P-0049		(2S)-N-[(1S)-1-(4-fluorophenyl)ethyl]-2-methyl-4-[6-(4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	460.3
P-0050		(2S)-N-[(1S)-1-(4-chlorophenyl)ethyl]-2-methyl-4-[6-(4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	476.2
P-0051		(2S)-N-[(1S)-1-(3-methoxyphenyl)ethyl]-2-methyl-4-[6-(4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	472.3
P-0052		4-[6-(2-cyclopropylethynyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-(4-dimethylaminophenyl)piperazine-1-carboxamide	430.1

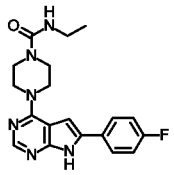
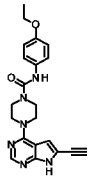
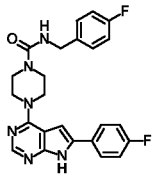
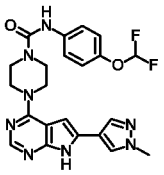
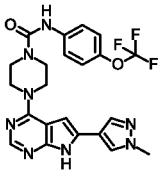
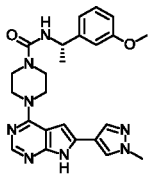
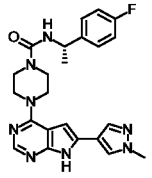
No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0053		4-[6-(2-cyclopropylethynyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[4-(trifluoromethoxy)phenyl]piperazine-1-carboxamide	471.4
P-0054		(2R)-2-methyl-N-[(1S)-1-phenylpropyl]-4-[6-(4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	456.1
P-0055		(2R)-2-methyl-N-(6-methyl-3-pyridyl)-4-[6-(4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	429.4
P-0056		(2R)-N-[(3-chlorophenyl)methyl]-2-methyl-4-[6-(4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	462.4
P-0057		(2R)-N-(6-methoxy-3-pyridyl)-2-methyl-4-[6-(4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	445.3
P-0058		(2R)-N-[(1S)-1-(4-fluorophenyl)ethyl]-2-methyl-4-[6-(4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	460.6
P-0059		(2R)-N-[(1S)-1-(4-chlorophenyl)ethyl]-2-methyl-4-[6-(4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	476.2

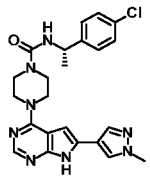
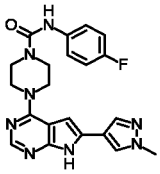
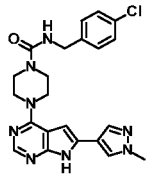
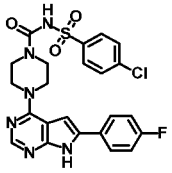
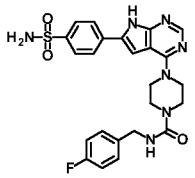
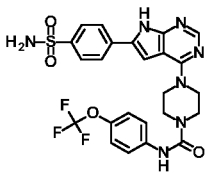
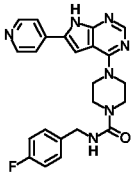
No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0060		(2R)-N-[(1S)-1-(3-methoxyphenyl)ethyl]-2-methyl-4-[6-(4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	472.3
P-0061		(2R)-N-[(4-fluorophenyl)methyl]-2-methyl-4-[6-(4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	446.2
P-0062		(2R)-N-(3-chloro-4-fluoro-phenyl)-2-methyl-4-[6-(4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	466.3
P-0063		(2R)-2-methyl-4-[6-(4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[4-(trifluoromethoxy)phenyl]piperazine-1-carboxamide	498.4
P-0064		(2R)-N-[(4-chlorophenyl)methyl]-2-methyl-4-[6-(4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	462.4
P-0065		(2R)-N-(4-chlorophenyl)-2-methyl-4-[6-(4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	448.3
P-0066		(2R)-N-(4-dimethylaminophenyl)-2-methyl-4-[6-(4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	457.3

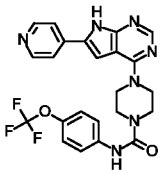
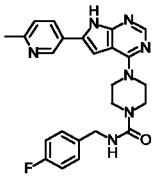
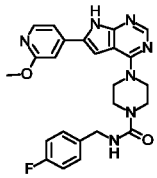
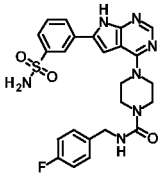
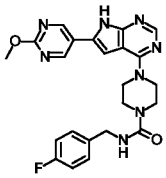
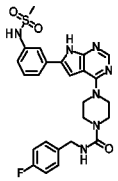
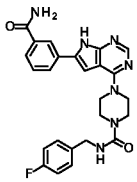
No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0067		4-[6-(2-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[4-(trifluoromethoxy)phenyl]piperazine-1-carboxamide	501.1
P-0068		2-methyl-N-phenyl-4-[6-(4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	414.4
P-0069		4-[6-(4-cyanophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[(1S)-1-(3-methoxyphenyl)ethyl]piperazine-1-carboxamide	482.1
P-0070		4-[6-(4-cyanophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-(4-dimethylaminophenyl)piperazine-1-carboxamide	467.0
P-0071		4-[(3S)-3-methylpiperazin-1-yl]-6-(4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine	295.2
P-0072		N-[(1S)-1-[3-(difluoromethoxy)phenyl]ethyl]-4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	511.4
P-0073		N-[[3-(difluoromethoxy)phenyl]methyl]-4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	

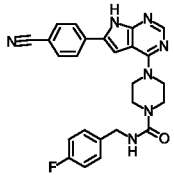
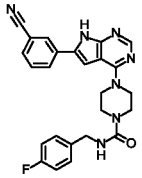
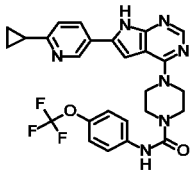
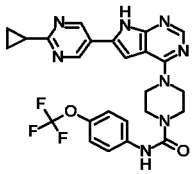
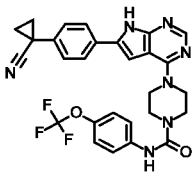
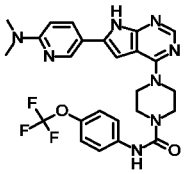
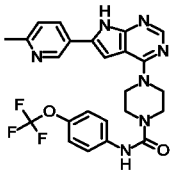
No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0074		4-[(3R)-3-methylpiperazin-1-yl]-6-(4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine	295.2
P-0075		4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[(1S)-1-[3-(trifluoromethoxy)phenyl]ethyl]piperazine-1-carboxamide	529.4
P-0076		4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[[3-(trifluoromethoxy)phenyl]methyl]piperazine-1-carboxamide	515.3
P-0077		4-[6-[4-(methanesulfonamido)phenyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[4-(trifluoromethoxy)phenyl]piperazine-1-carboxamide	576.4
P-0078		4-[6-(3-carbamoylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[4-(trifluoromethoxy)phenyl]piperazine-1-carboxamide	526.3
P-0079		N-[(4-fluorophenyl)methyl]-4-[6-(2-methylthiazol-5-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	452.2
P-0080		4-[6-(2-methylthiazol-5-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[4-(trifluoromethoxy)phenyl]piperazine-1-carboxamide	504.5

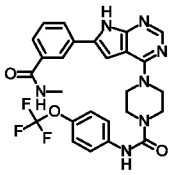
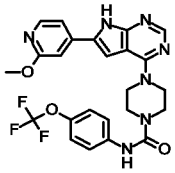
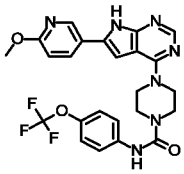
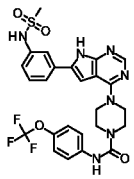
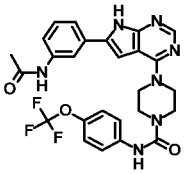
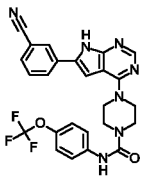
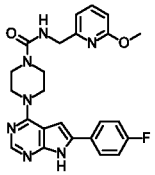
No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0081		N-[(4-fluorophenyl)methyl]-4-[6-[3-(methylcarbamoyl)phenyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	488.2
P-0082		4-[6-(3-acetamidophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[(4-fluorophenyl)methyl]piperazine-1-carboxamide	488.2
P-0083		4-[6-(3-sulfamoylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[4-(trifluoromethoxy)phenyl]piperazine-1-carboxamide	562.3
P-0084		4-[6-(6-acetamido-3-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[4-(trifluoromethoxy)phenyl]piperazine-1-carboxamide	541.3
P-0085		4-[6-[3-(dimethylcarbamoyl)phenyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[4-(trifluoromethoxy)phenyl]piperazine-1-carboxamide	554.2
P-0086		4-[6-(4-cyanophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[4-(trifluoromethoxy)phenyl]piperazine-1-carboxamide	508.3
P-0087		N-[(5-fluoro-6-methoxy-3-pyridyl)methyl]-4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	480.3

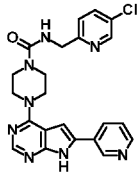
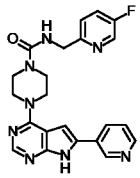
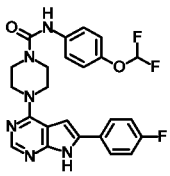
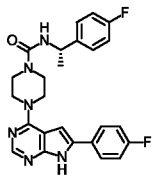
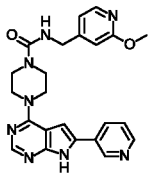
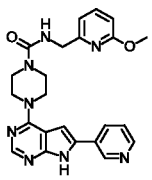
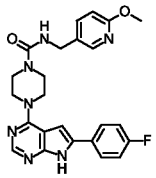
No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0088		N-ethyl-4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	369.0
P-0089		N-(4-ethoxyphenyl)-4-(6-ethynyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperazine-1-carboxamide	390.9
P-0090		N-[(4-fluorophenyl)methyl]-4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	449.0
P-0091		N-[4-(difluoromethoxy)phenyl]-4-[6-(1-methylpyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	469.3
P-0092		4-[6-(1-methylpyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[4-(trifluoromethoxy)phenyl]piperazine-1-carboxamide	487.3
P-0093		N-[(1S)-1-(3-methoxyphenyl)ethyl]-4-[6-(1-methylpyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	461.3
P-0094		N-[(1S)-1-(4-fluorophenyl)ethyl]-4-[6-(1-methylpyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	449.3

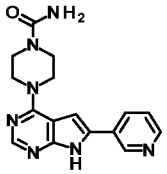
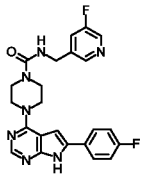
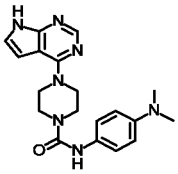
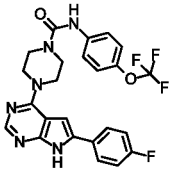
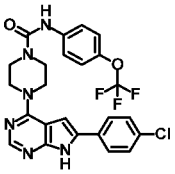
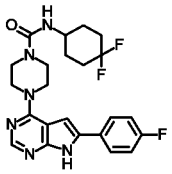
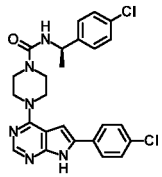
No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0095		N-[(1S)-1-(4-chlorophenyl)ethyl]-4-[6-(1-methylpyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	465.3
P-0096		N-(4-fluorophenyl)-4-[6-(1-methylpyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	421.2
P-0097		N-[(4-chlorophenyl)methyl]-4-[6-(1-methylpyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	451.2
P-0098		N-(4-chlorophenyl)sulfonyl-4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	514.9
P-0099		N-[(4-fluorophenyl)methyl]-4-[6-(4-sulfamoylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	510.4
P-0100		4-[6-(4-sulfamoylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[4-(trifluoromethoxy)phenyl]piperazine-1-carboxamide	562.3
P-0101		N-[(4-fluorophenyl)methyl]-4-[6-(4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	432.4

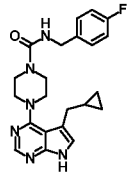
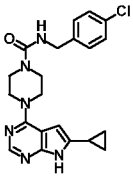
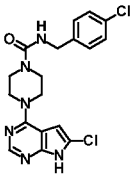
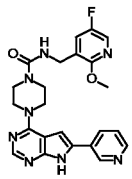
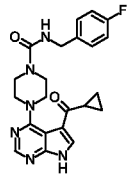
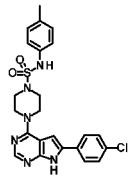
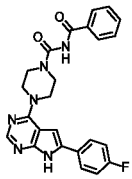
No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0102		4-[6-(4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[4-(trifluoromethoxy)phenyl]piperazine-1-carboxamide	484.3
P-0103		N-[(4-fluorophenyl)methyl]-4-[6-(6-methyl-3-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	446.2
P-0104		N-[(4-fluorophenyl)methyl]-4-[6-(2-methoxy-4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	462.4
P-0105		N-[(4-fluorophenyl)methyl]-4-[6-(3-sulfamoylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	510.4
P-0106		N-[(4-fluorophenyl)methyl]-4-[6-(2-methoxypyrimidin-5-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	463.3
P-0107		N-[(4-fluorophenyl)methyl]-4-[6-[3-(methanesulfonamido)phenyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	524.5
P-0108		4-[6-(3-carbamoylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[(4-fluorophenyl)methyl]piperazine-1-carboxamide	474.4

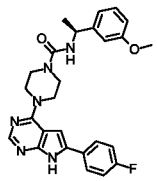
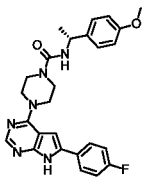
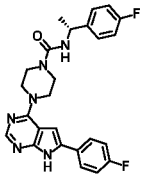
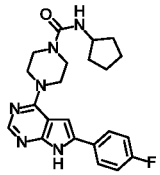
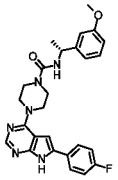
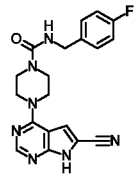
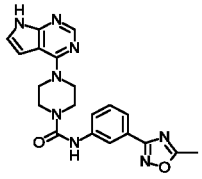
No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0109		4-[6-(4-cyanophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[(4-fluorophenyl)methyl]piperazine-1-carboxamide	456.4
P-0110		4-[6-(3-cyanophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[(4-fluorophenyl)methyl]piperazine-1-carboxamide	456.1
P-0111		4-[6-(6-cyclopropyl-3-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[4-(trifluoromethoxy)phenyl]piperazine-1-carboxamide	524.5
P-0112		4-[6-(2-cyclopropylpyrimidin-5-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[4-(trifluoromethoxy)phenyl]piperazine-1-carboxamide	525.4
P-0113		4-[6-[4-(1-cyanocyclopropyl)phenyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[4-(trifluoromethoxy)phenyl]piperazine-1-carboxamide	548.2
P-0114		4-[6-[6-(dimethylamino)-3-pyridyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[4-(trifluoromethoxy)phenyl]piperazine-1-carboxamide	527.2
P-0115		4-[6-(6-methyl-3-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[4-(trifluoromethoxy)phenyl]piperazine-1-carboxamide	498.4

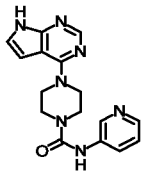
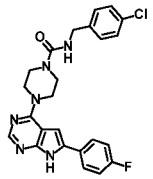
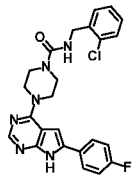
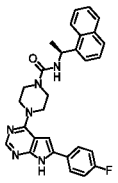
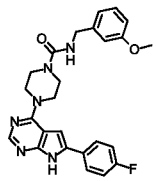
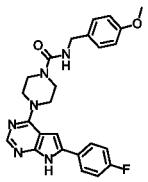
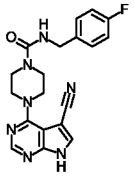
No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0116		4-[6-[3-(methylcarbamoyl)phenyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[4-(trifluoromethoxy)phenyl]piperazine-1-carboxamide	540.4
P-0117		4-[6-(2-methoxy-4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[4-(trifluoromethoxy)phenyl]piperazine-1-carboxamide	514.3
P-0118		4-[6-(6-methoxy-3-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[4-(trifluoromethoxy)phenyl]piperazine-1-carboxamide	514.3
P-0119		4-[6-[3-(methanesulfonamido)phenyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[4-(trifluoromethoxy)phenyl]piperazine-1-carboxamide	576.4
P-0120		4-[6-(3-acetamidophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[4-(trifluoromethoxy)phenyl]piperazine-1-carboxamide	540.4
P-0121		4-[6-(3-cyanophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[4-(trifluoromethoxy)phenyl]piperazine-1-carboxamide	508.3
P-0122		4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[(6-methoxy-2-pyridyl)methyl]piperazine-1-carboxamide	461.9

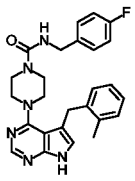
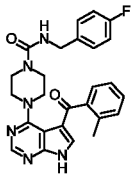
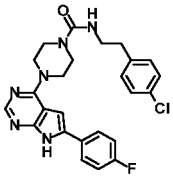
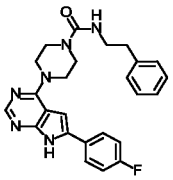
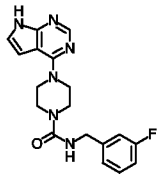
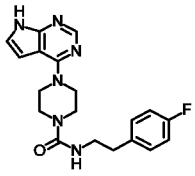
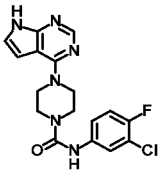
No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0123		N-[(5-chloro-2-pyridyl)methyl]-4-[6-(3-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	449.0
P-0124		N-[(5-fluoro-2-pyridyl)methyl]-4-[6-(3-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	433.2
P-0125		N-[4-(difluoromethoxy)phenyl]-4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	482.9
P-0126		N-[(1S)-1-(4-fluorophenyl)ethyl]-4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	462.9
P-0127		N-[(2-methoxy-4-pyridyl)methyl]-4-[6-(3-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	445.0
P-0128		N-[(6-methoxy-2-pyridyl)methyl]-4-[6-(3-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	445.0
P-0129		4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[(6-methoxy-3-pyridyl)methyl]piperazine-1-carboxamide	462.0

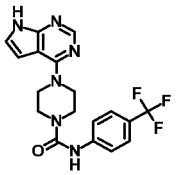
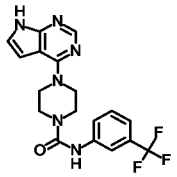
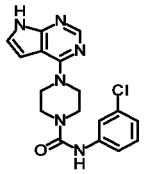
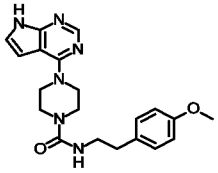
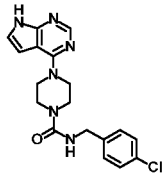
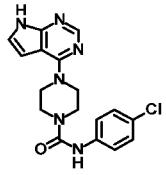
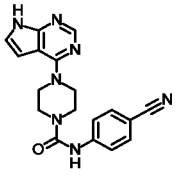
No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0130		4-[6-(3-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	323.9
P-0131		4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[(5-fluoro-3-pyridyl)methyl]piperazine-1-carboxamide	449.9
P-0132		N-(4-dimethylaminophenyl)-4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperazine-1-carboxamide	366.4
P-0133		4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[4-(trifluoromethoxy)phenyl]piperazine-1-carboxamide	501.0
P-0134		4-[6-(4-chlorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[4-(trifluoromethoxy)phenyl]piperazine-1-carboxamide	517.3
P-0135		N-(4,4-difluorocyclohexyl)-4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	459.0
P-0136		N-[(1R)-1-(4-chlorophenyl)ethyl]-4-[6-(4-chlorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	495.0

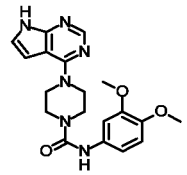
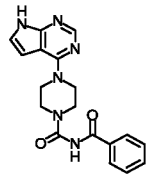
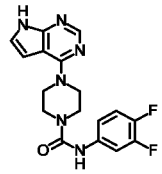
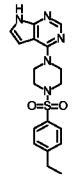
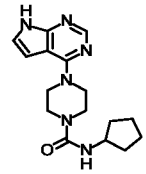
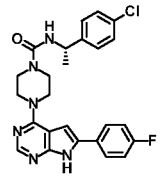
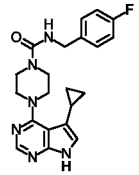
No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0137		4-[5-(cyclopropylmethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[(4-fluorophenyl)methyl]piperazine-1-carboxamide	409.1
P-0138		N-[(4-chlorophenyl)methyl]-4-(6-cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperazine-1-carboxamide	411.0
P-0139		N-[(4-chlorophenyl)methyl]-4-(6-chloro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperazine-1-carboxamide	406.8
P-0140		N-[(5-fluoro-2-methoxy-3-pyridyl)methyl]-4-[6-(3-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	463.3
P-0141		4-[5-(cyclopropanecarbonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[(4-fluorophenyl)methyl]piperazine-1-carboxamide	423.1
P-0142		4-[6-(4-chlorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-(p-tolyl)piperazine-1-sulfonamide	483.1
P-0143		N-benzoyl-4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	444.9

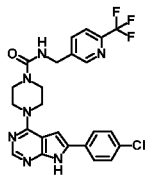
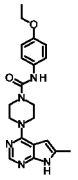
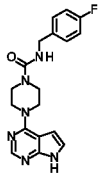
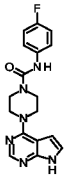
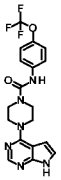
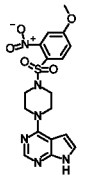
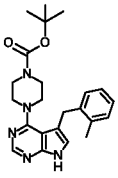
No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0144		4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[(1S)-1-(3-methoxyphenyl)ethyl]piperazine-1-carboxamide	475.0
P-0145		4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[(1R)-1-(4-methoxyphenyl)ethyl]piperazine-1-carboxamide	475.4
P-0146		N-[(1R)-1-(4-fluorophenyl)ethyl]-4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	475.0
P-0147		N-[(1R)-1-(4-fluorophenyl)ethyl]-4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	463.0
P-0148		N-cyclopentyl-4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	409.0
P-0149		4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[(1R)-1-(3-methoxyphenyl)ethyl]piperazine-1-carboxamide	475.0
P-0150		4-(6-cyano-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-N-[(4-fluorophenyl)methyl]piperazine-1-carboxamide	379.9

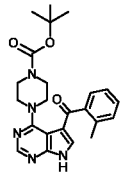
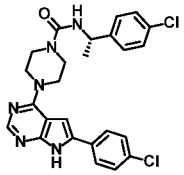
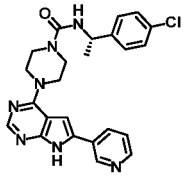
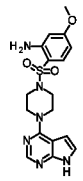
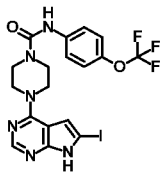
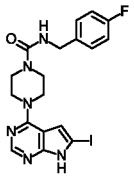
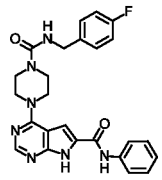
No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0151		N-[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperazine-1-carboxamide	405.4
P-0152		N-(3-pyridyl)-4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperazine-1-carboxamide	324.4
P-0153		N-[(4-chlorophenyl)methyl]-4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	465.0
P-0154		N-[(2-chlorophenyl)methyl]-4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	465.2
P-0155		4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[(1S)-1-(1-naphthyl)ethyl]piperazine-1-carboxamide	495.1
P-0156		4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[(3-methoxyphenyl)methyl]piperazine-1-carboxamide	461.3
P-0157		4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[(4-methoxyphenyl)methyl]piperazine-1-carboxamide	461.3

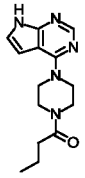
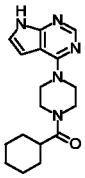
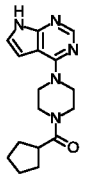
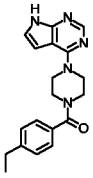
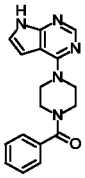
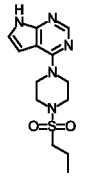
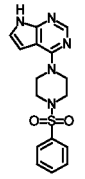
No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0158		4-(5-cyano-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-N-[(4-fluorophenyl)methyl]piperazine-1-carboxamide	380.0
P-0159		N-[(4-fluorophenyl)methyl]-4-[5-(o-tolylmethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	459.1
P-0160		N-[(4-fluorophenyl)methyl]-4-[5-(2-methylbenzoyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	473.0
P-0161		N-[2-(4-chlorophenyl)ethyl]-4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	478.9
P-0162		4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-phenethyl-piperazine-1-carboxamide	445.0
P-0163		N-[(3-fluorophenyl)methyl]-4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperazine-1-carboxamide	355.3
P-0164		N-[2-(4-fluorophenyl)ethyl]-4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperazine-1-carboxamide	369.4

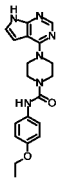
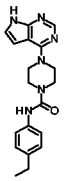
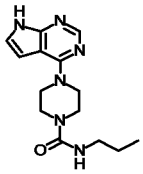
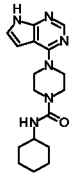
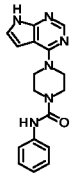
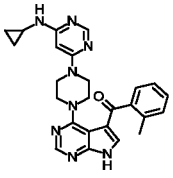
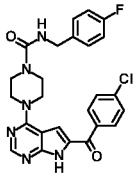
No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0165		N-(3-chloro-4-fluoro-phenyl)-4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperazine-1-carboxamide	375.4
P-0166		4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-N-[4-(trifluoromethyl)phenyl]piperazine-1-carboxamide	391.3
P-0167		4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-N-[3-(trifluoromethyl)phenyl]piperazine-1-carboxamide	391.3
P-0168		N-(3-chlorophenyl)-4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperazine-1-carboxamide	357.1
P-0169		N-[2-(4-methoxyphenyl)ethyl]-4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperazine-1-carboxamide	381.4
P-0170		N-[(4-chlorophenyl)methyl]-4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperazine-1-carboxamide	371.2
P-0171		N-(4-chlorophenyl)-4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperazine-1-carboxamide	357.1

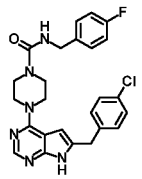
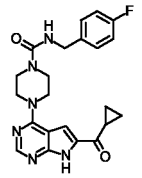
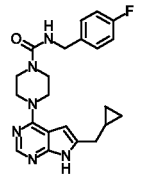
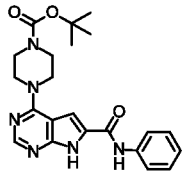
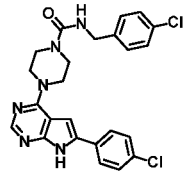
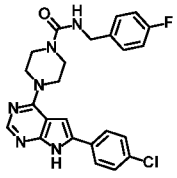
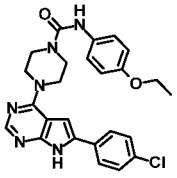
No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0172		N-(4-cyanophenyl)-4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperazine-1-carboxamide	348.4
P-0173		N-(3,4-dimethoxyphenyl)-4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperazine-1-carboxamide	383.2
P-0174		N-benzoyl-4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperazine-1-carboxamide	351.4
P-0175		N-(3,4-difluorophenyl)-4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperazine-1-carboxamide	359.2
P-0176		4-[4-(4-ethylphenyl)sulfonylpiperazin-1-yl]-7H-pyrrolo[2,3-d]pyrimidine	372.1
P-0177		N-cyclopentyl-4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperazine-1-carboxamide	315.4
P-0178		N-[(1S)-1-(4-chlorophenyl)ethyl]-4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	479.3

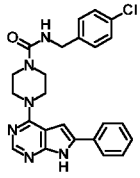
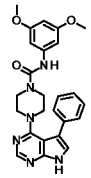
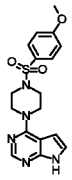
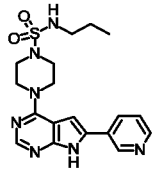
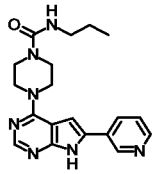
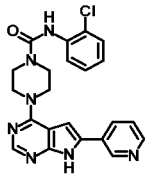
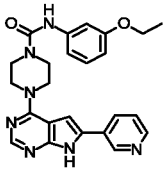
No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0179		4-(5-cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-N-[(4-fluorophenyl)methyl]piperazine-1-carboxamide	394.9
P-0180		4-[6-(4-chlorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[[6-(trifluoromethyl)-3-pyridyl]methyl]piperazine-1-carboxamide	515.9
P-0181		N-(4-ethoxyphenyl)-4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperazine-1-carboxamide	381.2
P-0182		N-[(4-fluorophenyl)methyl]-4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperazine-1-carboxamide	355.3
P-0183		N-(4-fluorophenyl)-4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperazine-1-carboxamide	341.2
P-0184		4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-N-[4-(trifluoromethoxy)phenyl]piperazine-1-carboxamide	407.2
P-0185		4-[4-(4-methoxy-2-nitro-phenyl)sulfonylpiperazin-1-yl]-7H-pyrrolo[2,3-d]pyrimidine	418.9

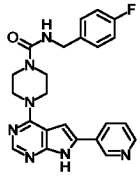
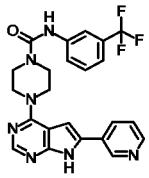
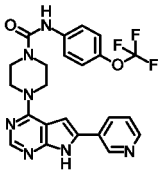
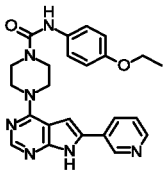
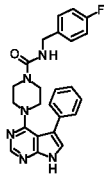
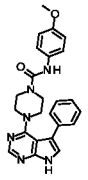
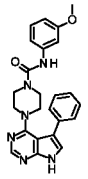
No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0186		tert-butyl 4-[5-(o-tolylmethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxylate	408.2
P-0187		tert-butyl 4-[5-(2-methylbenzoyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxylate	422.3
P-0188		N-[(1S)-1-(4-chlorophenyl)ethyl]-4-[6-(4-chlorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	495.2
P-0189		N-[(1S)-1-(4-chlorophenyl)ethyl]-4-[6-(3-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	462.2
P-0190		5-methoxy-2-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperazin-1-yl]sulfonyl-aniline	389.2
P-0191		4-(6-iodo-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-N-[4-(trifluoromethoxy)phenyl]piperazine-1-carboxamide	533.1
P-0192		N-[(4-fluorophenyl)methyl]-4-(6-iodo-7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperazine-1-carboxamide	481.1

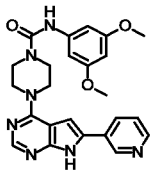
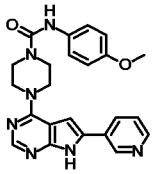
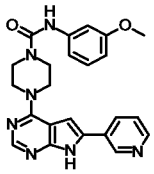
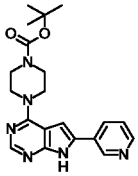
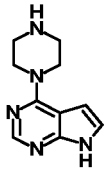
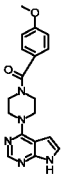
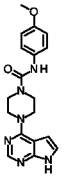
No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0193		4-[4-[(4-fluorophenyl)methylcarbamoyl]piperazin-1-yl]-N-phenyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide	474.0
P-0194		1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperazin-1-yl]butan-1-one	274.3
P-0195		cyclohexyl-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperazin-1-yl]methanone	314.2
P-0196		cyclopentyl-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperazin-1-yl]methanone	300.4
P-0197		(4-ethylphenyl)-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperazin-1-yl]methanone	336.4
P-0198		phenyl-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperazin-1-yl]methanone	308.5
P-0199		4-(4-propylsulfonylpiperazin-1-yl)-7H-pyrrolo[2,3-d]pyrimidine	310.3

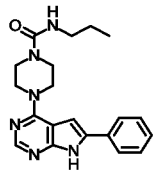
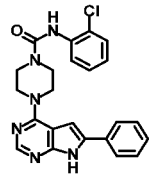
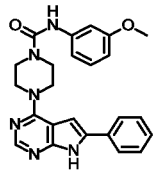
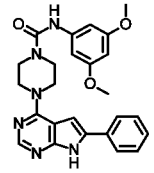
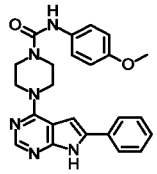
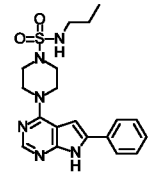
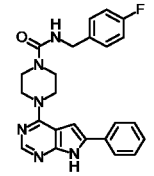
No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0200		4-[4-(benzenesulfonyl)piperazin-1-yl]-7H-pyrrolo[2,3-d]pyrimidine	344.2
P-0201		N-(4-ethoxyphenyl)-4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperazine-1-carboxamide	367.2
P-0202		N-(4-ethylphenyl)-4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperazine-1-carboxamide	351.4
P-0203		N-propyl-4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperazine-1-carboxamide	289.3
P-0204		N-cyclohexyl-4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperazine-1-carboxamide	329.5
P-0205		N-phenyl-4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperazine-1-carboxamide	323.5
P-0206		[4-[4-[6-(cyclopropylamino)pyrimidin-4-yl]piperazin-1-yl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-(o-tolyl)methanone	455.2

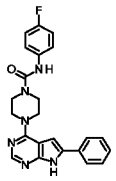
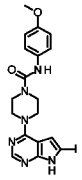
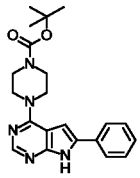
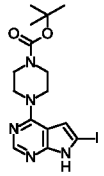
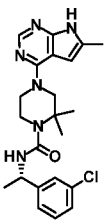
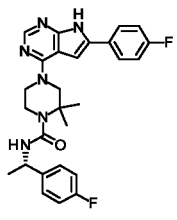
No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0207		4-[6-(4-chlorobenzoyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[(4-fluorophenyl)methyl]piperazine-1-carboxamide	493.0
P-0208		4-[6-[(4-chlorophenyl)methyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[(4-fluorophenyl)methyl]piperazine-1-carboxamide	479.0
P-0209		4-[6-(cyclopropanecarbonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[(4-fluorophenyl)methyl]piperazine-1-carboxamide	422.9
P-0210		4-[6-(cyclopropylmethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[(4-fluorophenyl)methyl]piperazine-1-carboxamide	409.0
P-0211		tert-butyl 4-[6-(phenylcarbamoyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxylate	423.0
P-0212		N-[(4-chlorophenyl)methyl]-4-[6-(4-chlorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	480.9
P-0213		4-[6-(4-chlorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[(4-fluorophenyl)methyl]piperazine-1-carboxamide	465.1

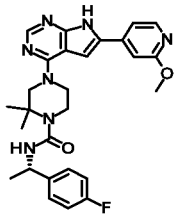
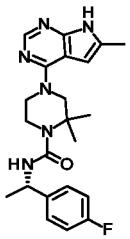
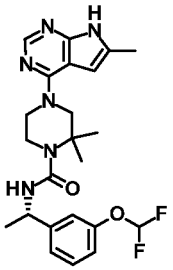
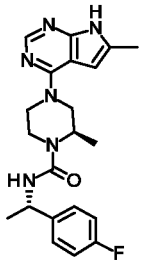
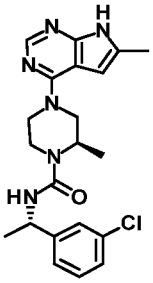
No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0214		4-[6-(4-chlorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-(4-ethoxyphenyl)piperazine-1-carboxamide	477.0
P-0215		N-[(4-chlorophenyl)methyl]-4-(6-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperazine-1-carboxamide	446.9
P-0216		N-(3,5-dimethoxyphenyl)-4-(5-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperazine-1-carboxamide	459.2
P-0217		4-[4-(4-methoxyphenyl)sulfonylpiperazin-1-yl]-7H-pyrrolo[2,3-d]pyrimidine	373.9
P-0218		N-propyl-4-[6-(3-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	402.2
P-0219		N-(2-chlorophenyl)-4-[6-(3-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	365.9
P-0220		N-(2-chlorophenyl)-4-[6-(3-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	433.9

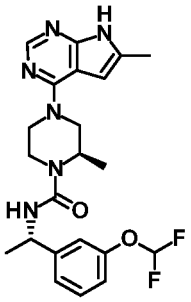
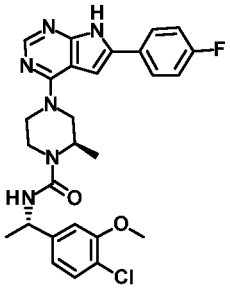
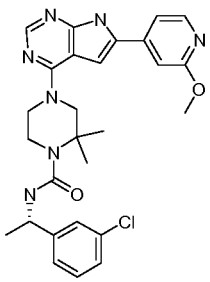
No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0221		N-(3-ethoxyphenyl)-4-[6-(3-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	444.3
P-0222		N-[(4-fluorophenyl)methyl]-4-[6-(3-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	432.0
P-0223		4-[6-(3-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[3-(trifluoromethyl)phenyl]piperazine-1-carboxamide	468.0
P-0224		4-[6-(3-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[4-(trifluoromethoxy)phenyl]piperazine-1-carboxamide	484.0
P-0225		N-(4-ethoxyphenyl)-4-[6-(3-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	444.0
P-0226		N-[(4-fluorophenyl)methyl]-4-(5-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperazine-1-carboxamide	431.0
P-0227		N-(4-methoxyphenyl)-4-(5-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperazine-1-carboxamide	429.0

No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0228		N-(3-methoxyphenyl)-4-(5-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperazine-1-carboxamide	429.0
P-0229		N-(3,5-dimethoxyphenyl)-4-[6-(3-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	460.0
P-0230		N-(4-methoxyphenyl)-4-[6-(3-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	430.0
P-0231		N-(3-methoxyphenyl)-4-[6-(3-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	430.0
P-0232		tert-butyl 4-[6-(3-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxylate	381.0
P-0233		4-piperazin-1-yl-7H-pyrrolo[2,3-d]pyrimidine	204.0
P-0234		(4-methoxyphenyl)-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperazin-1-yl]methanone	337.9

No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0235		N-(4-methoxyphenyl)-4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperazine-1-carboxamide	352.2
P-0236		4-(6-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-N-propyl-piperazine-1-carboxamide	365.0
P-0237		N-(2-chlorophenyl)-4-(6-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperazine-1-carboxamide	433.0
P-0238		N-(3-methoxyphenyl)-4-(6-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperazine-1-carboxamide	429.0
P-0239		N-(3,5-dimethoxyphenyl)-4-(6-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperazine-1-carboxamide	459.0
P-0240		N-(4-methoxyphenyl)-4-(6-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperazine-1-carboxamide	429.0
P-0241		4-(6-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-N-propyl-piperazine-1-sulfonamide	400.9

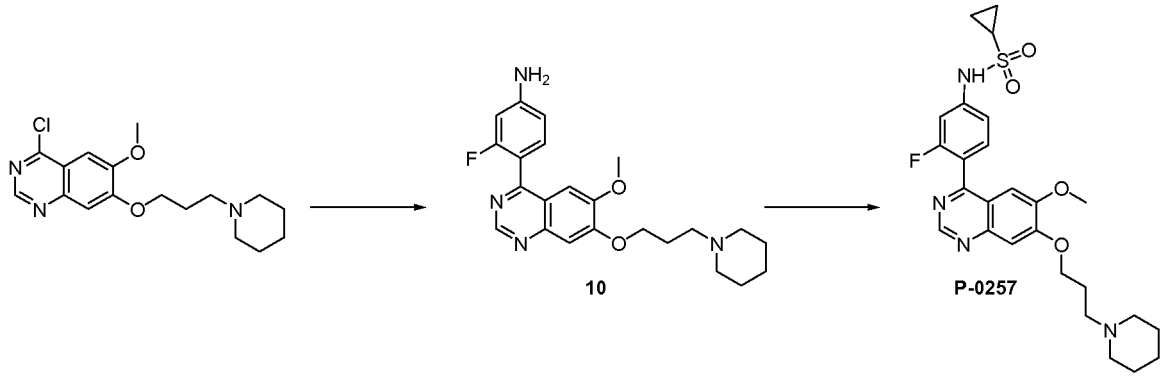
No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0242		N-[(4-fluorophenyl)methyl]-4-(6-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperazine-1-carboxamide	431.0
P-0243		N-(4-fluorophenyl)-4-(6-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperazine-1-carboxamide	417.0
P-0244		4-(6-iodo-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-N-(4-methoxyphenyl)piperazine-1-carboxamide	478.9
P-0245		tert-butyl 4-(6-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperazine-1-carboxylate	380.0
P-0641		N-[(1S)-1-(3-chlorophenyl)ethyl]-2,2-dimethyl-4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperazine-1-carboxamide	427.30
P-0642		N-[(1S)-1-(4-fluorophenyl)ethyl]-4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-2,2-dimethyl-piperazine-1-carboxamide	491.60

No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0643		N-[(1S)-1-(4-fluorophenyl)ethyl]-4-[6-(2-methoxy-4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-2,2-dimethyl-piperazine-1-carboxamide	504.55
P-0644		N-[(1S)-1-(4-fluorophenyl)ethyl]-2,2-dimethyl-4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperazine-1-carboxamide	411.30
P-0645		N-[(1S)-1-[3-(difluoromethoxy)phenyl]ethyl]-2,2-dimethyl-4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperazine-1-carboxamide	459.50
P-0646		(2R)-N-[(1S)-1-(4-fluorophenyl)ethyl]-2-methyl-4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperazine-1-carboxamide	397.30
P-0647		(2R)-N-[(1S)-1-(3-chlorophenyl)ethyl]-2-methyl-4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperazine-1-carboxamide	413.25

No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0648		(2R)-N-[(1S)-1-[3-(difluoromethoxy)phenyl]ethyl]-2-methyl-4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperazine-1-carboxamide	445.30
P-0649		(2R)-N-[(1S)-1-(4-chloro-3-methoxy-phenyl)ethyl]-4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-2-methyl-piperazine-1-carboxamide	523.80
P-0650		N-[(1S)-1-(3-chlorophenyl)ethyl]-4-[6-(2-methoxy-4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-2,2-dimethyl-piperazine-1-carboxamide	520.00

Example 3: Preparation of cyclopropanesulfonic acid {3-fluoro-4-[6-methoxy-7-(3-piperidin-1-yl-propoxy)-quinazolin-4-yl]-phenyl}-amide (P-0257).

Scheme 3

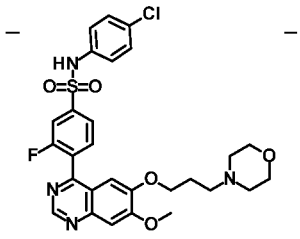
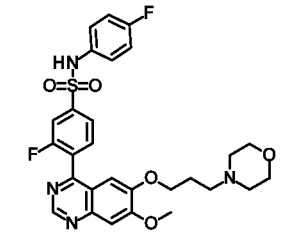
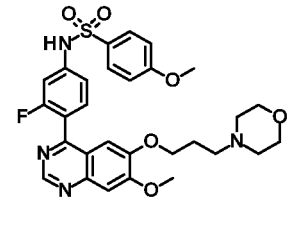
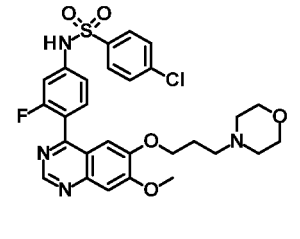
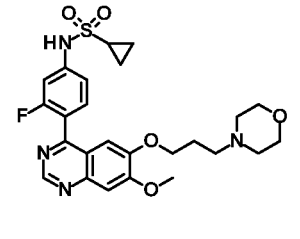


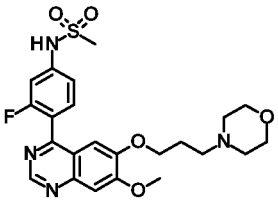
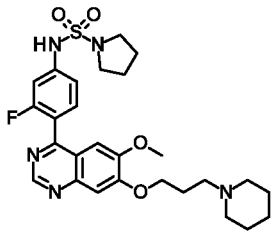
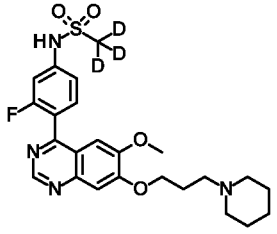
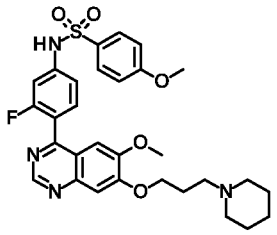
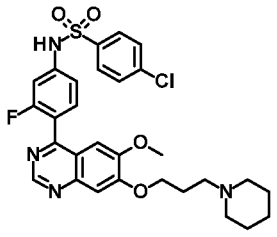
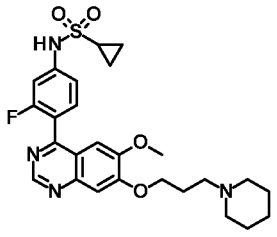
[0285] Step 1 – Synthesis of 3-fluoro-4-[6-methoxy-7-[3-(1-piperidyl)propoxy]-4a,8a-dihydroquinazolin-4-yl]aniline (10): To 4-chloro-6-methoxy-7-[3-(1-piperidyl)propoxy]quinazoline (0.8 g, 2.38 mmol) in acetonitrile (9 ml), were added 3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.55 g, 2.32 mmol), 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (0.05 g, 0.06 mmol) and potassium carbonate (3 ml, 33.44 mmol) in water. The reaction was micro-waved at 170 °C for 15 minutes. The reaction was poured into water, and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, and filtered. The filtrate was concentrated, and purified with silica gel column chromatography eluting with 2% to 25% methanol in methylene chloride containing 0.25% triethylamine to give product (**10**), 0.50 g.

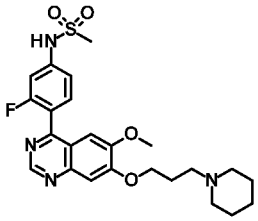
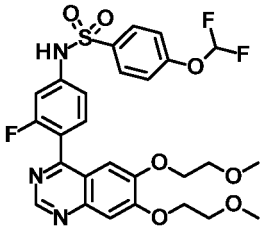
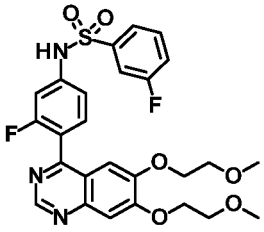
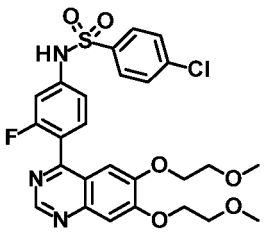
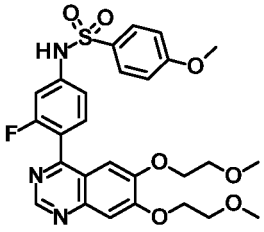
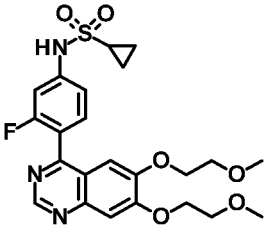
[0286] Step 2 – Synthesis of cyclopropanesulfonic acid {3-fluoro-4-[6-methoxy-7-(3-piperidin-1-yl-propoxy)-quinazolin-4-yl]-phenyl}-amide (P-0257): To 3-fluoro-4-[6-methoxy-7-[3-(1-piperidyl)propoxy]-4a,8a-dihydroquinazolin-4-yl]aniline (**10**) (0.07 g, 0.17 mmol) in pyridine (2 g, 0.03 mol) was added cyclopropanesulfonyl chloride (0.1 g, 0.71 mmol). The reaction was stirred at room temperature overnight. The reaction was concentrated, and purified with silica gel column chromatography eluting with 2% to 20% methanol in methylene chloride, and then further purified by prep HPLC to give 0.0181 g of product (**P-0257**). MS (ESI) $[M+H^+]^+ = 515.0$. The data from the ^1H NMR spectrum were consistent with the structure of the compound.

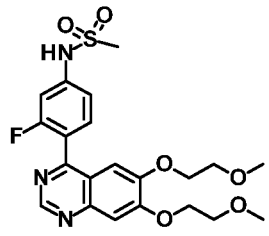
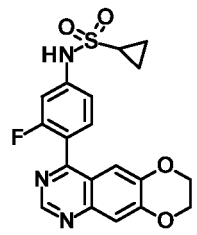
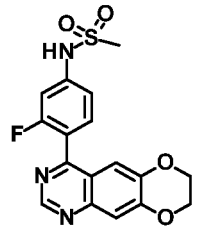
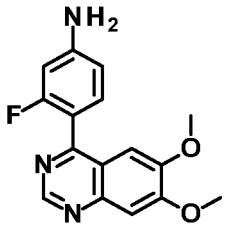
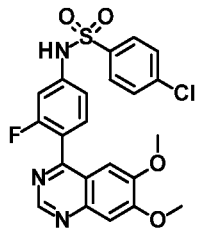
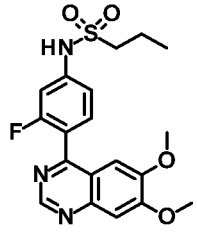
[0287] Compounds listed in Table 2 below, e.g., compounds P-0247 to P-0280 were prepared according to the protocols set forth in Example 3 and Scheme 3. The structures of the compounds in Table 2 were confirmed by ^1H NMR and mass spectroscopy.

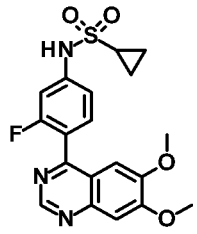
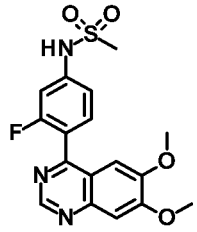
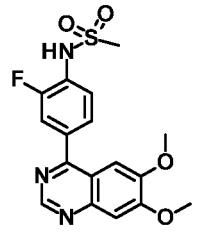
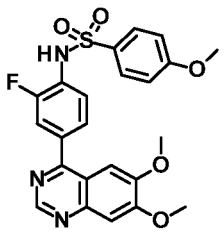
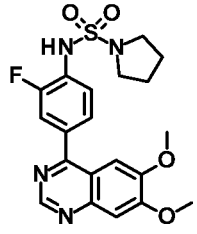
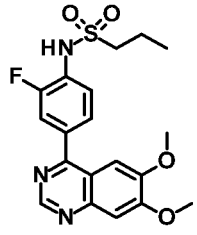
TABLE 2

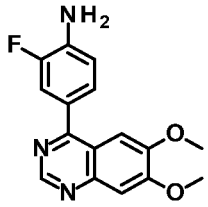
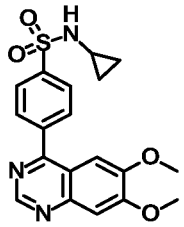
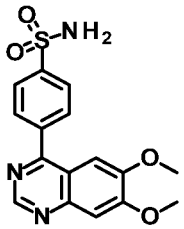
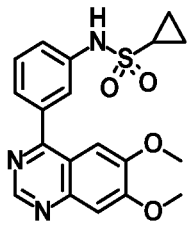
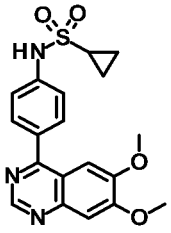
No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0247		N-(4-chlorophenyl)-3-fluoro-4-[7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-yl]benzenesulfonamide	588.4
P-0248		3-fluoro-N-(4-fluorophenyl)-4-[7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-yl]benzenesulfonamide	571.5
P-0249		N-[3-fluoro-4-[7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-yl]phenyl]-4-methoxy-benzenesulfonamide	581.1*
P-0250		4-chloro-N-[3-fluoro-4-[7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-yl]phenyl]benzenesulfonamide	585.1*
P-0251		N-[3-fluoro-4-[7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-yl]phenyl]cyclopropanesulfonamide	515.1*

No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0252		N-[3-fluoro-4-[7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-yl]phenyl]methanesulfonamide	491.4
P-0253		N-[3-fluoro-4-[6-methoxy-7-[3-(1-piperidyl)propoxy]quinazolin-4-yl]phenyl]pyrrolidine-1-sulfonamide	544.4
P-0254		1,1,1-trideuterio-N-[3-fluoro-4-[6-methoxy-7-[3-(1-piperidyl)propoxy]quinazolin-4-yl]phenyl]methanesulfonamide	492.0
P-0255		N-[3-fluoro-4-[6-methoxy-7-[3-(1-piperidyl)propoxy]quinazolin-4-yl]phenyl]-4-methoxy-benzenesulfonamide	581.4
P-0256		4-chloro-N-[3-fluoro-4-[6-methoxy-7-[3-(1-piperidyl)propoxy]quinazolin-4-yl]phenyl]benzenesulfonamide	585.3
P-0257		N-[3-fluoro-4-[6-methoxy-7-[3-(1-piperidyl)propoxy]quinazolin-4-yl]phenyl]cyclopropanesulfonamide	515.0

No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0258		N-[3-fluoro-4-[6-methoxy-7-[3-(1-piperidyl)propoxy]quinazolin-4-yl]phenyl]methanesulfonamide	489.0
P-0259		N-[4-[6,7-bis(2-methoxyethoxy)quinazolin-4-yl]-3-fluoro-phenyl]-4-(difluoromethoxy)benzenesulfonamide	594.3
P-0260		N-[4-[6,7-bis(2-methoxyethoxy)quinazolin-4-yl]-3-fluoro-phenyl]-3-fluoro-benzenesulfonamide	544.3*
P-0261		N-[4-[6,7-bis(2-methoxyethoxy)quinazolin-4-yl]-3-fluoro-phenyl]-4-chloro-benzenesulfonamide	562.3
P-0262		N-[4-[6,7-bis(2-methoxyethoxy)quinazolin-4-yl]-3-fluoro-phenyl]-4-methoxy-benzenesulfonamide	558.0
P-0263		N-[4-[6,7-bis(2-methoxyethoxy)quinazolin-4-yl]-3-fluoro-phenyl]cyclopropanesulfonamide	492.0

No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0264		N-[4-[6,7-bis(2-methoxyethoxy)quinazolin-4-yl]-3-fluoro-phenyl]methanesulfonamide	466.2
P-0265		N-[4-(7,8-dihydro-[1,4]dioxino[2,3-g]quinazolin-4-yl)-3-fluoro-phenyl]cyclopropanesulfonamide	402.0
P-0266		N-[4-(7,8-dihydro-[1,4]dioxino[2,3-g]quinazolin-4-yl)-3-fluoro-phenyl]methanesulfonamide	376.0
P-0267		4-(6,7-dimethoxyquinazolin-4-yl)-3-fluoro-aniline	300.0
P-0268		4-chloro-N-[4-(6,7-dimethoxyquinazolin-4-yl)-3-fluoro-phenyl]benzenesulfonamide	473.9
P-0269		N-[4-(6,7-dimethoxyquinazolin-4-yl)-3-fluoro-phenyl]propane-1-sulfonamide	405.8

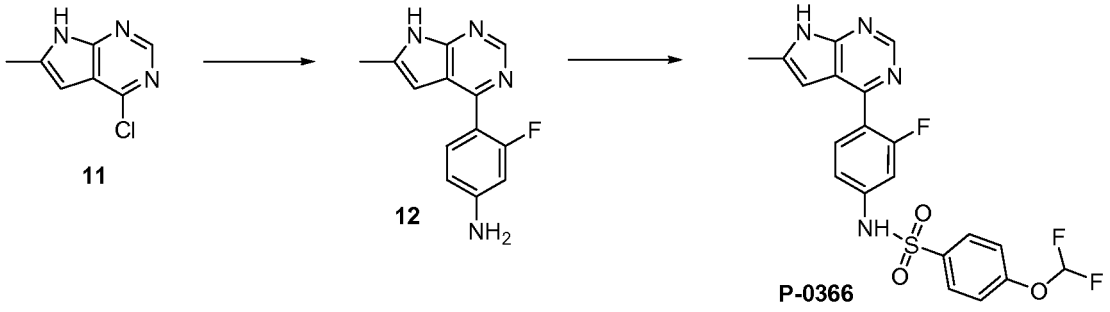
No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0270		N-[4-(6,7-dimethoxyquinazolin-4-yl)-3-fluoro-phenyl]cyclopropanesulfonamide	403.8
P-0271		N-[4-(6,7-dimethoxyquinazolin-4-yl)-3-fluoro-phenyl]methanesulfonamide	377.8
P-0272		N-[4-(6,7-dimethoxyquinazolin-4-yl)-2-fluoro-phenyl]methanesulfonamide	377.9
P-0273		N-[4-(6,7-dimethoxyquinazolin-4-yl)-2-fluoro-phenyl]-4-methoxy-benzenesulfonamide	470.0
P-0274		N-[4-(6,7-dimethoxyquinazolin-4-yl)-2-fluoro-phenyl]pyrrolidine-1-sulfonamide	432.9
P-0275		N-[4-(6,7-dimethoxyquinazolin-4-yl)-2-fluoro-phenyl]propane-1-sulfonamide	405.9

No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0276		4-(6,7-dimethoxyquinazolin-4-yl)-2-fluoro-aniline	299.8
P-0277		N-cyclopropyl-4-(6,7-dimethoxyquinazolin-4-yl)benzenesulfonamide	385.8
P-0278		4-(6,7-dimethoxyquinazolin-4-yl)benzenesulfonamide	346.0
P-0279		N-[3-(6,7-dimethoxyquinazolin-4-yl)phenyl]cyclopropanesulfonamide	385.9
P-0280		N-[4-(6,7-dimethoxyquinazolin-4-yl)phenyl]cyclopropanesulfonamide	385.9

The asterisk * in Table 2 indicates the observed MS (ESI) $[M-H^+]^-$ molecular weights.

Example 4: Preparation of 4-Difluoromethoxy-N-[3-fluoro-4-(6-methyl-7H-pyrrolo[2,3 d]pyrimidin-4-yl)-phenyl]-benzenesulfonamide (P-0366).

Scheme 4.

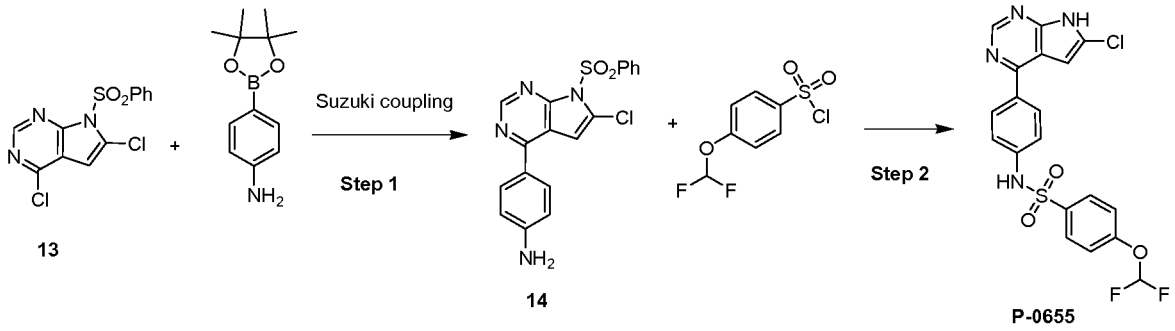


[0288] Step 1 – Synthesis of 3-fluoro-4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)aniline (12): To a microwave vessel, 4-chloro-6-methyl-7H-pyrrolo[2,3-d]pyrimidine (**11**), [4-(methanesulfonamido)phenyl]boronic acid (0.1 g, 0.597 mmol), acetonitrile (3.11 ml), K_2CO_3 (1M, aq) (1.79 ml, 0.2 mmol), and 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride (0.045g, 0.0597 mmol) were combined and heated at 90 °C for 40 minutes. LC-MS analysis on reaction showed complete transformation with no starting materials left. After cooling, the product precipitated. The material was filtered and washed with MeOH. The filtrate was concentrated and evaporated and absorbed onto silica and purified with MeOH in dichloromethane(1-20%) over 20 minutes. The product (orange solution) was eluted at ~ 9% MeOH in dichloromethane. The fractions were concentrated to give a yellow solid. LC-MS $[M+H^+]^+ = 243.00$.

[0289] Step 2: 4-Difluoromethoxy-N-[3-fluoro-4-(6-methyl-7H-pyrrolo[2,3 d]pyrimidin-4-yl)-phenyl]-benzenesulfonamide (P-0366): To a reaction vial, 3-fluoro-4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)aniline (**12**) (0.05 g, 0.206 mmol) was dissolved in pyridine (2.5 ml). 4-(difluoromethoxy)benzenesulfonyl chloride (0.1 g, 0.412 mmol) was added. The reaction was allowed to stir overnight at ambient conditions. LC-MS check of the crude showed starting material was consumed. The reaction was evaporated under reduced pressure and the resulting crude material was absorbed onto silica and purified via flash chromatography with MeOH in CH_2Cl_2 (0-20%) to obtain the desired product. The product was concentrated to reveal an off-white solid (22.0 mg, 23.8% yield). The data from the ^1H NMR spectrum were consistent with the structure of the compound. LC-MS $[M+H^+]^+ = 449.25$.

Example 5: Preparation of N-[4-(6-chloro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]-4-(difluoromethoxy)benzenesulfonamide (P-0655)

Scheme 5

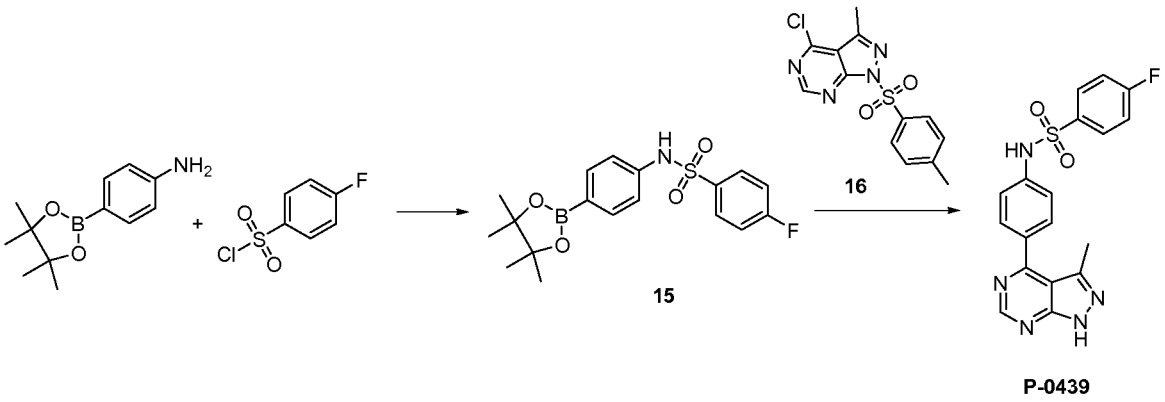


[0290] Step 1 – Synthesis of 4-[7-(benzenesulfonyl)-6-chloro-pyrrolo[2,3-d]pyrimidin-4-yl]aniline (14): A mixture of 7-(benzenesulfonyl)-4,6-dichloro-pyrrolo[2,3-d]pyrimidine (**13**) (328.17 mg, 1 mmol, 1 eq), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (262.91 mg, 1.2 mmol, 1.2 eq) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (73.18 mg, 0.1 mmol, 0.1 eq) in acetonitrile (10 ml) was purged with nitrogen gas then 1.2 mL of 2.5M aqueous K_2CO_3 (3 eq) was added. The reaction mixture was heated at 100 °C for 4 hrs. The resulting mixture was cooled and filtered through a pad of celite. The filtrate was dried over Na_2SO_4, collected and concentrated down. The obtained residue was purified by flash chromatography eluting with 50% ethyl acetate in hexanes to provide 4-[7-(benzenesulfonyl)-6-chloro-pyrrolo[2,3-d]pyrimidin-4-yl]aniline **(14)** (75 mg, 19.5 % yield) as a yellow oil. LC-MS (ESI) $[M+H^+]^+ = 385.2$ $(M+H^+)$. The data from the ^1H NMR spectrum were consistent with the structure of the compound.

[0291] Step 2- Synthesis of N-[4-(6-chloro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]-4-(difluoromethoxy)benzenesulfonamide (P-0655): To a mixture of compound **(14)** (75 mg, 0.19 mmol, 1eq) in pyridine (1.0 ml) was added 4-(difluoromethoxy)benzenesulfonyl chloride (70.93 mg, 0.29 mmol, 1.5eq). The reaction mixture was stirred at room temperature for 24 hrs then concentrated down under reduced pressure and elevated temperature to effect sulfonamide deprotection. The crude sample was purified by flash chromatography eluting with 30-50% ethyl acetate in hexanes. The purified sample was triturated with dichloromethane to afford N-[4-(6-chloro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]-4-(difluoromethoxy)benzenesulfonamide **(P-0655)** (24.2 mg, 27.5% yield) as a pale yellow solid. The data from the ^1H NMR spectrum were consistent with the structure of the compound. LC-MS (ESI) $[M+H^+]^+ = 451.1$.

Example 6: Preparation of 4-fluoro-N-[4-(5-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-phenyl]-benzenesulfonamide (P-0439).

Scheme 6.

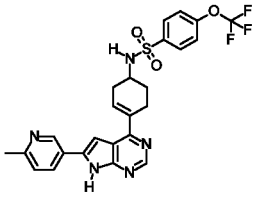
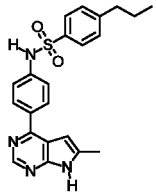
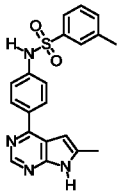
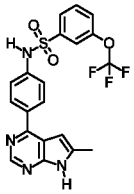
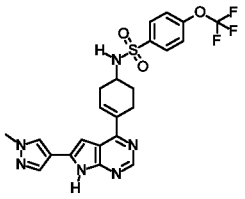
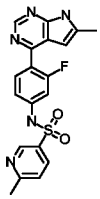
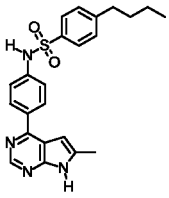


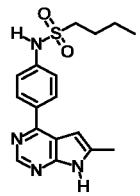
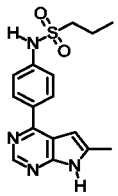
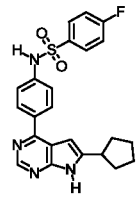
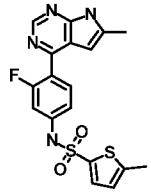
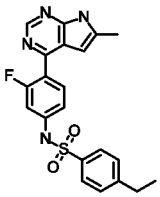
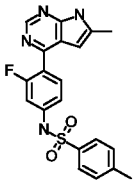
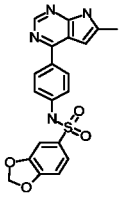
[0292] Step 1- Synthesis of 4-fluoro-N-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]benzenesulfonamide (15): 4-fluorobenzenesulfonyl chloride (0.2 g, 1.028 mmol) and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.248 g, 1.13 mmol) were taken up in pyridine (5.541 mL, 68.51 mmol) and heated to 50 °C for 30 minutes. Ethyl acetate was added and the mixture was evaporated to dryness several times to remove pyridine resulting in the desired product (0.300 g, 73.51% yield). The material was carried on to the next step.

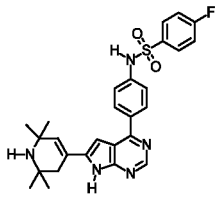
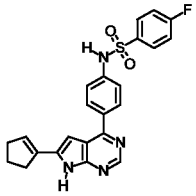
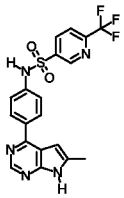
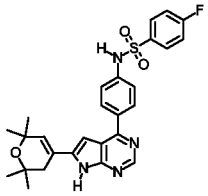
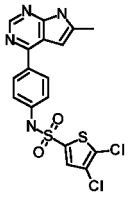
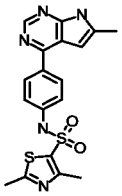
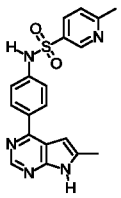
[0293] Step 2 – Synthesis of 4-fluoro-N-[4-(3-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)phenyl]benzenesulfonamide (P-0439): Compound **15** (0.3 g, 0.795 mmol) and compound **16** (0.295 g, 0.954 mmol) were taken up in acetonitrile (1.154 mL, 79.53 mmol). Potassium carbonate (1M, 3.976 mL, 3.976 mmol) and 1,1-bis(diphenylphosphino)ferrocene (0.046 g, 0.08 mmol) were added and the mixture was heated to 140 °C for 1 hour in the microwave reactor. LCMS showed that the reaction went to completion, and the mixture was diluted with water and extracted with ethyl acetate (3 X 100 mL). The resulting organic layers were combined, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude product was then purified by silica gel chromatography eluting with a gradient of 2-15% MeOH in dichloromethane over 30 minutes to give the desired product (0.035 g, 11.48% yield) in > 99% purity. The structure was confirmed by ^{1}H NMR spectroscopy. LC-MS (ESI) $[M+H^+]^+$ = 384.1.

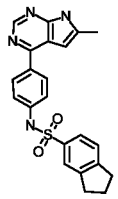
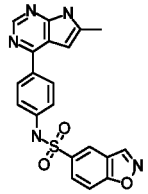
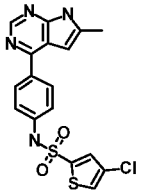
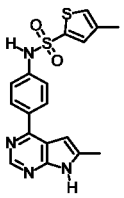
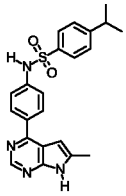
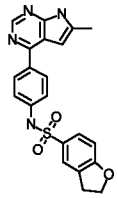
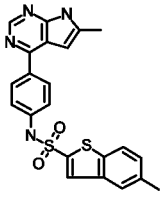
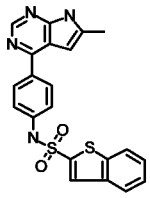
[0294] Compounds listed in Table 3 below, e.g., compounds P-0281 to P-0450, P-0651 to P-0655 and P-0729 were prepared according to the protocols set forth in Examples 5 and 6 and Schemes 5 and 6. The structures of the compounds in Table 3 were confirmed by ^{1}H NMR and mass spectroscopy.

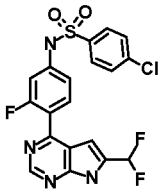
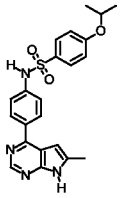
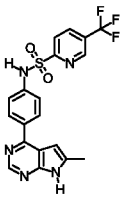
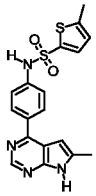
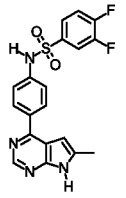
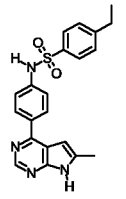
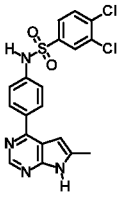
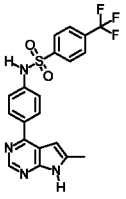
TABLE 3

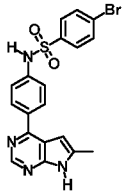
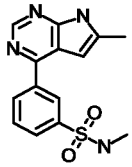
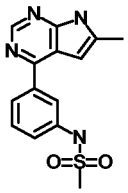
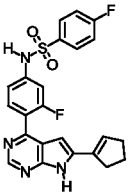
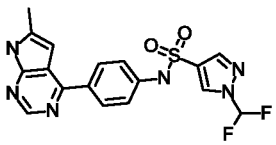
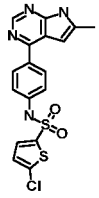
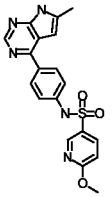
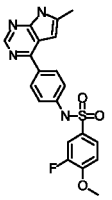
No	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0281		N-[4-[6-(6-methyl-3-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]cyclohex-3-en-1-yl]-4-(trifluoromethoxy)benzenesulfonamide	530.3
P-0282		N-[4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]-4-propyl-benzenesulfonamide	407.6
P-0283		3-methyl-N-[4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]benzenesulfonamide	379.5
P-0284		N-[4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]-3-(trifluoromethoxy)benzenesulfonamide	449.5
P-0285		N-[4-[6-(1-methylpyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]cyclohex-3-en-1-yl]-4-(trifluoromethoxy)benzenesulfonamide	519.5
P-0286		N-[3-fluoro-4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]-6-methyl-pyridine-3-sulfonamide	397.8
P-0287		4-butyl-N-[4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]benzenesulfonamide	421.7

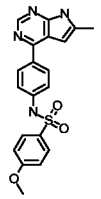
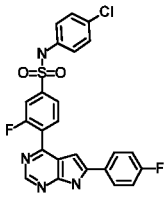
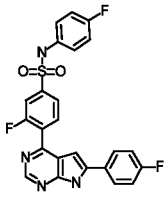
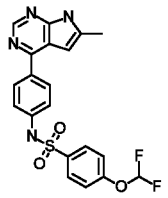
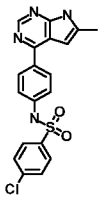
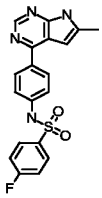
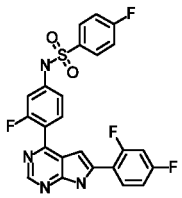
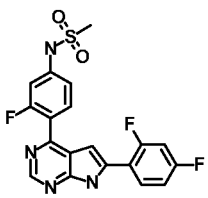
No	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0288		N-[4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]butane-1-sulfonamide	345.2
P-0289		N-[4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]propane-1-sulfonamide	331.2
P-0290		N-[4-(6-cyclopentyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]-4-fluoro-benzenesulfonamide	437.9
P-0291		N-[3-fluoro-4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]-5-methyl-thiophene-2-sulfonamide	403.2
P-0292		4-ethyl-N-[3-fluoro-4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]benzenesulfonamide	411.4
P-0293		N-[3-fluoro-4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]-4-methyl-benzenesulfonamide	396.8
P-0294		N-[4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]-1,3-benzodioxole-5-sulfonamide	409.2

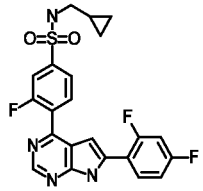
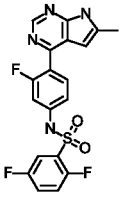
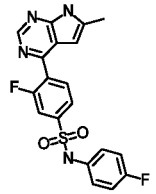
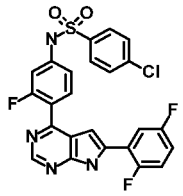
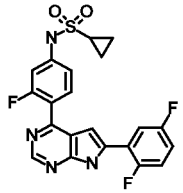
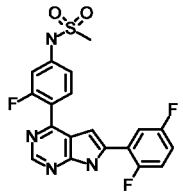
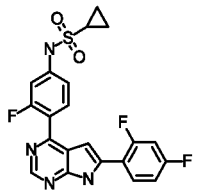
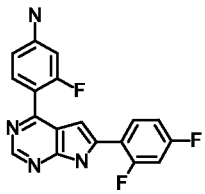
No	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0295		4-fluoro-N-[4-[6-(2,2,6,6-tetramethyl-1,3-dihydropyridin-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]phenyl]benzenesulfonamide	506.0
P-0296		N-[4-[6-(cyclopenten-1-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]phenyl]-4-fluoro-benzenesulfonamide	434.9
P-0297		N-[4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]-6-(trifluoromethyl)pyridine-3-sulfonamide	434.2
P-0298		4-fluoro-N-[4-[6-(2,2,6,6-tetramethyl-3H-pyran-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]phenyl]benzenesulfonamide	507.0
P-0299		4,5-dichloro-N-[4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]thiophene-2-sulfonamide	440.5
P-0300		2,4-dimethyl-N-[4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]thiazole-5-sulfonamide	400.2
P-0301		6-methyl-N-[4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]pyridine-3-sulfonamide	380.4

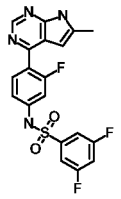
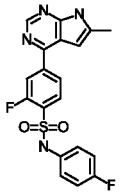
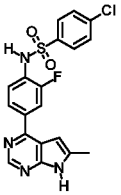
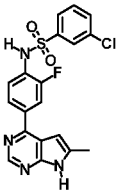
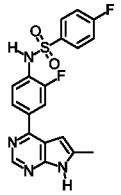
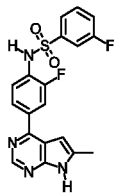
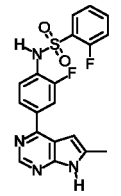
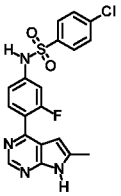
No	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0302		N-[4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]indane-5-sulfonamide	405.8
P-0303		N-[4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]-1,2-benzoxazole-5-sulfonamide	406.2
P-0304		4-chloro-N-[4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]thiophene-2-sulfonamide	404.9
P-0305		4-methyl-N-[4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]thiophene-2-sulfonamide	385.2
P-0306		4-isopropyl-N-[4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]benzenesulfonamide	407.3
P-0307		N-[4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]-2,3-dihydrobenzofuran-5-sulfonamide	407.2
P-0308		5-methyl-N-[4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]benzothiophene-2-sulfonamide	435.3
P-0309		N-[4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]benzothiophene-2-sulfonamide	420.8

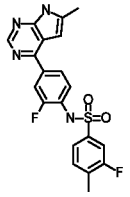
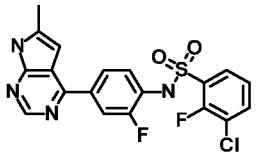
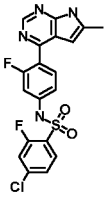
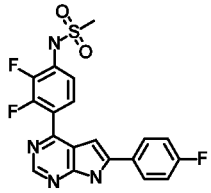
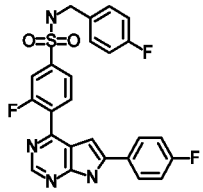
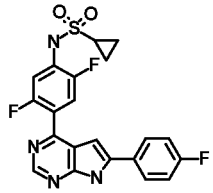
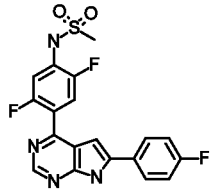
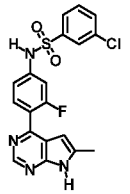
No	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0310		4-chloro-N-[4-[6-(difluoromethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-3-fluoro-phenyl]benzenesulfonamide	452.8
P-0311		4-isopropoxy-N-[4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]benzenesulfonamide	423.5
P-0312		N-[4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]-5-(trifluoromethyl)pyridine-2-sulfonamide	434.4
P-0313		5-methyl-N-[4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]thiophene-2-sulfonamide	385.5
P-0314		3,4-difluoro-N-[4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]benzenesulfonamide	401.4
P-0315		4-ethyl-N-[4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]benzenesulfonamide	
P-0316		3,4-dichloro-N-[4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]benzenesulfonamide	434.4
P-0317		N-[4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]-4-(trifluoromethyl)benzenesulfonamide	433.5

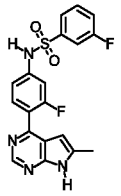
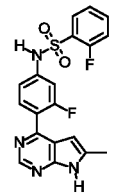
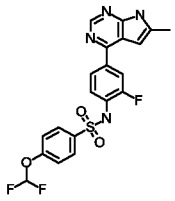
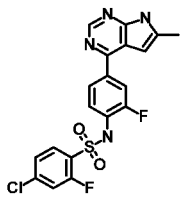
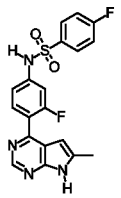
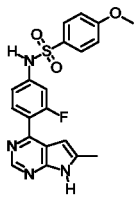
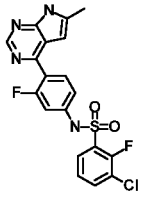
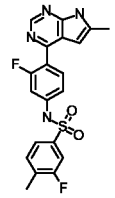
No	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0318		4-bromo-N-[4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]benzenesulfonamide	444.4
P-0319		N-methyl-3-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)benzenesulfonamide	303.2
P-0320		N-[3-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]methanesulfonamide	303.1
P-0321		N-[4-[6-(cyclopenten-1-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-3-fluoro-phenyl]-4-fluoro-benzenesulfonamide	453.5
P-0322		1-(difluoromethyl)-N-[4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]pyrazole-4-sulfonamide	405.4
P-0323		5-chloro-N-[4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]thiophene-2-sulfonamide	404.7
P-0324		6-methoxy-N-[4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]pyridine-3-sulfonamide	396.5
P-0325		3-fluoro-4-methoxy-N-[4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]benzenesulfonamide	413.2

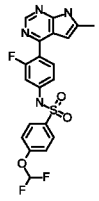
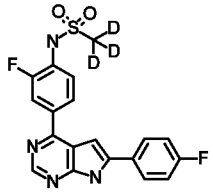
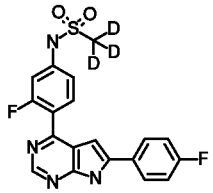
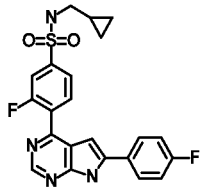
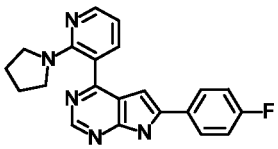
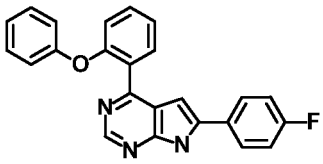
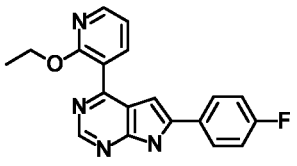
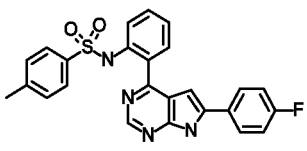
No	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0326		4-methoxy-N-[4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]benzenesulfonamide	395.4
P-0327		N-(4-chlorophenyl)-3-fluoro-4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]benzenesulfonamide	497.4
P-0328		3-fluoro-N-(4-fluorophenyl)-4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]benzenesulfonamide	480.9
P-0329		4-(difluoromethoxy)-N-[4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]benzenesulfonamide	431.3
P-0330		4-chloro-N-[4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]benzenesulfonamide	399.1
P-0331		4-fluoro-N-[4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]benzenesulfonamide	383.2
P-0332		N-[4-[6-(2,4-difluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-3-fluoro-phenyl]-4-fluoro-benzenesulfonamide	498.9
P-0333		N-[4-[6-(2,4-difluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-3-fluoro-phenyl]methanesulfonamide	419.2

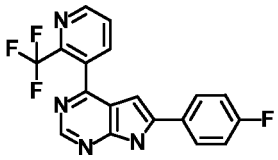
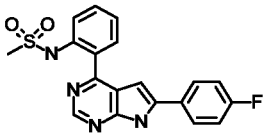
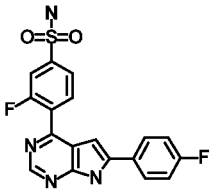
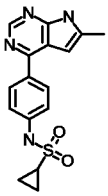
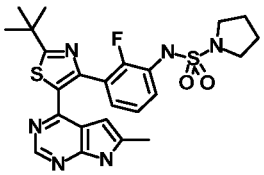
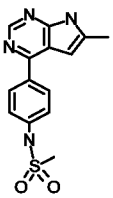
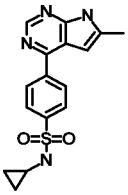
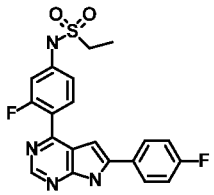
No	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0334		N-(cyclopropylmethyl)-4-[6-(2,4-difluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-3-fluoro-benzenesulfonamide	459.3
P-0335		2,5-difluoro-N-[3-fluoro-4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]benzenesulfonamide	419.6
P-0336		3-fluoro-N-(4-fluorophenyl)-4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)benzenesulfonamide	401.3
P-0337		4-chloro-N-[4-[6-(2,5-difluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-3-fluoro-phenyl]benzenesulfonamide	514.8
P-0338		N-[4-[6-(2,5-difluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-3-fluoro-phenyl]cyclopropanesulfonamide	444.9
P-0339		N-[4-[6-(2,5-difluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-3-fluoro-phenyl]methanesulfonamide	418.9
P-0340		N-[4-[6-(2,4-difluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-3-fluoro-phenyl]cyclopropanesulfonamide	444.9
P-0341		4-[6-(2,4-difluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-3-fluoro-aniline	341.1

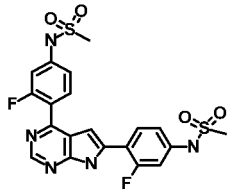
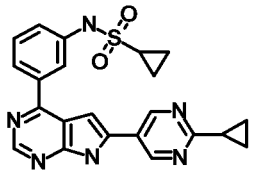
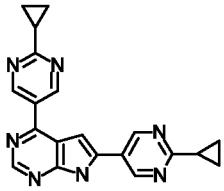
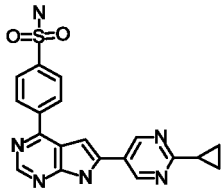
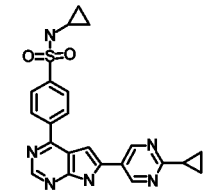
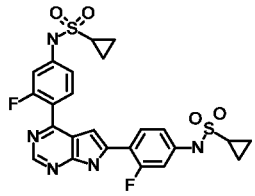
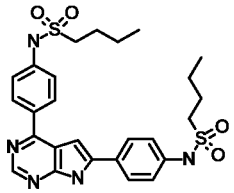
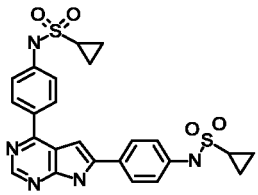
No	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0342		3,5-difluoro-N-[3-fluoro-4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]benzenesulfonamide	419.2
P-0343		2-fluoro-N-(4-fluorophenyl)-4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)benzenesulfonamide	401.2
P-0344		4-chloro-N-[2-fluoro-4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]benzenesulfonamide	416.8
P-0345		3-chloro-N-[2-fluoro-4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]benzenesulfonamide	416.9
P-0346		4-fluoro-N-[2-fluoro-4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]benzenesulfonamide	400.4
P-0347		3-fluoro-N-[2-fluoro-4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]benzenesulfonamide	401.5
P-0348		2-fluoro-N-[2-fluoro-4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]benzenesulfonamide	400.4
P-0349		4-chloro-N-[3-fluoro-4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]benzenesulfonamide	417.1

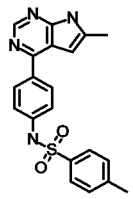
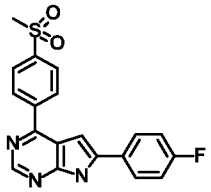
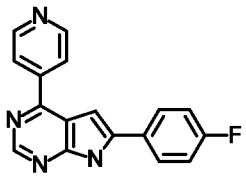
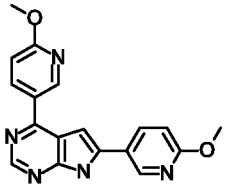
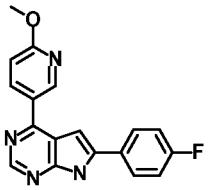
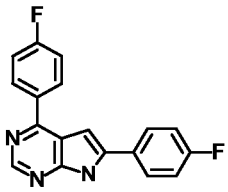
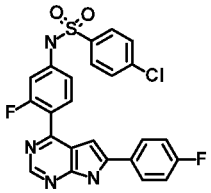
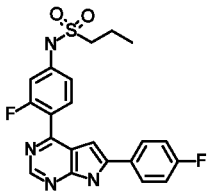
No	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0350		3-fluoro-N-[2-fluoro-4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]-4-methyl-benzenesulfonamide	415.3
P-0351		3-chloro-2-fluoro-N-[2-fluoro-4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]benzenesulfonamide	435.2
P-0352		4-chloro-2-fluoro-N-[3-fluoro-4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]benzenesulfonamide	434.8
P-0353		N-[2,3-difluoro-4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]phenyl]methanesulfonamide	418.9
P-0354		3-fluoro-N-[(4-fluorophenyl)methyl]-4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]benzenesulfonamide	495.0
P-0355		N-[2,5-difluoro-4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]phenyl]cyclopropanesulfonamide	444.9
P-0356		N-[2,5-difluoro-4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]phenyl]methanesulfonamide	419.0
P-0357		3-chloro-N-[3-fluoro-4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]benzenesulfonamide	417.1

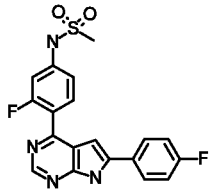
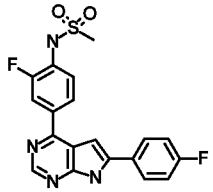
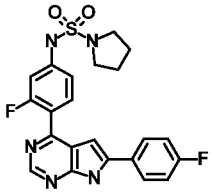
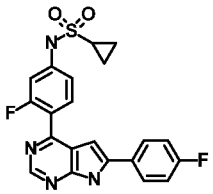
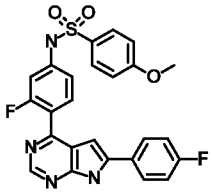
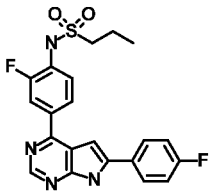
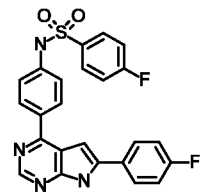
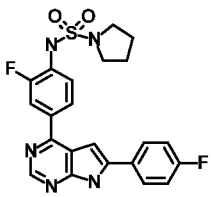
No	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0358		3-fluoro-N-[3-fluoro-4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]benzenesulfonamide	401.2
P-0359		2-fluoro-N-[3-fluoro-4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]benzenesulfonamide	400.8
P-0360		4-(difluoromethoxy)-N-[2-fluoro-4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]benzenesulfonamide	449.5
P-0361		4-chloro-2-fluoro-N-[2-fluoro-4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]benzenesulfonamide	435.1
P-0362		4-fluoro-N-[3-fluoro-4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]benzenesulfonamide	400.9
P-0363		N-[3-fluoro-4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]-4-methoxy-benzenesulfonamide	413.3
P-0364		3-chloro-2-fluoro-N-[3-fluoro-4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]benzenesulfonamide	435.0
P-0365		3-fluoro-N-[3-fluoro-4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]-4-methyl-benzenesulfonamide	415.2

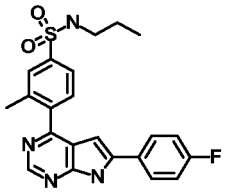
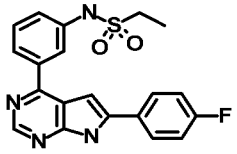
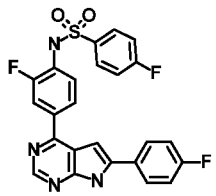
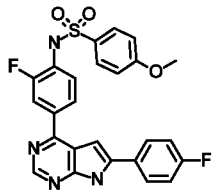
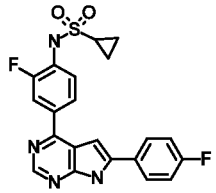
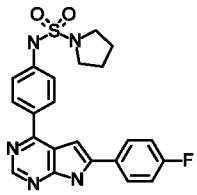
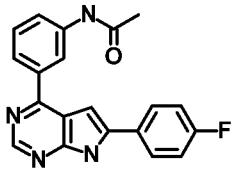
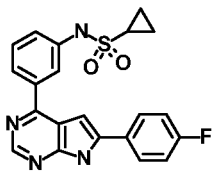
No	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0366		4-(difluoromethoxy)-N-[3-fluoro-4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]benzenesulfonamide	449.3
P-0367		1,1,1-trideuterio-N-[2-fluoro-4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]phenyl]methanesulfonamide	403.8
P-0368		1,1,1-trideuterio-N-[3-fluoro-4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]phenyl]methanesulfonamide	404.0
P-0369		N-(cyclopropylmethyl)-3-fluoro-4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]benzenesulfonamide	440.9
P-0370		6-(4-fluorophenyl)-4-(2-pyrrolidin-1-yl-3-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine	359.9
P-0371		6-(4-fluorophenyl)-4-(2-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidine	381.9
P-0372		4-(2-ethoxy-3-pyridyl)-6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidine	335.2
P-0373		N-[2-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]phenyl]-4-methyl-benzenesulfonamide	459.2

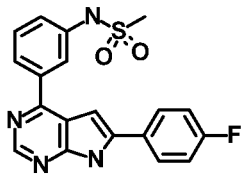
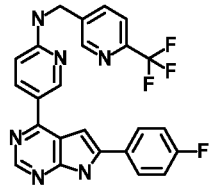
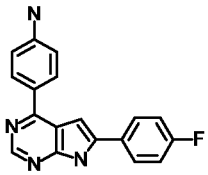
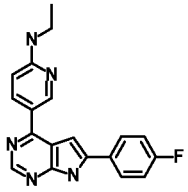
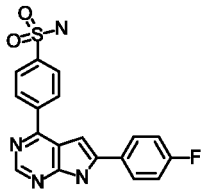
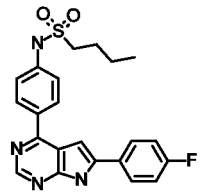
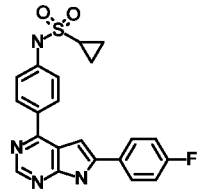
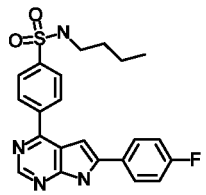
No	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0374		6-(4-fluorophenyl)-4-[2-(trifluoromethyl)-3-pyridyl]-7H-pyrrolo[2,3-d]pyrimidine	357.1
P-0375		N-[2-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]phenyl]methanesulfonamide	383.2
P-0376		3-fluoro-4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]benzenesulfonamide	386.8
P-0377		N-[4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]cyclopropanesulfonamide	329.1
P-0378		N-[3-[2-tert-butyl-5-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)thiazol-4-yl]-2-fluoro-phenyl]pyrrolidine-1-sulfonamide	515.1
P-0379		N-[4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]methanesulfonamide	302.8
P-0380		N-cyclopropyl-4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)benzenesulfonamide	328.8
P-0381		N-[3-fluoro-4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]phenyl]ethanesulfonamide	414.8

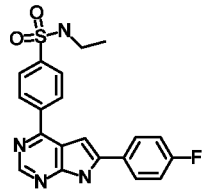
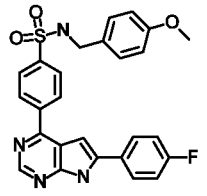
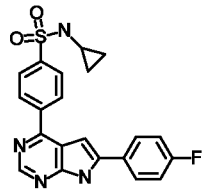
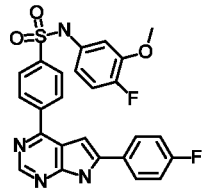
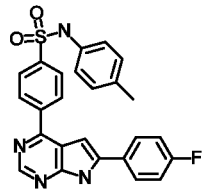
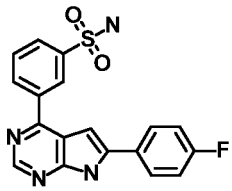
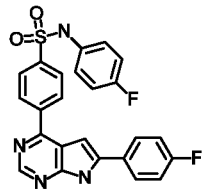
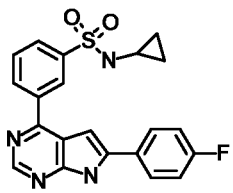
No	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0382		N-[3-fluoro-4-[4-[2-fluoro-4-(methanesulfonamido)phenyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]phenyl]methanesulfonamide	494.0
P-0383		N-[3-[6-(2-cyclopropylpyrimidin-5-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]phenyl]cyclopropanesulfonamide	432.9
P-0384		4,6-bis(2-cyclopropylpyrimidin-5-yl)-7H-pyrrolo[2,3-d]pyrimidine	355.9
P-0385		4-[6-(2-cyclopropylpyrimidin-5-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]benzenesulfonamide	392.9
P-0386		N-cyclopropyl-4-[6-(2-cyclopropylpyrimidin-5-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]benzenesulfonamide	432.9
P-0387		N-[4-[4-[4-(cyclopropylsulfonylamino)-2-fluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]-3-fluoro-phenyl]cyclopropanesulfonamide	545.9
P-0388		N-[4-[4-[4-(butylsulfonylamino)phenyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]phenyl]butane-1-sulfonamide	542.0
P-0389		N-[4-[4-[4-(cyclopropylsulfonylamino)phenyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]phenyl]cyclopropanesulfonamide	509.9

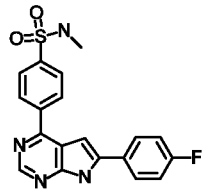
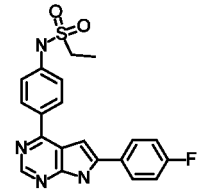
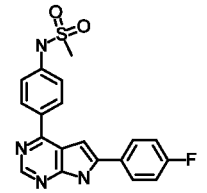
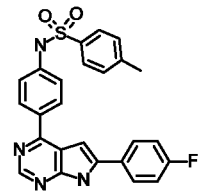
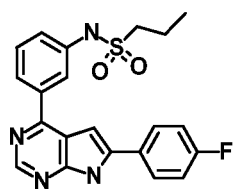
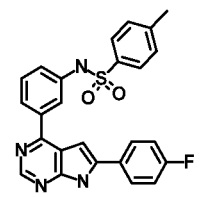
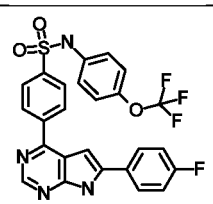
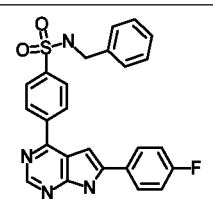
No	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0390		4-methyl-N-[4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]benzenesulfonamide	379.3
P-0391		6-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-7H-pyrrolo[2,3-d]pyrimidine	367.8
P-0392		6-(4-fluorophenyl)-4-(4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine	290.8
P-0393		4,6-bis(6-methoxy-3-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine	333.8
P-0394		6-(4-fluorophenyl)-4-(6-methoxy-3-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine	320.8
P-0395		4,6-bis(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidine	308.0
P-0396		4-chloro-N-[3-fluoro-4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]phenyl]benzenesulfonamide	496.8
P-0397		N-[3-fluoro-4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]phenyl]propane-1-sulfonamide	428.9

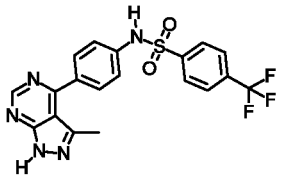
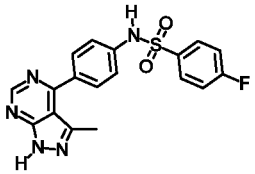
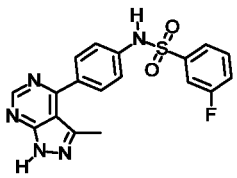
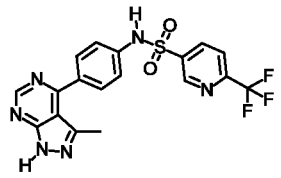
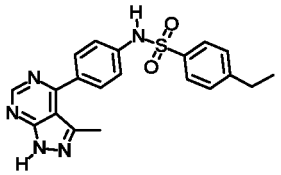
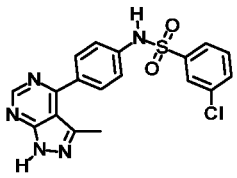
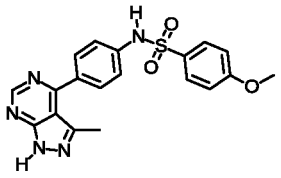
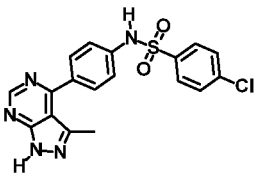
No	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0398		N-[3-fluoro-4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]phenyl]methanesulfonamide	400.8
P-0399		N-[2-fluoro-4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]phenyl]methanesulfonamide	400.8
P-0400		N-[3-fluoro-4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]phenyl]pyrrolidine-1-sulfonamide	456.2
P-0401		N-[3-fluoro-4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]phenyl]cyclopropanesulfonamide	426.8
P-0402		N-[3-fluoro-4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]phenyl]-4-methoxy-benzenesulfonamide	493.0
P-0403		N-[2-fluoro-4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]phenyl]propane-1-sulfonamide	428.9
P-0404		4-fluoro-N-[4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]phenyl]benzenesulfonamide	463.2
P-0405		N-[2-fluoro-4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]phenyl]pyrrolidine-1-sulfonamide	455.9

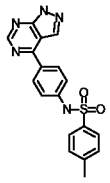
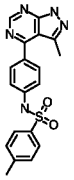
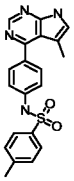
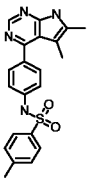
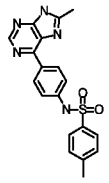
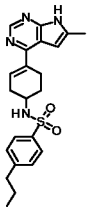
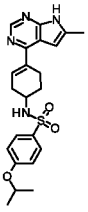
No	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0406		4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-3-methyl-N-propyl-benzenesulfonamide	424.9
P-0407		N-[3-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]phenyl]ethanesulfonamide	397.0
P-0408		4-fluoro-N-[2-fluoro-4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]phenyl]benzenesulfonamide	480.9
P-0409		N-[2-fluoro-4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]phenyl]-4-methoxy-benzenesulfonamide	493.0
P-0410		N-[2-fluoro-4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]phenyl]cyclopropanesulfonamide	426.9
P-0411		N-[4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]phenyl]pyrrolidine-1-sulfonamide	438.1
P-0412		N-[3-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]phenyl]acetamide	347.2
P-0413		N-[3-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]phenyl]cyclopropanesulfonamide	409.2

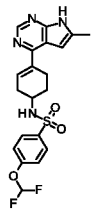
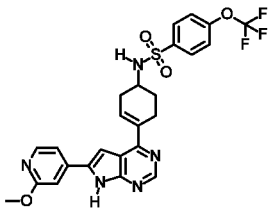
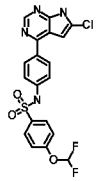
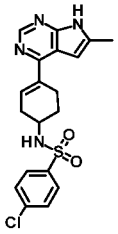
No	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0414		N-[3-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]phenyl]methanesulfonamide	383.2
P-0415		5-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[[6-(trifluoromethyl)-3-pyridyl]methyl]pyridin-2-amine	465.0
P-0416		4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]aniline	304.8
P-0417		N-ethyl-5-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]pyridin-2-amine	333.8
P-0418		4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]benzenesulfonamide	369.0
P-0419		N-[4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]phenyl]butane-1-sulfonamide	425.2
P-0420		N-[4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]phenyl]cyclopropanesulfonamide	409.1
P-0421		N-butyl-4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]benzenesulfonamide	425.2

No	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0422		N-ethyl-4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]benzenesulfonamide	397.1
P-0423		4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[(4-methoxyphenyl)methyl]benzenesulfonamide	489.2
P-0424		N-cyclopropyl-4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]benzenesulfonamide	409.1
P-0425		N-(4-fluoro-3-methoxy-phenyl)-4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]benzenesulfonamide	493.2
P-0426		4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-(p-tolyl)benzenesulfonamide	459.2
P-0427		3-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]benzenesulfonamide	368.9
P-0428		N-(4-fluorophenyl)-4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]benzenesulfonamide	463.0
P-0429		N-cyclopropyl-3-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]benzenesulfonamide	408.9

No	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0430		4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-methyl-benzenesulfonamide	382.8
P-0431		N-[4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]phenyl]ethanesulfonamide	397.0
P-0432		N-[4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]phenyl]methanesulfonamide	383.1
P-0433		N-[4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]phenyl]-4-methyl-benzenesulfonamide	458.9
P-0434		N-[3-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]phenyl]propane-1-sulfonamide	411.1
P-0435		N-[3-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]phenyl]-4-methyl-benzenesulfonamide	458.9
P-0436		4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[4-(trifluoromethoxy)phenyl]benzenesulfonamide	529.1
P-0437		N-benzyl-4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]benzenesulfonamide	459.0

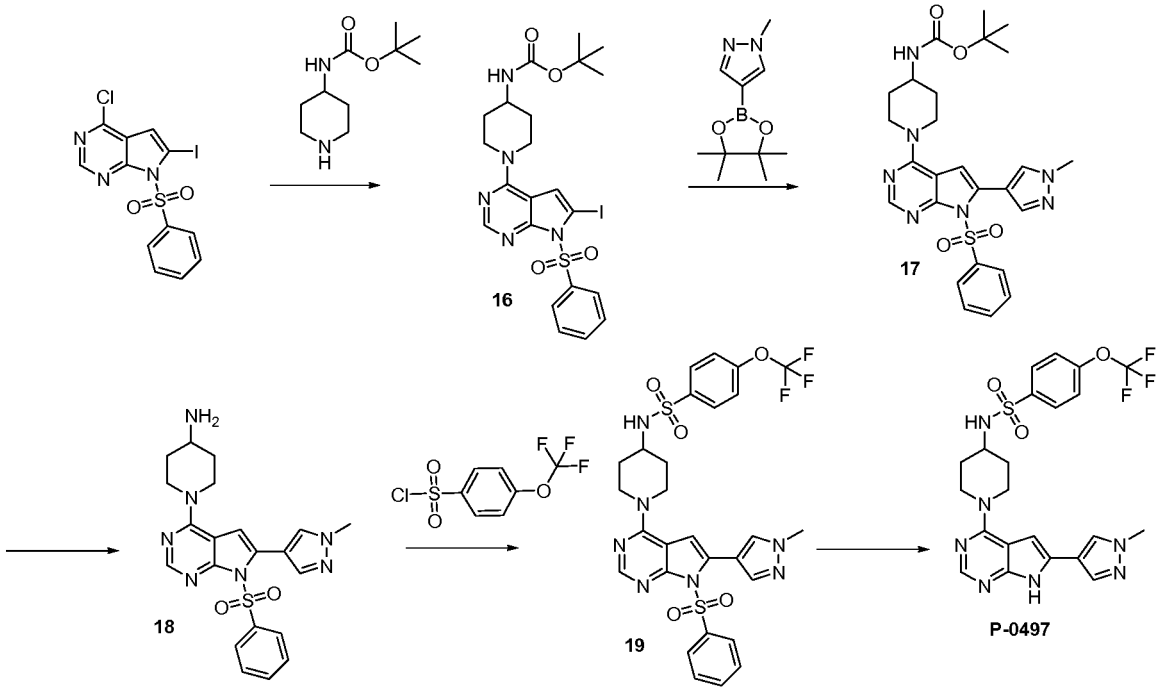
No	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0438		N-[4-(3-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)phenyl]-4-(trifluoromethyl)benzenesulfonamide	433.8
P-0439		4-fluoro-N-[4-(3-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)phenyl]benzenesulfonamide	384.1
P-0440		3-fluoro-N-[4-(3-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)phenyl]benzenesulfonamide	384.1
P-0441		N-[4-(3-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)phenyl]-6-(trifluoromethyl)pyridine-3-sulfonamide	435.2
P-0442		4-ethyl-N-[4-(3-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)phenyl]benzenesulfonamide	394.4
P-0443		3-chloro-N-[4-(3-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)phenyl]benzenesulfonamide	400.1
P-0444		4-methoxy-N-[4-(3-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)phenyl]benzenesulfonamide	396.2
P-0445		4-chloro-N-[4-(3-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)phenyl]benzenesulfonamide	400.0

No	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0446		4-methyl-N-[4-(1H-pyrazolo[3,4-d]pyrimidin-4-yl)phenyl]benzenesulfonamide	366.0
P-0447		4-methyl-N-[4-(3-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)phenyl]benzenesulfonamide	380.2
P-0448		4-methyl-N-[4-(5-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]benzenesulfonamide	379.4
P-0449		N-[4-(5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]-4-methyl-benzenesulfonamide	393.3
P-0450		4-methyl-N-[4-(8-methyl-9H-purin-6-yl)phenyl]benzenesulfonamide	380.2
P-0651		N-[4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)cyclohex-3-en-1-yl]-4-propyl-benzenesulfonamide	411.3
P-0652		4-isopropoxy-N-[4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)cyclohex-3-en-1-yl]benzenesulfonamide	427.35

No	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0653		4-(difluoromethoxy)-N-[4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)cyclohex-3-en-1-yl]benzenesulfonamide	435.5
P-0654		N-[4-[6-(2-methoxy-4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]cyclohex-3-en-1-yl]-4-(trifluoromethoxy)benzenesulfonamide	546.1
P-0655		N-[4-(6-chloro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]-4-(difluoromethoxy)benzenesulfonamide	451.1
P-0729		4-chloro-N-[4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)cyclohex-3-en-1-yl]benzenesulfonamide	403.2

Example 7: Preparation of N-[1-[6-(1-methylpyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]-4-(trifluoromethoxy)benzenesulfonamide (P-0497).

Scheme 7.



[0295] Step 1 – Synthesis of [1-(7-Benzenesulfonyl-6-iodo-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-piperidin-4-yl]-carbamic acid tert-butyl ester (16): To a solution of 7-(benzenesulfonyl)-4-chloro-6-iodo-pyrrolo[2,3-d]pyrimidine (1 eq., 0.05 g, 0.119 mmol) in acetonitrile (100 eq., 2 mL) was added tert-butyl N-(4-piperidyl)carbamate (2 eq., 0.036 g, 0.178 mmol) and the mixture was stirred at 100°C for 40 minutes. The solution was then concentrated under reduced pressure to give compound 1 (0.060 g, 84% yield).

[0296] Step 2: Synthesis of {1-[7-Benzenesulfonyl-6-(1-methyl-1H-pyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-piperidin-4-yl}-carbamic acid tert-butyl ester (17): Compound **16** (1 eq., 1.0 g, 1.714 mmol) was taken up in acetonitrile (80 eq., 7.235 mL) and 1M potassium carbonate (5 eq., 8.57 mL). To this solution was added [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.05 eq., 0.06 g, 0.09 mmol), and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (2 eq., 0.72 g, 3.43 mmol). The reaction mixture was heated to 90 °C for 40 minutes in a microwave reactor. Upon completion, the mixture was diluted with water and extracted with ethyl acetate (3 X 100 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give compound 2 (1.5 g, 72% yield).

[0297] Step 3 – Synthesis of 1-[7-Benzenesulfonyl-6-(1-methyl-1H-pyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-piperidin-4-ylamine (18): Compound **17** (0.4 g, 0.744 mmol) was taken up in dichloromethane (5 mL) and cooled to 0°C. Trifluoroacetic acid (5 eq., 4.0 mmol, 0.285 mL) was added

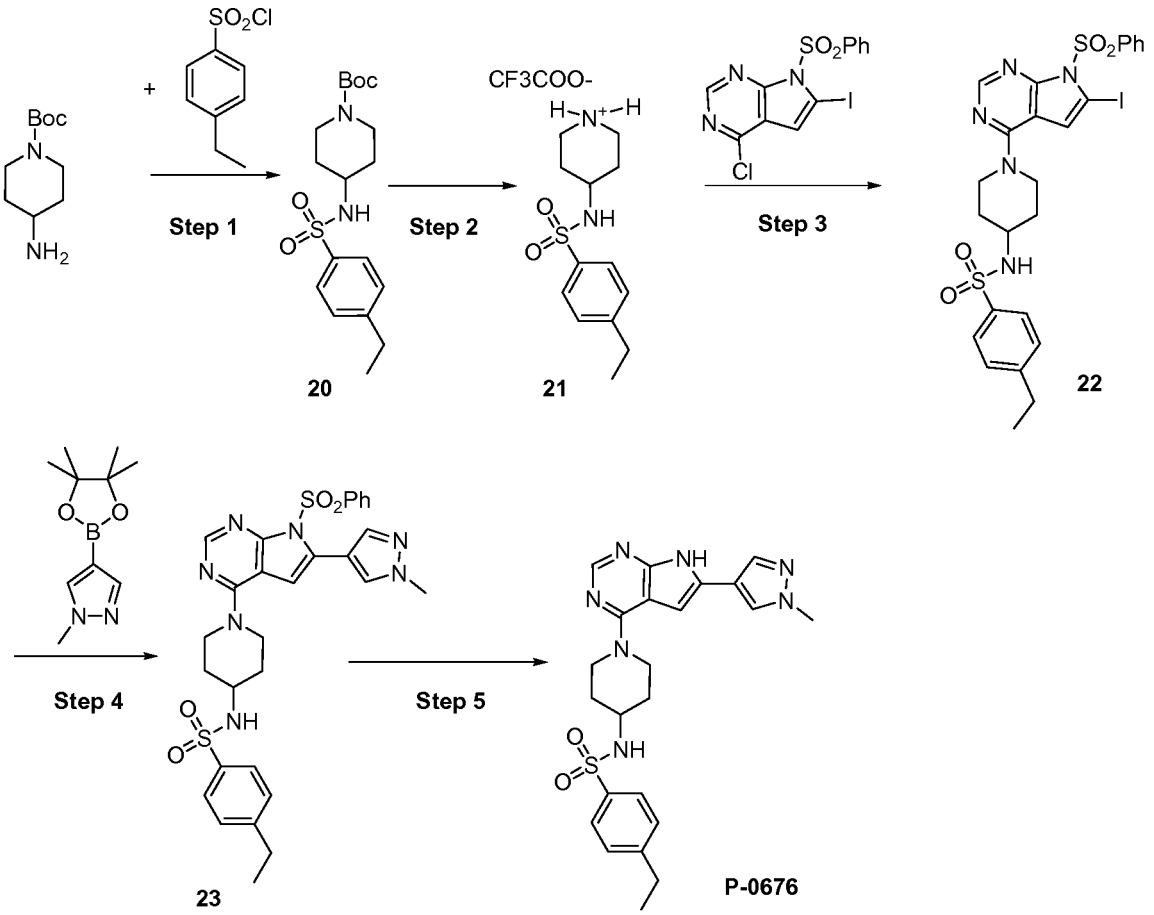
and the solution was stirred for 1 hour. The reaction was extracted with 1M sodium bicarbonate. The organic layer was dried over magnesium sulfate, filtered and the solution was then concentrated under reduced pressure and washed with diethyl ether (5 mL). The resulting solid was frozen then lyophilized overnight affording compound **18** (0.315 g, 96% yield).

[0298] Step 4 – Synthesis of compound N-{1-[7-Benzenesulfonyl-6-(1-methyl-1H-pyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-piperidin-4-yl}-4-trifluoromethoxy-benzenesulfonamide (19): Compound **18** (0.1 g, 0.229 mmol) was taken up in tetrahydrofuran (80 eq., 1.483mL) and cooled to 0 °C. Once completely dissolved, sodium hydride (1.5 eq., 0.008 mg) was added and the solution was stirred for 5 minutes before the addition of 4-(trifluoromethoxy)benzenesulfonyl chloride (3 eq., 0.117 mL). After 2 hours the solution was diluted with water and extracted with ethyl acetate (3 x 100 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give compound **19** (0.126 g, 83.4% yield).

[0299] Step 5 – Synthesis of N-[1-[6-(1-methylpyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]-4-(trifluoromethoxy)benzenesulfonamide (P-0497) :Compound **19** (0.028g, 0.0423 mmol) was taken up in methanol (80 eq., 3.0 mmol, 0.136 mL) and treated with 1M potassium hydroxide in water (20 eq., 0.846 mmol, 0.846 mL). The solution was stirred at 50 °C for 30 minutes. Upon completion, the solution was diluted with water and extracted with ethyl acetate (3 X 100 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, filtered, and then concentrated under reduced pressure. The resulting solid purified by silica gel column chromatography eluting with a gradient of 2-15% MeOH in dichloromethane over 30 minutes (Agilent FPS, 8g column) resulting in N-[1-[6-(1-methylpyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]-4-(trifluoromethoxy)benzenesulfonamide **(P-0497)** (0.013g, 56% yield). The structure was confirmed by ^1H NMR spectroscopy. LC-MS (ESI) $[M+H^+]^+ = 521.9$.

Example 8: Preparation of 4-Ethyl-N-[1-[6-(1-methylpyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]benzenesulfonamide (P-0676).

Scheme 8.



[0300] Step 1 – Synthesis of tert-butyl 4-[(4-ethylphenyl)sulfonylamino]piperidine-1-carboxylate (20): To a mixture of tert-butyl 4-aminopiperidine-1-carboxylate (300.42 mg, 1.5 mmol, 1 eq) and triethylamine (0.418 mL, 3.0 mmol, 1.5 eq) in 15 mL of THF was added 4-ethylbenzenesulfonyl chloride (337.71 mg, 1.65 mmol, 1.1 eq). The mixture was stirred at room temperature for 2 hrs. The reaction mixture was quenched with H_2O and extracted with ethyl acetate. The organic phase was washed with H_2O, brine, dried with Na_2SO_4 and concentrated under reduced pressure to provide tert-butyl 4-[(4-ethylphenyl) sulfonylamino]piperidine-1-carboxylate **(20)** (552 mg, 99.9% yield) as a brittle foam which was used for the next step without purification. LC-MS (ESI) $[M+H^+]^+ = 313.15$.

[0301] Step 2- Synthesis of 4-ethyl-N-(4-piperidyl) benzenesulfonamide-2,2,2-trifluoroacetic acid (21): A mixture of **(20)** (552 mg, 1.5 mmol) in 25% trifluoro acetic acid (TFA)/dichloromethane (3 ml) was stirred at room temperature for 1 hr. The solvent and excess TFA was removed under reduced pressure to provide 4-ethyl-N-(4-piperidyl) benzenesulfonamide-2,2,2-trifluoroacetic acid **(21)** (570 mg, 99.5% yield) as a semi-solid which was used for the next step without purification. LC-MS (ESI)

$[M+H^+]^+ = 269.1$.

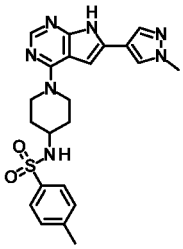
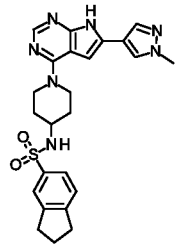
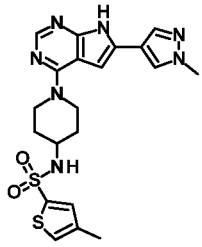
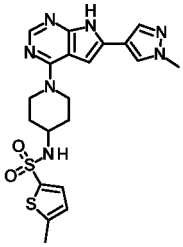
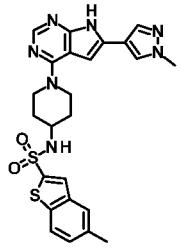
[0302] Step 3 – Synthesis of N-[1-[7-(benzenesulfonyl)-6-iodo-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]-4-ethylbenzenesulfonamide (22): To a mixture of **(21)** (382.4 mg, 1 mmol, 1 eq) and triethylamine (0.56 ml, 4 mmol, 4 eq) in MeCN (10 ml) was added 7-(benzenesulfonyl)-4-chloro-6-iodo-pyrrolo[2,3-d]pyrimidine (419.63 mg, 1 mmol, 1 eq). The mixture was heated at 100 °C for 30 minutes. The reaction mixture was quenched with H_2O and extracted with ethyl acetate. The organic phase was washed with H_2O, brine, dried with Na_2SO_4 and concentrated under reduced pressure. The sample was purified by flash chromatography eluting with 50-80% ethyl acetate in hexane to provide of N-[1-[7-(benzenesulfonyl)-6-iodo-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]-4-ethylbenzenesulfonamide **(22)** (329.7 mg, 50.6% yield) as a white solid. LC-MS (ESI) $[M+H^+]^+ = 652.20$.

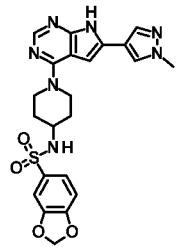
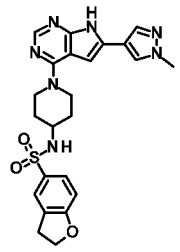
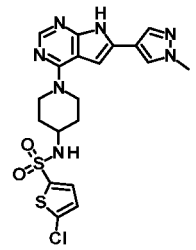
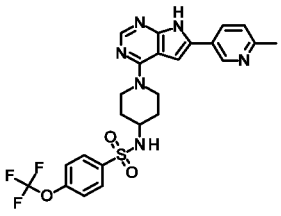
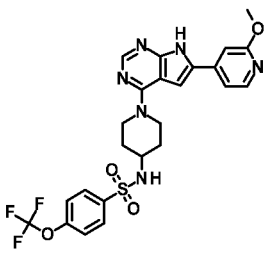
[0303] Step 4 – Synthesis of N-[1-[7-(benzenesulfonyl)-6-(1-methylpyrazol-4-yl)pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]-4-ethyl-benzenesulfonamide (23): A mixture of **(22)** (156.37 mg, 0.24 mmol, 1 eq), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (74.9 mg, 0.36 mmol, 1.5 eq), [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II) (17.56 mg, 0.02 mmol, 0.1 eq) in acetonitrile (2.5 ml) was purged with nitrogen gas then added 0.288 mL of 2.5M aqueous K_2CO_3(3 eq. The resulting mixture was cooled and filtered through a pad of celite. The filtrate was dried over Na_2SO_4, collected and concentrated. The obtained residue was purified by flash chromatography eluting with 80% ethyl acetate in hexane to provide N-[1-[7-(benzenesulfonyl)-6-(1-methylpyrazol-4-yl)pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]-4-ethyl-benzenesulfonamide **(23)** (68.3 mg, 47% yield) as an off-white solid. LC-MS (ESI) $[M+H^+]^+ = 606.40$.

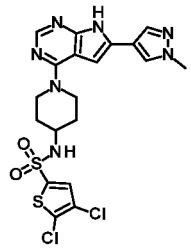
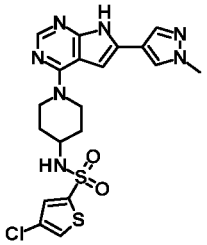
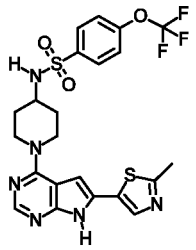
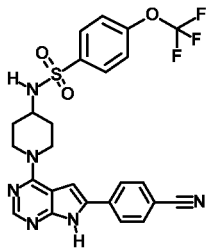
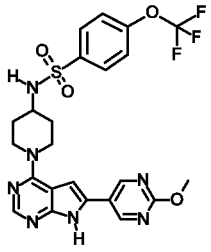
[0304] Step 5 – Synthesis of 4-ethyl-N-[1-[6-(1-methylpyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl] benzenesulfonamide (P-0676) : To a solution of compound **(23)** (68.3 mg, 0.11 mmol, 1 eq) in 2.0 mL of (1:1) THF/MeOH was added 0.450 mL of 1M aqueous KOH (4 eq) heated at 50 °C for 1 hr. The reaction mixture was concentrated under reduced pressure and purified by flash chromatography eluting with 5% MeOH in DCM. The purified sample was triturated with DCM to afford 4-ethyl-N-[1-[6-(1-methylpyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl] benzenesulfonamide **(P-0676)** (13.4 mg, 24.2% yield) as a white solid. The structure was confirmed by ^1H NMR spectroscopy. LC-MS (ESI) $[M+H^+]^+ = 466.55$.

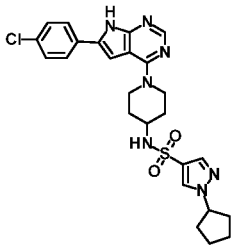
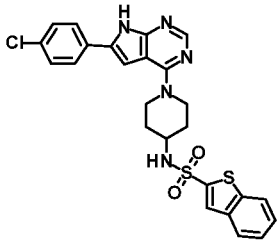
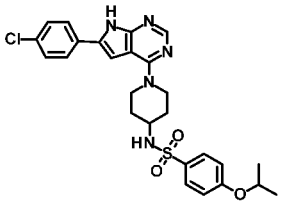
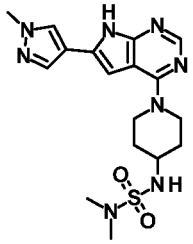
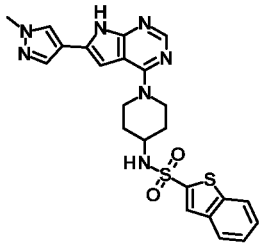
[0305] Compounds listed in Table 4 below, e.g., compounds P-0451 to P-0545, P-0656 to P-0676 and P-0726 to P-0728 and P-0730 were prepared according to the protocols set forth in Examples 7 and 8 and Schemes 7 and 8. The structures of the compounds in Table 4 were confirmed by ^1H NMR and mass spectroscopy.

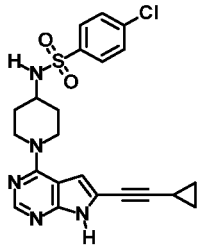
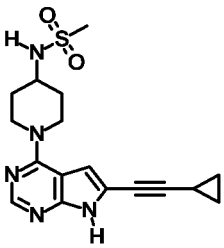
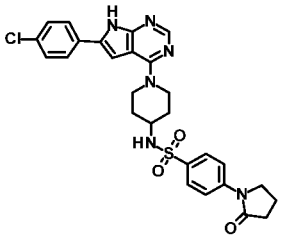
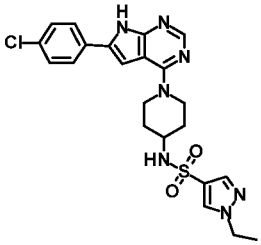
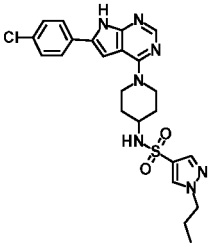
TABLE 4

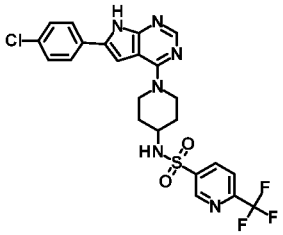
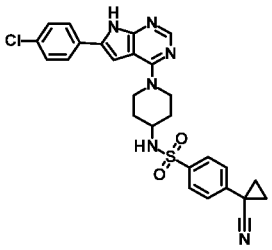
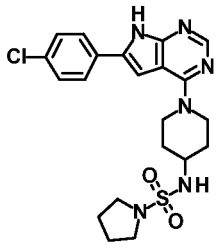
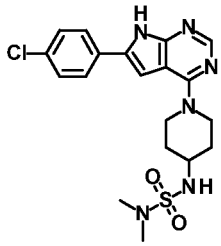
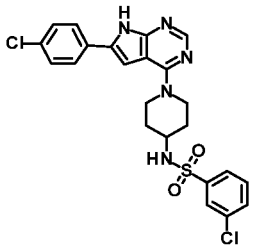
No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0451		4-methyl-N-[1-[6-(1-methylpyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]benzenesulfonamide	452.3
P-0452		N-[1-[6-(1-methylpyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]indane-5-sulfonamide	478.3
P-0453		4-methyl-N-[1-[6-(1-methylpyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]thiophene-2-sulfonamide	458.3
P-0454		5-methyl-N-[1-[6-(1-methylpyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]thiophene-2-sulfonamide	458.3
P-0455		5-methyl-N-[1-[6-(1-methylpyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]benzothiophene-2-sulfonamide	508.3

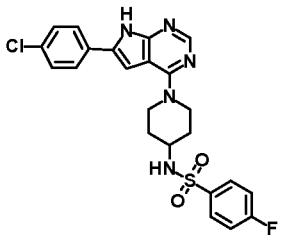
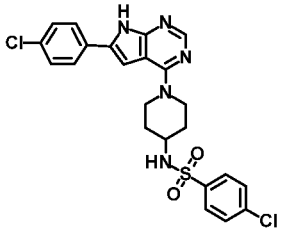
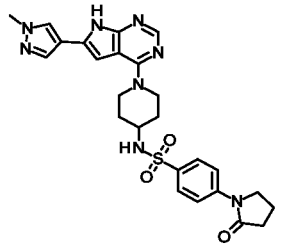
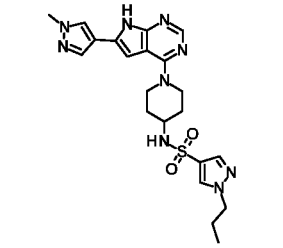
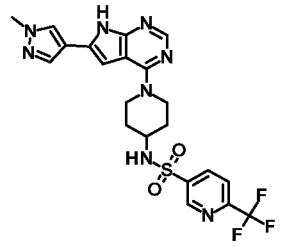
No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0456		N-[1-[6-(1-methylpyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]-1,3-benzodioxole-5-sulfonamide	482.6
P-0457		N-[1-[6-(1-methylpyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]-2,3-dihydrobenzofuran-5-sulfonamide	480.0
P-0458		5-chloro-N-[1-[6-(1-methylpyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]thiophene-2-sulfonamide	478.9
P-0459		N-[1-[6-(6-methyl-3-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]-4-(trifluoromethoxy)benzenesulfonamide	533.2
P-0460		N-[1-[6-(2-methoxy-4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]-4-(trifluoromethoxy)benzenesulfonamide	549.4

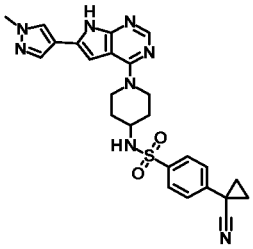
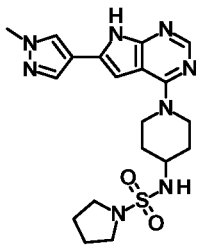
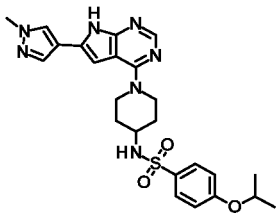
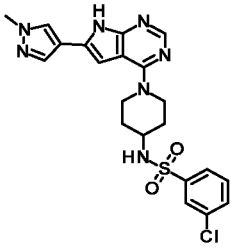
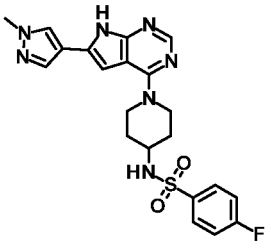
No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0461		4,5-dichloro-N-[1-[6-(1-methylpyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]thiophene-2-sulfonamide	511.8
P-0462		4-chloro-N-[1-[6-(1-methylpyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]thiophene-2-sulfonamide	477.9
P-0463		N-[1-[6-(2-methylthiazol-5-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]-4-(trifluoromethoxy)benzenesulfonamide	539.6
P-0464		N-[1-[6-(4-cyanophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]-4-(trifluoromethoxy)benzenesulfonamide	543.0
P-0465		N-[1-[6-(2-methoxypyrimidin-5-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]-4-(trifluoromethoxy)benzenesulfonamide	550.0

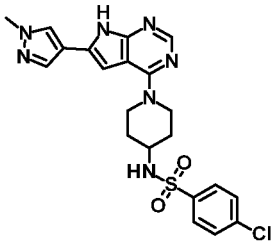
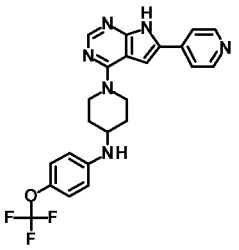
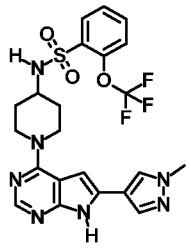
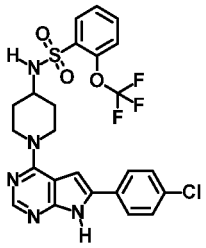
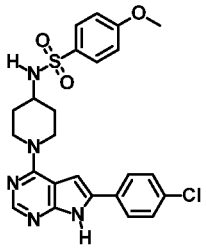
No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0466		N-[1-[6-(4-chlorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]-1-cyclopentyl-pyrazole-4-sulfonamide	526.3
P-0467		N-[1-[6-(4-chlorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]benzothiophene-2-sulfonamide	524.5
P-0468		N-[1-[6-(4-chlorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]-4-isopropoxy-benzenesulfonamide	526.3
P-0469		4-[4-(dimethylsulfamoylamino)-1-piperidyl]-6-(1-methylpyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidine	405.4
P-0470		N-[1-[6-(1-methylpyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]benzothiophene-2-sulfonamide	494.2

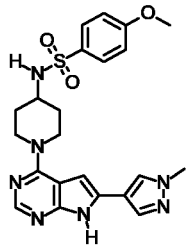
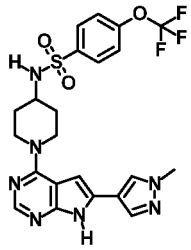
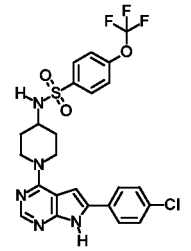
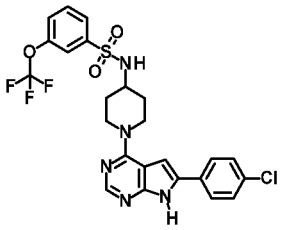
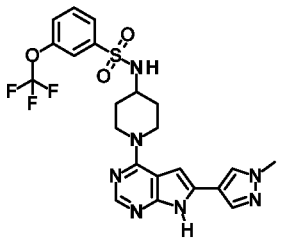
No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0471		4-chloro-N-[1-[6-(2-cyclopropylethynyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]benzenesulfonamide	456.15
P-0472		N-[1-[6-(2-cyclopropylethynyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]methanesulfonamide	359.9
P-0473		N-[1-[6-(4-chlorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]-4-(2-oxopyrrolidin-1-yl)benzenesulfonamide	551.5
P-0474		N-[1-[6-(4-chlorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]-1-ethyl-pyrazole-4-sulfonamide	486.4
P-0475		N-[1-[6-(4-chlorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]-1-propyl-pyrazole-4-sulfonamide	500.2

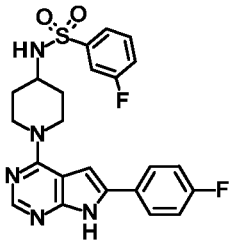
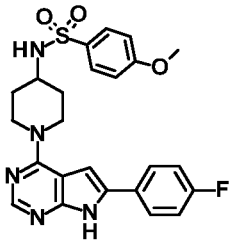
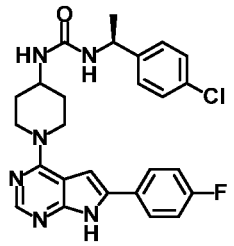
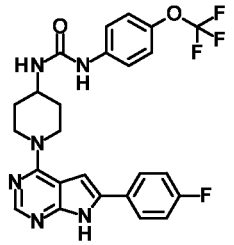
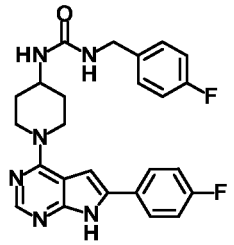
No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0476		N-[1-[6-(4-chlorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]-6-(trifluoromethyl)pyridine-3-sulfonamide	537.4
P-0477		N-[1-[6-(4-chlorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]-4-(1-cyanocyclopropyl)benzenesulfonamide	533.2
P-0478		N-[1-[6-(4-chlorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]pyrrolidine-1-sulfonamide	461.5
P-0479		6-(4-chlorophenyl)-4-[4-(dimethylsulfamoylamino)-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	435.1
P-0480		3-chloro-N-[1-[6-(4-chlorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]benzenesulfonamide	502.3

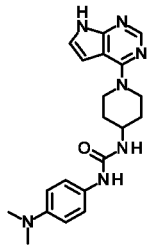
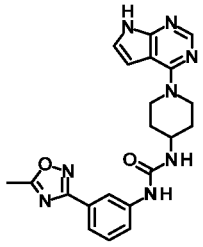
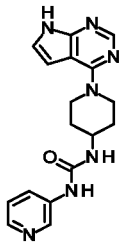
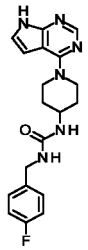
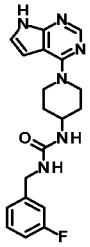
No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0481		N-[1-[6-(4-chlorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]-4-fluoro-benzenesulfonamide	486.4
P-0482		4-chloro-N-[1-[6-(4-chlorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]benzenesulfonamide	502.3
P-0483		N-[1-[6-(1-methylpyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]-4-(2-oxopyrrolidin-1-yl)benzenesulfonamide	521.5
P-0484		N-[1-[6-(1-methylpyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]-1-propyl-pyrazole-4-sulfonamide	470.5
P-0485		N-[1-[6-(1-methylpyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]-6-(trifluoromethyl)pyridine-3-sulfonamide	507.4

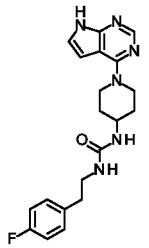
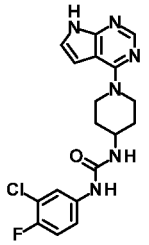
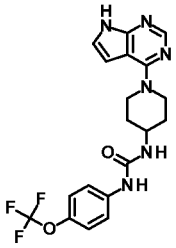
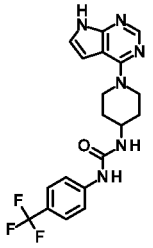
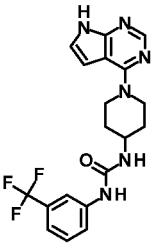
No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0486		4-(1-cyanocyclopropyl)-N-[1-[6-(1-methylpyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]benzenesulfonamide	503.2
P-0487		N-[1-[6-(1-methylpyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]pyrrolidine-1-sulfonamide	431.2
P-0488		4-isopropoxy-N-[1-[6-(1-methylpyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]benzenesulfonamide	496.6
P-0489		3-chloro-N-[1-[6-(1-methylpyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]benzenesulfonamide	472.3
P-0490		4-fluoro-N-[1-[6-(1-methylpyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]benzenesulfonamide	456.4

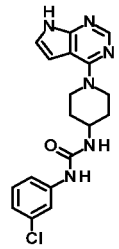
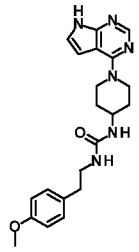
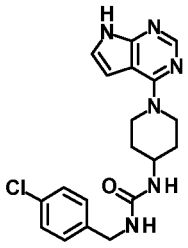
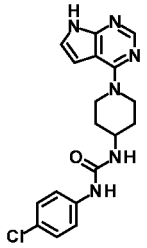
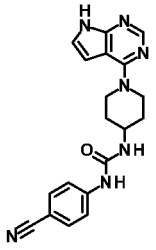
No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0491		4-chloro-N-[1-[6-(1-methylpyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]benzenesulfonamide	472.3
P-0492		1-[6-(4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[4-(trifluoromethoxy)phenyl]piperidin-4-amine	455.5
P-0493		N-[1-[6-(1-methylpyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]-2-(trifluoromethoxy)benzenesulfonamide	522.15
P-0494		N-[1-[6-(4-chlorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]-2-(trifluoromethoxy)benzenesulfonamide	551.9
P-0495		N-[1-[6-(4-chlorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]-4-methoxy-benzenesulfonamide	497.9

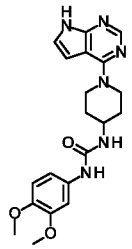
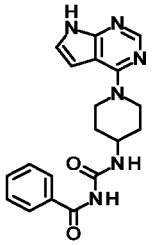
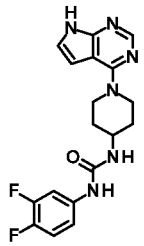
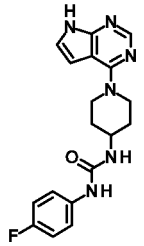
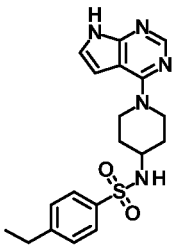
No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0496		4-methoxy-N-[1-[6-(1-methylpyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]benzenesulfonamide	467.95
P-0497		N-[1-[6-(1-methylpyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]-4-(trifluoromethoxy)benzenesulfonamide	521.9
P-0498		N-[1-[6-(4-chlorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]-4-(trifluoromethoxy)benzenesulfonamide	551.85
P-0499		N-[1-[6-(4-chlorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]-3-(trifluoromethoxy)benzenesulfonamide	551.85
P-0500		N-[1-[6-(1-methylpyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]-3-(trifluoromethoxy)benzenesulfonamide	521.2

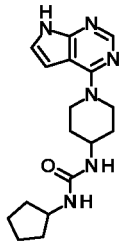
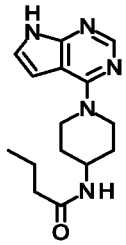
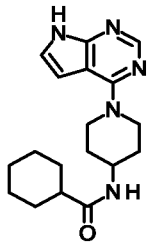
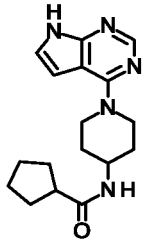
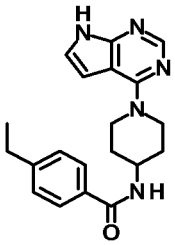
No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0501		3-fluoro-N-[1-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]benzenesulfonamide	470.2
P-0502		N-[1-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]-4-methoxy-benzenesulfonamide	482.2
P-0503		1-[(1S)-1-(4-chlorophenyl)ethyl]-3-[1-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]urea	493.05
P-0504		1-[1-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]-3-[4-(trifluoromethoxy)phenyl]urea	515
P-0505		1-[(4-fluorophenyl)methyl]-3-[1-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]urea	463.1

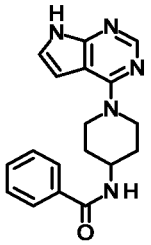
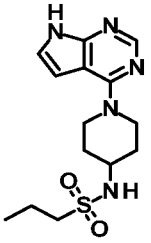
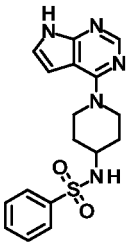
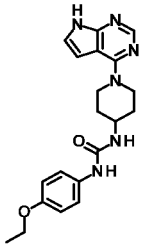
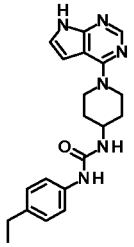
No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0506		1-(4-dimethylaminophenyl)-3-[1-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-piperidyl]urea	380.5
P-0507		1-[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-3-[1-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-piperidyl]urea	419.2
P-0508		1-(3-pyridyl)-3-[1-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-piperidyl]urea	338.2
P-0509		1-[(4-fluorophenyl)methyl]-3-[1-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-piperidyl]urea	369.4
P-0510		1-[(3-fluorophenyl)methyl]-3-[1-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-piperidyl]urea	369.4

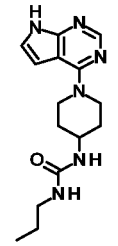
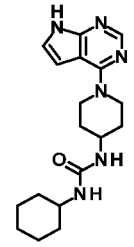
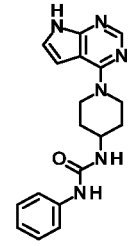
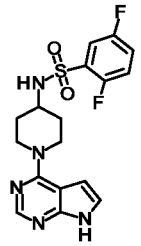
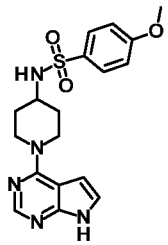
No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0511		1-[2-(4-fluorophenyl)ethyl]-3-[1-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-piperidyl]urea	383.5
P-0512		1-(3-chloro-4-fluoro-phenyl)-3-[1-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-piperidyl]urea	389.2
P-0513		1-[1-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-piperidyl]-3-[4-(trifluoromethoxy)phenyl]urea	421.3
P-0514		1-[1-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-piperidyl]-3-[4-(trifluoromethyl)phenyl]urea	405.4
P-0515		1-[1-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-piperidyl]-3-[3-(trifluoromethyl)phenyl]urea	405.4

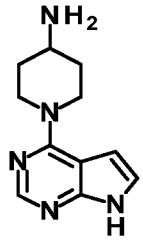
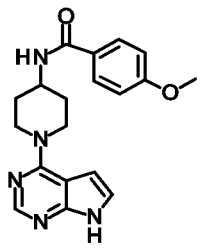
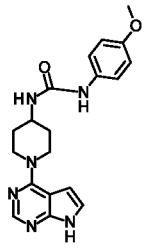
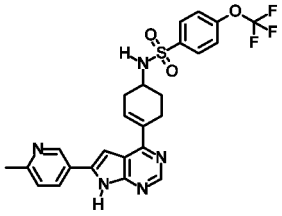
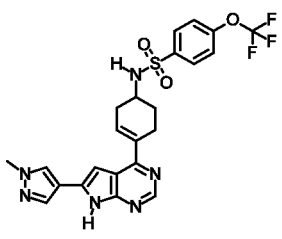
No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0516		1-(3-chlorophenyl)-3-[1-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-piperidyl]urea	371.2
P-0517		1-[2-(4-methoxyphenyl)ethyl]-3-[1-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-piperidyl]urea	395.2
P-0518		1-[(4-chlorophenyl)methyl]-3-[1-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-piperidyl]urea	385.3
P-0519		1-(4-chlorophenyl)-3-[1-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-piperidyl]urea	371.2
P-0520		1-(4-cyanophenyl)-3-[1-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-piperidyl]urea	362.5

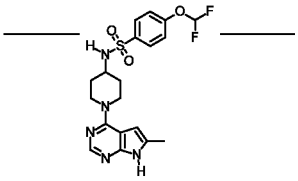
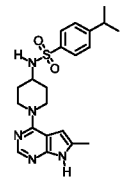
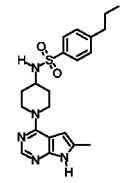
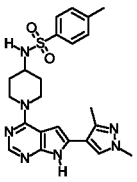
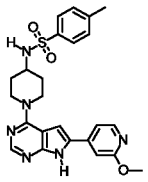
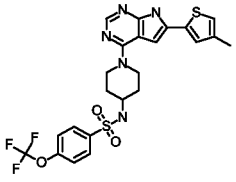
No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0521		1-(3,4-dimethoxyphenyl)-3-[1-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-piperidyl]urea	397.3
P-0522		N-[[1-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-piperidyl]carbamoyl]benzamide	365.2
P-0523		1-(3,4-difluorophenyl)-3-[1-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-piperidyl]urea	373.3
P-0524		1-(4-fluorophenyl)-3-[1-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-piperidyl]urea	355.3
P-0525		4-ethyl-N-[1-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-piperidyl]benzenesulfonamide	386.2

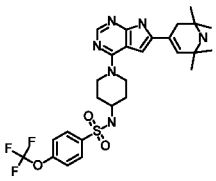
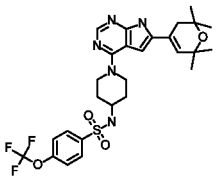
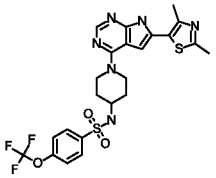
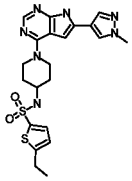
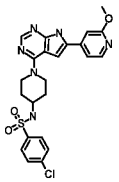
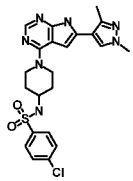
No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0526		1-cyclopentyl-3-[1-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-piperidyl]urea	329.5
P-0527		N-[1-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-piperidyl]butanamide	288.1
P-0528		N-[1-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-piperidyl]cyclohexanecarboxamide	328.6
P-0529		N-[1-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-piperidyl]cyclopentanecarboxamide	314.2
P-0530		4-ethyl-N-[1-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-piperidyl]benzamide	350.5

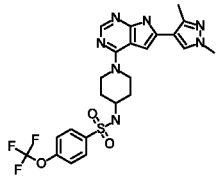
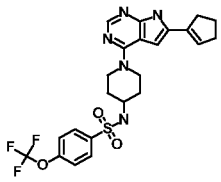
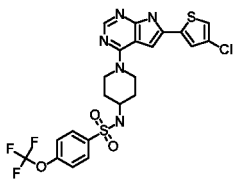
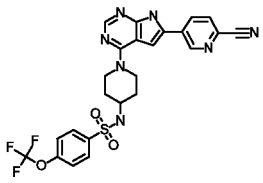
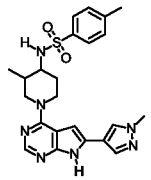
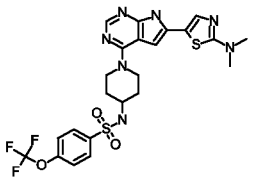
No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0531		N-[1-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-piperidyl]benzamide	322.3
P-0532		N-[1-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-piperidyl]propane-1-sulfonamide	324.4
P-0533		N-[1-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-piperidyl]benzenesulfonamide	358.3
P-0534		1-(4-ethoxyphenyl)-3-[1-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-piperidyl]urea	381.4
P-0535		1-(4-ethylphenyl)-3-[1-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-piperidyl]urea	365.2

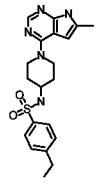
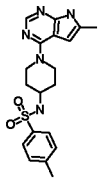
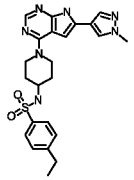
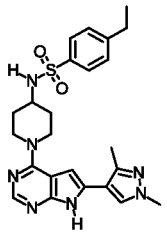
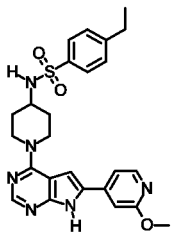
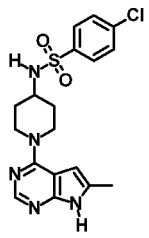
No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0536		1-propyl-3-[1-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-piperidyl]urea	303.4
P-0537		1-cyclohexyl-3-[1-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-piperidyl]urea	343.3
P-0538		1-phenyl-3-[1-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-piperidyl]urea	337.3
P-0539		2,5-difluoro-N-[1-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-piperidyl]benzenesulfonamide	394.2
P-0540		4-methoxy-N-[1-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-piperidyl]benzenesulfonamide	388.3

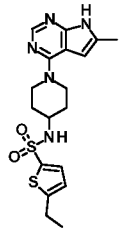
No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0541		1-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperidin-4-amine	218.1
P-0542		4-methoxy-N-[1-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-piperidyl]benzamide	351.9
P-0543		1-(4-methoxyphenyl)-3-[1-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-piperidyl]urea	367.0
P-0544		N-[4-[6-(6-methyl-3-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]cyclohex-3-en-1-yl]-4-(trifluoromethoxy)benzenesulfonamide	530.3
P-0545		N-[4-[6-(1-methylpyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]cyclohex-3-en-1-yl]-4-(trifluoromethoxy)benzenesulfonamide	519.5

No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0656		4-(difluoromethoxy)-N-[1-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-piperidyl]benzenesulfonamide	437.9
P-0657		4-isopropyl-N-[1-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-piperidyl]benzenesulfonamide	414.35
P-0658		N-[1-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-piperidyl]-4-propyl-benzenesulfonamide	414.6
P-0659		N-[1-[6-(1,3-dimethylpyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]-4-methyl-benzenesulfonamide	465.95
P-0660		N-[1-[6-(2-methoxy-4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]-4-methyl-benzenesulfonamide	479.4
P-0661		N-[1-[6-(4-methyl-2-thienyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]-4-(trifluoromethoxy)benzenesulfonamide	538.3

No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0662		N-[1-[6-(2,2,6,6-tetramethyl-1,3-dihydropyridin-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]-4-(trifluoromethoxy)benzenesulfonamide	579.4
P-0663		N-[1-[6-(2,2,6,6-tetramethyl-3H-pyran-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]-4-(trifluoromethoxy)benzenesulfonamide	580.3
P-0664		N-[1-[6-(2,4-dimethylthiazol-5-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]-4-(trifluoromethoxy)benzenesulfonamide	553
P-0665		5-ethyl-N-[1-[6-(1-methylpyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]thiophene-2-sulfonamide	472.15
P-0666		4-chloro-N-[1-[6-(2-methoxy-4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]benzenesulfonamide	497.2
P-0667		4-chloro-N-[1-[6-(1,3-dimethylpyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]benzenesulfonamide	486.15

No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0668		N-[1-[6-(1,3-dimethylpyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]-4-(trifluoromethoxy)benzenesulfonamide	536.2
P-0669		N-[1-[6-(cyclopenten-1-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]-4-(trifluoromethoxy)benzenesulfonamide	508.3
P-0670		N-[1-[6-(4-chloro-2-thienyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]-4-(trifluoromethoxy)benzenesulfonamide	557.8
P-0671		N-[1-[6-(6-cyano-3-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]-4-(trifluoromethoxy)benzenesulfonamide	544.3
P-0672		4-methyl-N-[3-methyl-1-[6-(1-methylpyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]benzenesulfonamide	466.6
P-0673		N-[1-[6-[2-(dimethylamino)thiazol-5-yl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]-4-(trifluoromethoxy)benzenesulfonamide	568.3

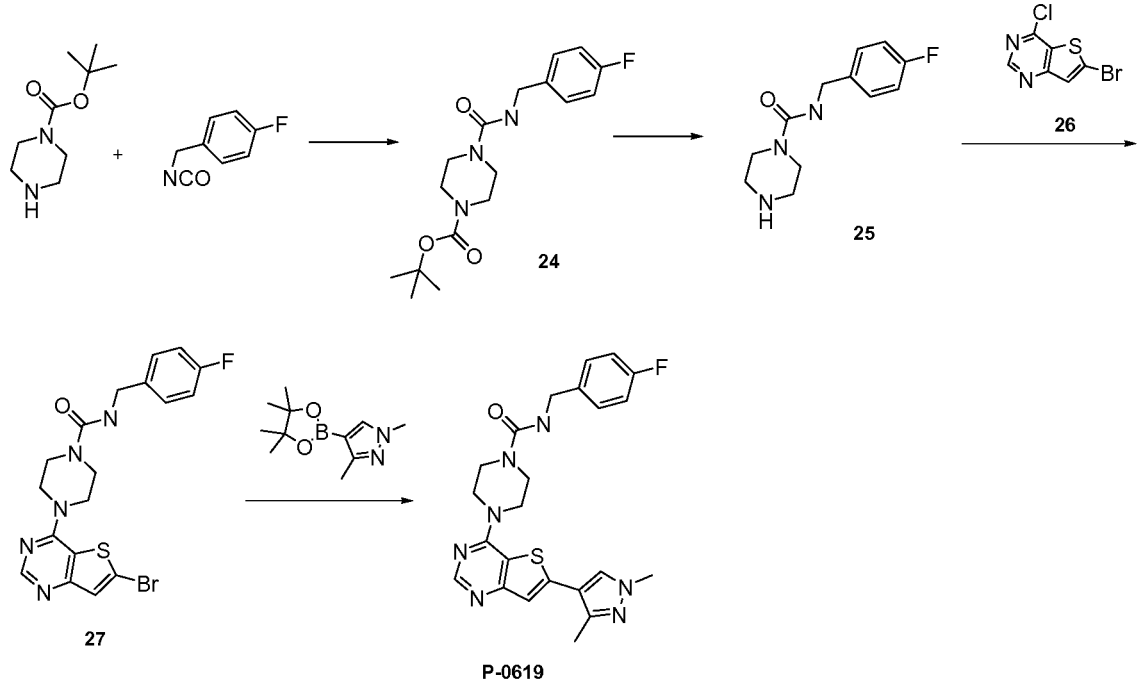
No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0674		4-ethyl-N-[1-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-piperidyl]benzenesulfonamide	400.3
P-0675		4-methyl-N-[1-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-piperidyl]benzenesulfonamide	386.2
P-0676		4-ethyl-N-[1-[6-(1-methylpyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]benzenesulfonamide	466.55
P-0726		N-[1-[6-(1,3-dimethylpyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]-4-ethyl-benzenesulfonamide	480.8
P-0727		4-ethyl-N-[1-[6-(2-methoxy-4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-piperidyl]benzenesulfonamide	493.4
P-0728		4-chloro-N-[1-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-piperidyl]benzenesulfonamide	406.9

No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0730		5-ethyl-N-[1-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-piperidyl]thiophene-2-sulfonamide	406.2

Example 9: **Preparation of 4-[6-(1,3-dimethylpyrazol-4-yl)thieno[3,2-d]pyrimidin-4-yl]-N-[(4-fluorophenyl)methyl]piperazine-1-carboxamide (P-0619).**

[0306] Compound **P-0619** was prepared in four steps from *tert*-butyl piperazine-1-carboxylate and 1-fluoro-4-(isocyanatomethyl)benzene as shown in Scheme 9.

Scheme 9.



[0307] Step 1 – Synthesis of tert-butyl 4-[(4-fluorophenyl)methylcarbamoyl]piperazine-1-carboxylate (24): To *tert*-butyl piperazine-1-carboxylate (2 g, 10.7 mmol) in tetrahydrofuran (50 mL) was added triethylamine (3 ml) followed by 1-fluoro-4-(isocyanatomethyl)benzene (1.8 g, 11.9 mmol). The reaction mixture was stirred at room temperature for two days. The precipitate was collected by filtration and washed with acetonitrile to provide compound (**24**) (2.9 g, 80%). It was used for subsequent reaction without further purification.

[0308] Step 2 – Synthesis of N-[(4-fluorophenyl)methyl]piperazine-1-carboxamide (25): To *tert*-butyl 4-(benzylcarbamoyl)piperazine-1-carboxylate (2.9 g, 9.08 mmol) in tetrahydrofuran (5 mL) was added hydrochloric acid (10 mL, 4.0 M in 1,4-dioxane). The resulting mixture was stirred at room temperature overnight. After removal of solvent, the residue was washed with acetonitrile and then dried under vacuum to provide hydrochloric salt form of compound (**25**) as a white solid (1.2 g, 58%). It was used for subsequent reaction without further purification.

[0309] Step 3 – Synthesis of 4-(6-bromothieno[3,2-d]pyrimidin-4-yl)-N-[(4-fluorophenyl)methyl]piperazine-1-carboxamide (27): A mixture of 6-bromo-4-chloro-thieno[3,2-d]pyrimidine (**26**) (0.5 g, 2 mmol), N-[(4-fluorophenyl)methyl]piperazine-1-carboxamide (0.5 g, 2.11 mmol), and N,N-Diisopropylethylamine (1 mL, 5.8 mmol) in acetonitrile (50 mL) was stirred at 50 °C for four hours. The reaction mixture was partitioned between ethyl acetate, washed with brine, and dried under anhydrous sodium sulfate. After removal of drying agent and solvent, the residue was purified by flash chromatography to provide compound (**27**) as a white solid (0.6 g, 66%). MS (ESI) $[M+H^+]^+$ = 450.0 and 452.10.

[0310] Step 4 – Synthesis of 4-[6-(1,3-dimethylpyrazol-4-yl)thieno[3,2-d]pyrimidin-4-yl]-N-[(4-fluorophenyl)methyl]piperazine-1-carboxamide (P-0619): To 4-(6-bromothieno[3,2-d]pyrimidin-4-yl)-N-[(4-fluorophenyl)methyl]piperazine-1-carboxamide (**27**) (22 mg, 0.05 mmol) in acetonitrile (3 ml) was added 1,3-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (14 mg, 0.06 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (7 mg, 0.009 mmol), and aqueous potassium carbonate (1 ml, 1 M). The reaction mixture was irradiated by microwave at 100 °C for 15 minutes. The reaction mixture was concentrated, partitioned between ethyl acetate, washed with brine, and dried under anhydrous sodium sulfate. After removal of drying agent and solvent, the residue was purified by column chromatography followed by preparative HPLC to provide compound (**P-0619**) as a white solid (13 mg, 57% yield). The structure was confirmed by ^{1}H NMR spectroscopy. MS (ESI) $[M+H^+]^+$ = 466.35.

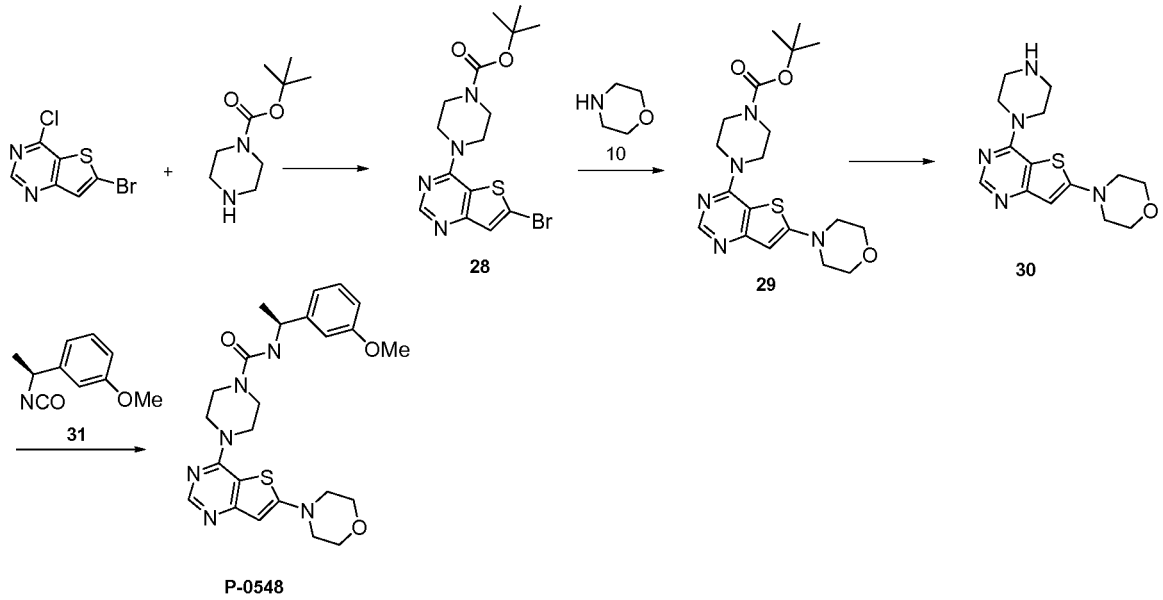
[0311] Compounds 4-(6-tert-butylthieno[3,2-d]pyrimidin-4-yl)-N-[(4-fluorophenyl)methyl]piperazine-1-carboxamide (P-0637), N-[(4-fluorophenyl)methyl]-4-thieno[3,2-d]pyrimidin-4-yl-piperazine-1-carboxamide (P-0638), 4-(6-tert-butylthieno[3,2-d]pyrimidin-4-yl)-N-(4-fluorophenyl)piperazine-1-carboxamide (P-0639), N-(4-fluorophenyl)-4-thieno[3,2-d]pyrimidin-4-yl-piperazine-1-carboxamide (P-0640), N-benzyl-4-(6-bromothieno[3,2-d]pyrimidin-4-yl)piperazine-1-carboxamide (P-0629), 4-[6-(1,5-dimethylpyrazol-4-yl)thieno[3,2-d]pyrimidin-4-yl]-N-[(4-fluorophenyl)methyl]piperazine-1-carboxamide (P-0620), N-[(4-fluorophenyl)methyl]-4-[6-(1,3,5-trimethylpyrazol-4-yl)thieno[3,2-d]pyrimidin-4-yl]piperazine-1-carboxamide (P-0618) and N-[(1S)-1-(3-chlorophenyl)ethyl]-4-[6-(1,3-dimethylpyrazol-4-yl)thieno[3,2-d]pyrimidin-4-yl]-2,2-dimethyl-piperazine-1-carboxamide (P-0564) were prepared

according to the synthetic protocol set forth in Example 9 and Scheme 9. The structures of the compounds were confirmed by ^{1}H NMR and mass spectroscopy.

Example 10: **Preparation of N-[(1S)-1-(3-methoxyphenyl)ethyl]-4-(6-morpholinothieno[3,2-d]pyrimidin-4-yl)piperazine-1-carboxamide (P-0548)**

[0312] Compound **P-0548** was prepared in four steps from *tert*-butyl piperazine-1-carboxylate and 6-bromo-4-chloro-thieno[3,2-d]pyrimidine as shown in Scheme 10.

Scheme 10.



[0313] Step 1 – Synthesis of tert-butyl 4-(6-bromothieno[3,2-d]pyrimidin-4-yl)piperazine-1-carboxylate (28): A mixture of 6-bromo-4-chloro-thieno[3,2-d]pyrimidine (1 g, 4.01 mmol), *tert*-butyl piperazine-1-carboxylate (1.1 g, 5.91 mmol), and N,N-diisopropylethylamine (1 mL, 5.8 mmol) in acetonitrile (50 mL) was stirred at room temperature overnight. The reaction mixture was partitioned between ethyl acetate, washed with brine, and dried under anhydrous sodium sulfate. After removal of drying agent and solvent, the residue was purified by flash chromatography on silica gel to provide compound **28** as a white solid (1.5 g, 93% yield). MS (ESI) [M+H+]+ = 400.80.

[0314] Step 2 – Synthesis of tert-butyl 4-(6-morpholinothieno[3,2-d]pyrimidin-4-yl)piperazine-1-carboxylate (29): To *tert*-butyl 4-(6-bromothieno[3,2-d]pyrimidin-4-yl)piperazine-1-carboxylate (74 mg, 0.19 mmol) in N,N-dimethylformamide (3 ml) was added morpholine (0.1 mL). The reaction mixture was irradiated by microwave at 180 °C for 10 minutes. To the reaction mixture was added additional morpholine (0.5 mL) and the reaction mixture was irradiated by microwave at 160°C for two hours. The reaction mixture was concentrated and the residue was purified by column chromatography on silica gel to provide compound **29** as a light yellow solid (11 mg, 14% yield). MS(ESI) [M+H+]+ = 406.20.

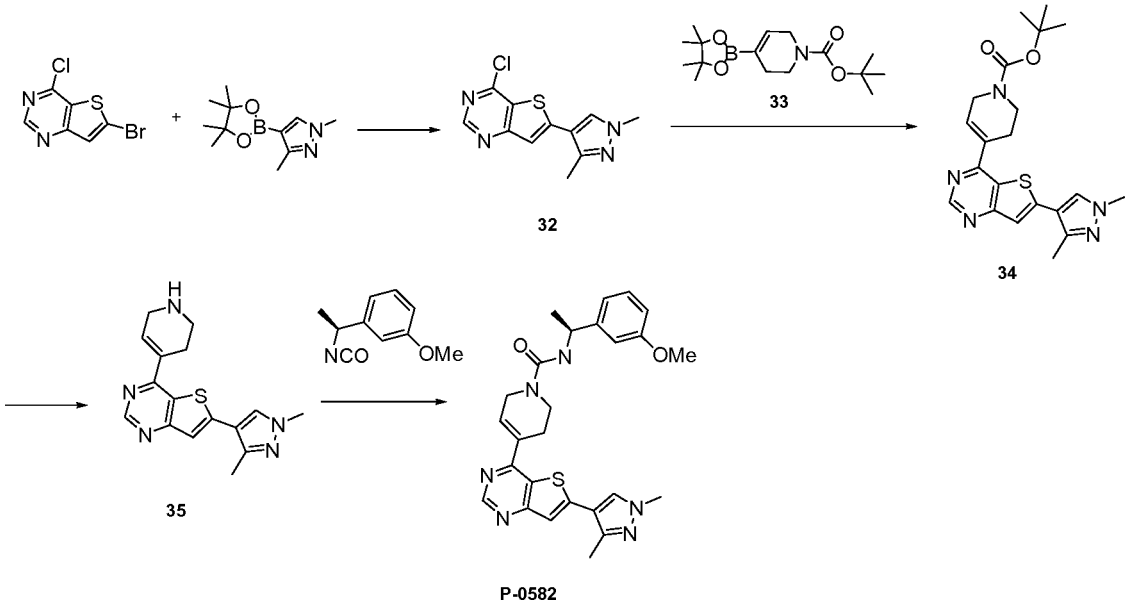
[0315] Step 3 – Synthesis of 4-(4-piperazin-1-ylthieno[3,2-d]pyrimidin-6-yl)morpholine (30): To *tert*-butyl 4-(6-morpholinothieno[3,2-d]pyrimidin-4-yl)piperazine-1-carboxylate (6 mg, 0.01 mmol) in acetonitrile (0.5 ml) was added hydrochloric acid in 1,4-dioxane (1 mL, 4 M). The reaction mixture was stirred at room temperature for four hours. After removal of solvent, the residue was dried under vacuum to provide compound **30** as a hydrochloric acid salt (4 mg, 88% yield). It was used for subsequent reaction without purification.

[0316] Step 4 – Synthesis of N-[(1S)-1-(3-methoxyphenyl)ethyl]-4-(6-morpholinothieno[3,2-d]pyrimidin-4-yl)piperazine-1-carboxamide (P-0548): To 4-(4-piperazin-1-ylthieno[3,2-d]pyrimidin-6-yl)morpholine (25 mg, 0.08 mmol) in N,N-dimethylformamide (3 ml) was added 1-[(1S)-1-isocyanatoethyl]-3-methoxy-benzene (**31**) (0.04 g, 0.2 mmol) followed by N,N-diisopropylethylamine (0.1 mL). The reaction mixture was stirred at room temperature for five hours. The mixture was prepared for purification by column chromatography followed by preparative HPLC to provide compound **P-0548** (5 mg, 12.6% yield). The data from the ^{1}H NMR spectrum were consistent with the structure of the compound. MS ESI $[M+H^+]^+ = 483.3$.

[0317] Compounds N-[(1S)-1-(3-chlorophenyl)ethyl]-2,2-dimethyl-4-(6-morpholinothieno[3,2-d]pyrimidin-4-yl)piperazine-1-carboxamide (P-0558), N-[(1S)-1-(4-fluorophenyl)ethyl]-4-(6-morpholinothieno[3,2-d]pyrimidin-4-yl)piperazine-1-carboxamide (P-0589), and N-[(1S)-1-(3-methoxyphenyl)ethyl]-2,2-dimethyl-4-(6-morpholinothieno[3,2-d]pyrimidin-4-yl)piperazine-1-carboxamide (P-0560) were prepared according to the synthetic protocol set forth in Example 10 and Scheme 10. The structures of the compounds were confirmed by ^{1}H NMR and mass spectroscopy.

Example 11: **Preparation of 4-[6-(1,3-dimethylpyrazol-4-yl)thieno[3,2-d]pyrimidin-4-yl]-N-[(1S)-1-(3-methoxyphenyl)ethyl]-3,6-dihydro-2H-pyridine-1-carboxamide (P-0582).**

Scheme 11



[0318] Step 1 – Synthesis of 4-chloro-6-(1,3-dimethylpyrazol-4-yl)thieno[3,2-d]pyrimidine (32): To 6-bromo-4-chloro-thieno[3,2-d]pyrimidine (0.2 g, 0.8 mmol) in acetonitrile (3 ml) was added 1,3-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (0.3 g, 1.35 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (45 mg, 0.06 mmol), and aqueous potassium carbonate (1 ml, 1 M). The reaction mixture was stirred in a sealed tube at 80 °C for five hours. The reaction mixture was partitioned between ethyl acetate, washed with brine, and dried under anhydrous sodium sulfate. After removal of drying agent and solvent, the residue was purified by flash chromatography to provide compound **32** as pale yellow solid (0.21 g, 84%). MS (ESI) [M+H+]+ = 265.00.

[0319] Step 2 – Synthesis of tert-butyl 4-[6-(1,3-dimethylpyrazol-4-yl)thieno[3,2-d]pyrimidin-4-yl]-3,6-dihydro-2H-pyridine-1-carboxylate (34): To 4-chloro-6-(1,3-dimethylpyrazol-4-yl)thieno[3,2-d]pyrimidine (**32**) (0.2 g, 0.755 mmol) in acetonitrile (3 ml) was added tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (**33**) (0.3 g, 0.97 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (8 mg, 0.011 mmol) and aqueous potassium carbonate (1 ml, 1 M). The reaction mixture was irradiated by microwave at 100°C for 10 minutes. The reaction mixture was partitioned between ethyl acetate, washed with brine, and dried under anhydrous sodium sulfate. After removal of drying agent and solvent, the residue was purified by flash chromatography on silica gel to provide compound **34** as a yellow solid (0.22 g, 63% yield). MS (ESI) [M+H+]+ = 412.25.

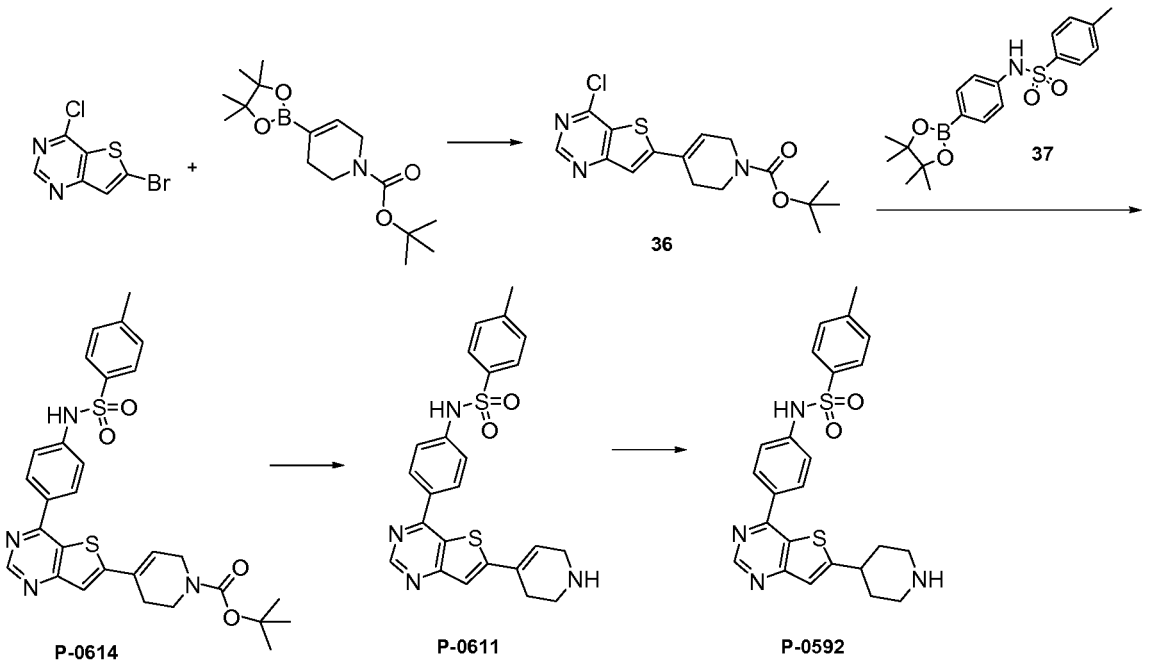
[0320] Step 3 – Synthesis of 6-(1,3-dimethylpyrazol-4-yl)-4-(1,2,3,6-tetrahydropyridin-4-yl)thieno[3,2-d]pyrimidine (35): To *tert*-butyl 4-[6-(1,3-dimethylpyrazol-4-yl)thieno[3,2-d]pyrimidin-4-yl]-3,6-dihydro-2H-pyridine-1-carboxylate (**34**) (40 mg, 0.08 mmol) in acetonitrile (2 ml) was added hydrochloric acid in dioxane (2 ml, 4 M). The reaction mixture was stirred at room temperature for two hours. After removal of the solvent, the residue was washed with ethyl acetate to provide compound **35** as hydrochloric acid salt (8 mg, 29% yield). MS (ESI) [M+H+]+ = 312.00. This material was used for subsequent reaction without purification.

[0321] Step 4 – Synthesis of 4-[6-(1,3-dimethylpyrazol-4-yl)thieno[3,2-d]pyrimidin-4-yl]-N-[(1S)-1-(3-methoxyphenyl)ethyl]-3,6-dihydro-2H-pyridine-1-carboxamide (P-0582): To 6-(1,3-dimethylpyrazol-4-yl)-4-(1,2,3,6-tetrahydropyridin-4-yl)thieno[3,2-d]pyrimidine (**35**) (6 mg, 0.02 mmol) in acetonitrile (3 ml) was added 1-[(1S)-1-isocyanatoethyl]-3-methoxy-benzene (5 mg, 0.03 mmol) followed by N,N-diisopropylethylamine (0.1 mL). The reaction mixture was stirred at room temperature for eight hours. The reaction mixture was concentrated, partitioned between ethyl acetate, washed with brine, and dried under anhydrous sodium sulfate. After removal of drying agent and solvent, the residue was purified by column chromatography followed by preparative HPLC to provide compound **P-0582** as a white solid (2 mg, 21% yield). The data from the ^{1}H NMR spectrum were consistent with the structure of the compound. MS (ESI) [M+H+]+ = 489.0.

[0322] Compounds 4-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]-N-(1-methyl-1-phenyl-ethyl)-3,6-dihydro-2H-pyridine-1-carboxamide (P-0679), 6-(1-methylpyrazol-4-yl)-4-(2,2,6,6-tetramethyl-1,3-dihydropyridin-4-yl)thieno[3,2-d]pyrimidine (P-0617), N-(4-chlorophenyl)-4-[6-(1,3-dimethylpyrazol-4-yl)thieno[3,2-d]pyrimidin-4-yl]-3,6-dihydro-2H-pyridine-1-carboxamide (P-0612), and 4-[6-(1,3-dimethylpyrazol-4-yl)thieno[3,2-d]pyrimidin-4-yl]-N-[(4-fluorophenyl)methyl]-3,6-dihydro-2H-pyridine-1-carboxamide (P-0613) were prepared according to the synthetic protocol set forth in Example 11 and Scheme 11. The data from the ^{1}H NMR spectra and observed molecular weights (Table 5) were consistent with the structures of the compounds.

Example 12: Preparation of tert-butyl 4-[4-[4-(p-tolylsulfonylamino)phenyl]thieno[3,2-d]pyrimidin-6-yl]-3,6-dihydro-2H-pyridine-1-carboxylate (P-0614) and 4-methyl-N-[4-[6-(1,2,3,6-tetrahydropyridin-4-yl)thieno[3,2-d]pyrimidin-4-yl]phenyl]benzenesulfonamide (P-0611) and 4-methyl-N-[4-[6-(4-piperidyl)thieno[3,2-d]pyrimidin-4-yl]phenyl]benzenesulfonamide (P-0592).

Scheme 12.



[0323] Step 1 – Synthesis of tert-butyl 4-(4-chlorothieno[3,2-d]pyrimidin-6-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (36): To 6-bromo-4-chloro-thieno[3,2-d]pyrimidine (0.29 g, 1.16 mmol) in acetonitrile (3 ml) was added *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (0.45 g, 1.46 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (45 mg, 0.06 mmol), and aqueous potassium carbonate (1 ml, 1 M). The reaction mixture was stirred at 80 °C for five hours. The reaction mixture was partitioned between ethyl acetate, washed with brine, and dried under anhydrous sodium sulfate. After removal of drying agent and solvent, the residue was dried to provide compound **36** as a brownish solid (0.4 g, purity 90%, 88% yield). It was used for subsequent reaction without further purification.

[0324] Step 2 – Synthesis of tert-butyl 4-[4-[4-(p-tolylsulfonylamino)phenyl]thieno[3,2-d]pyrimidin-6-yl]-3,6-dihydro-2H-pyridine-1-carboxylate (P-0614): To *tert*-butyl 4-(4-chlorothieno[3,2-d]pyrimidin-6-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (**36**) (0.1 g, 0.28 mmol) in acetonitrile (3 ml) was added 4-methyl-N-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]benzenesulfonamide (**37**) (0.15 g, 0.4 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (29 mg, 0.038 mmol), and aqueous potassium

carbonate (1 ml, 1 M). The reaction mixture was irradiated by microwave at 120 °C for 20 minutes. The reaction mixture was partitioned between ethyl acetate, washed with brine, and dried under anhydrous sodium sulfate. After removal of drying agent and solvent, the residue was purified by flash chromatography on silica gel followed by preparative HPLC to provide compound **P-0614** as an off-white solid (48 mg, 27% yield). The data from the ^{1}H NMR spectrum were consistent with the structure of the compound. MS (ESI) [M+H+]+ = 563.0.

Example 13: Preparation of 4-methyl-N-[4-[6-(1,2,3,6-tetrahydropyridin-4-yl)thieno[3,2-d]pyrimidin-4-yl]phenyl]benzenesulfonamide (P-0611).

[0325] To *tert*-butyl 4-[4-[4-(p-tolylsulfonylamino)phenyl]thieno[3,2-d]pyrimidin-6-yl]-3,6-dihydro-2H-pyridine-1-carboxylate (**P-0614**) (30 mg, 0.05 mmol) in tetrahydrofuran (2 ml) was added hydrochloric acid in 1,4-dioxane (3 mL, 4 M). The mixture was stirred at room temperature overnight. After removal of solvent, the residue was washed with ethyl acetate to provide hydrochloric acid salt of compound **P-0611** as a light yellow solid (18 mg, 65% yield). The data from the ^{1}H NMR spectrum were consistent with the structure of the compound. MS (ESI) [M-H+]+ = 461.0.

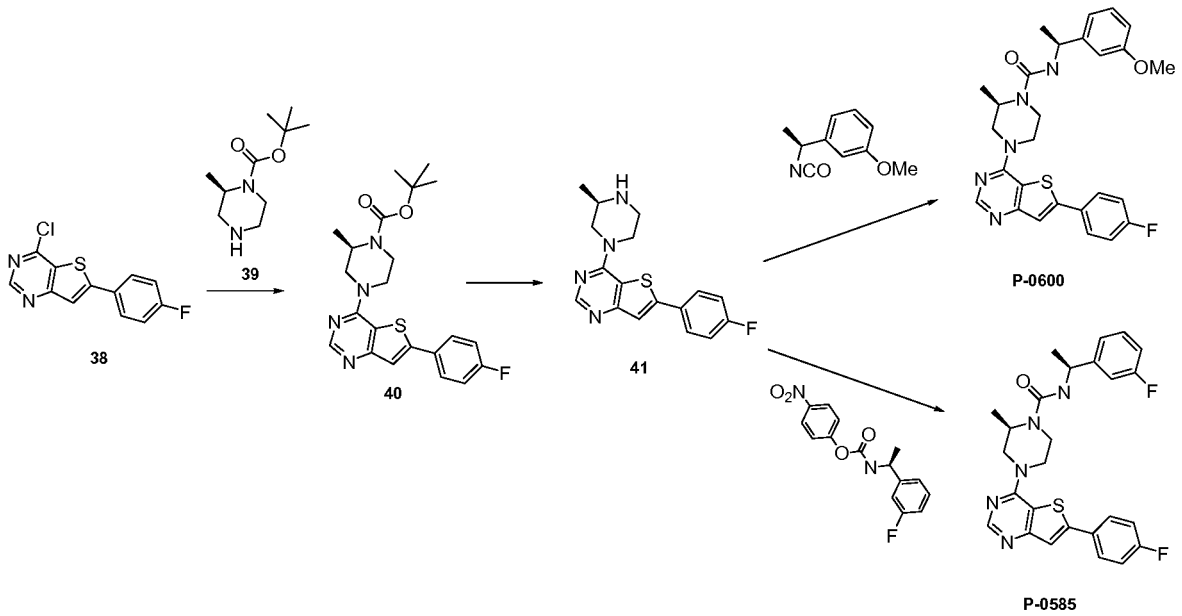
Example 14: Preparation of 4-methyl-N-[4-[6-(4-piperidyl)thieno[3,2-d]pyrimidin-4-yl]phenyl]benzenesulfonamide (P-0592).

[0326] To 4-methyl-N-[4-[6-(1,2,3,6-tetrahydropyridin-4-yl)thieno[3,2-d]pyrimidin-4-yl]phenyl]benzenesulfonamide hydrochloride (**P-0611**) (10 mg, 0.02 mmol) in methanol (2 ml) was added palladium on carbon (10%, wet, Degussa, 3 mg). The reaction mixture was shaken under hydrogen (55 psi) at room temperature for six hours. After removal of catalyst and solvent, the residue was purified by preparative HPLC to provide compound **P-0592** as a pale yellow solid (5 mg, 44% yield). The data from the ^{1}H NMR spectrum were consistent with the structure of the compound. MS(ESI) [M+H+]+ = 464.9.

[0327] Compound 4-methyl-N-[4-[6-(1-methylpyrazol-4-yl)thieno[3,2-d]pyrimidin-4-yl]phenyl]benzenesulfonamide (P-0628) was prepared according to the synthetic protocols set forth in Examples 12-14 and Scheme 12. The data from the ^{1}H NMR and mass spectroscopy data were consistent with the structure of the compound.

Example 15: **Preparation of (2R)-4-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]-N-[(1S)-1-(3-methoxyphenyl)ethyl]-2-methyl-piperazine-1-carboxamide (P-0600) and (2R)-N-[(1S)-1-(3-fluorophenyl)ethyl]-4-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]-2-methyl-piperazine-1-carboxamide (P-0585).**

Scheme 13.



[0328] Step 1 – Synthesis of tert-butyl (2R)-4-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]-2-methyl-piperazine-1-carboxylate (40): In a round bottom flask, 4-chloro-6-(4-fluorophenyl)thieno[3,2-d]pyrimidine (**38**) (1 g, 3.778 mmol), and *tert*-butyl (2R)-2-methylpiperazine-1-carboxylate (**39**) (0.794 g, 3.967 mmol) were dissolved in acetonitrile (50 mL). Triethylamine (1.58 mL, 11.33 mmol) was added, and the reaction mixture was flushed with argon. The reaction was stirred at 50 °C for two days. The reaction was cooled to room temperature, quenched with water, extracted with ethyl acetate, and washed with brine. The organic layer was dried with anhydrous sodium sulfate. After removal of drying agent and solvent, the residue was then triturated with minimal ethyl acetate. The precipitate was collected by filtration and dried under vacuum to provide compound **40** as a white solid (1.59 g, 98% yield).

[0329] Step 2 – Synthesis of 6-(4-fluorophenyl)-4-[(3R)-3-methylpiperazin-1-yl]thieno[3,2-d]pyrimidine hydrochloride (41): In a round bottom flask, to a suspension of *tert*-butyl (2R)-4-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]-2-methyl-piperazine-1-carboxylate (**40**) (0.667 g, 1.557 mmol) in acetonitrile (15 mL) was added hydrochloric acid in dioxane (3.9 mL, 4.0M). The reaction mixture was stirred at room temperature for three hours. After removal of solvent, the residue was triturated with ethyl acetate to provide hydrochloric acid salt of compound **41** as a white solid (0.54 g, 85% yield). MS (ESI) $[M+H^+]^+$= 329.15.

[0330] Step 3 – Synthesis of (2R)-4-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]-N-[(1S)-1-(3-methoxyphenyl)ethyl]-2-methyl-piperazine-1-carboxamide (P-0600): To 6-(4-fluorophenyl)-4-[(3R)-3-methylpiperazin-1-yl]thieno[3,2-d]pyrimidine hydrochloride (**41**) (30 mg, 0.082 mmol) in acetonitrile (2 mL) was added 1-[(1S)-1-isocyanatoethyl]-3-methoxy-benzene (15.3 mg, 0.086 mmol) and triethylamine (0.034 mL, 0.247 mmol). The reaction mixture was stirred at room temperature overnight. After removal of solvent, the residue was purified by preparative HPLC to provide compound **P-0600** as a white solid (20 mg, 48% yield). The data from the ^{1}H NMR spectrum were consistent with the structure of the compound. MS (ESI) $[M+H^+]^+ = 506.4$.

Example 16: Synthesis of (2R)-N-[(1S)-1-(3-fluorophenyl)ethyl]-4-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]-2-methyl-piperazine-1-carboxamide (P-0585).

[0331] To 6-(4-fluorophenyl)-4-[(3R)-3-methylpiperazin-1-yl]thieno[3,2-d]pyrimidine hydrochloride (30 mg, 0.082 mmol) (**41**) in acetonitrile (3 mL) was added (4-nitrophenyl) N-[(1S)-1-(3-fluorophenyl)ethyl]carbamate (50 mg, 0.16 mmol) and triethylamine (0.034 mL, 0.247 mmol). The reaction mixture was irradiated by microwave at 100 °C for 30 minutes. After removal of solvent, the residue was purified by preparative HPLC to provide compound **P-0585** (15 mg, 37% yield). ^{1}HNMR spectrum was consistent with the structure of the compound. MS (ESI) $[M+H^+]^+ = 494.4$.

[0332] The following compounds were prepared according to the synthetic protocols set forth in Examples 15 and 16 and Scheme 13. The data from the ^{1}H NMR and mass spectroscopy data were consistent with the structures of the compounds:

4-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]-2,2-dimethyl-N-(1-methyl-1-phenyl-ethyl)piperazine-1-carboxamide (P-0678),

N-(4-fluorophenyl)-5-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]-2,5-diazabicyclo[2.2.2]octane-2-carboxamide (P-0546),

5-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]-N-[(3-methoxyphenyl)methyl]-2,5-diazabicyclo[2.2.2]octane-2-carboxamide (P-0547),

N-(4-fluorophenyl)-8-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxamide (P-0549),

8-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]-N-[(1S)-1-(3-methoxyphenyl)ethyl]-3,8-diazabicyclo[3.2.1]octane-3-carboxamide (P-0550),

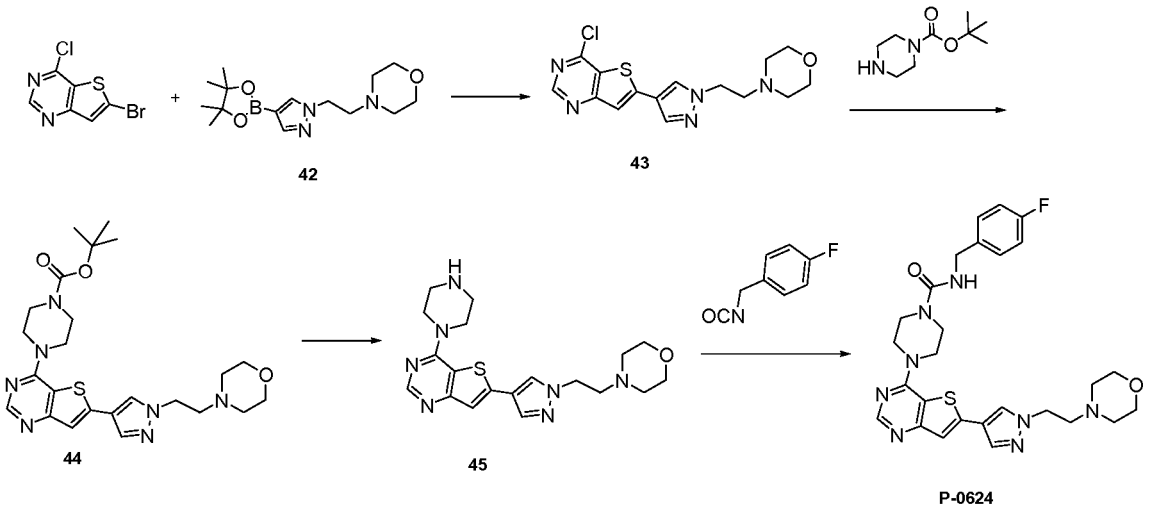
8-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]-N-[(3-methoxyphenyl)methyl]-3,8-diazabicyclo[3.2.1]octane-3-carboxamide (P-0551),

(2R,6S)-4-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]-N-[(3-methoxyphenyl)methyl]-2,6-dimethyl-piperazine-1-carboxamide (P-0562),

(2R,6S)-4-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]-N-[(1S)-1-(3-methoxyphenyl)ethyl]-2,6-dimethyl-piperazine-1-carboxamide (P-0563),
5-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]-N-[(1S)-1-(3-methoxyphenyl)ethyl]-2,5-diazabicyclo[2.2.2]octane-2-carboxamide (P-0566),
3-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]-N-[(1S)-1-(3-methoxyphenyl)ethyl]-3,8-diazabicyclo[3.2.1]octane-8-carboxamide (P-0567),
N-[(1S)-1-[3-(difluoromethoxy)phenyl]ethyl]-4-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]-3,6-dihydro-2H-pyridine-1-carboxamide (P-0573),
N-[(1S)-1-(4-chlorophenyl)ethyl]-4-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]-2,2-dimethyl-piperazine-1-carboxamide (P-0575),
4-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]-N-[(1S)-1-(4-methoxyphenyl)ethyl]-2,2-dimethyl-piperazine-1-carboxamide (P-0576),
N-[(1S)-1-[3-(difluoromethoxy)phenyl]ethyl]-4-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]-2,2-dimethyl-piperazine-1-carboxamide (P-0577),
N-[(1S)-1-(3-fluorophenyl)ethyl]-4-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]-2,2-dimethyl-piperazine-1-carboxamide (P-0578),
N-[(1S)-1-(3-chlorophenyl)ethyl]-4-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]-3,6-dihydro-2H-pyridine-1-carboxamide (P-0579),
N-[(1S)-1-(3-chlorophenyl)ethyl]-4-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]-2,2-dimethyl-piperazine-1-carboxamide (P-0580),
4-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]-N-[(1S)-1-(3-methoxyphenyl)ethyl]-3,6-dihydro-2H-pyridine-1-carboxamide (P-0581),
(2R)-N-[(1S)-1-[3-(difluoromethoxy)phenyl]ethyl]-4-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]-2-methyl-piperazine-1-carboxamide (P-0586),
N-[(1S)-1-(4-fluorophenyl)ethyl]-4-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]-2,2-dimethyl-piperazine-1-carboxamide (P-0593),
4-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]-N-[(1S)-1-(3-methoxyphenyl)ethyl]-2,2-dimethyl-piperazine-1-carboxamide (P-0594),
4-(3,3-dimethylpiperazin-1-yl)-6-(4-fluorophenyl)thieno[3,2-d]pyrimidine (P-0595),
(2R)-N-[(1S)-1-(4-fluorophenyl)ethyl]-4-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]-2-methyl-piperazine-1-carboxamide (P-0601),
(2R)-N-[(4-fluorophenyl)methyl]-4-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]-2-methyl-piperazine-1-carboxamide (P-0602), and
(2R)-4-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]-N-[(1R)-1-(3-methoxyphenyl)ethyl]-2-methyl-piperazine-1-carboxamide (P-0605).

Example 17: Preparation of N-[(4-fluorophenyl)methyl]-4-[6-[1-(2-morpholinoethyl)pyrazol-4-yl]thieno[3,2-d]pyrimidin-4-yl]piperazine-1-carboxamide (P-0624)

Scheme 14.



[0333] Step 1 – Synthesis of 4-[2-[4-(4-chlorothieno[3,2-d]pyrimidin-6-yl)pyrazol-1-yl]ethyl]morpholine (43): To 6-bromo-4-chloro-thieno[3,2-d]pyrimidine (0.2 g, 0.8 mmol) in acetonitrile (3 ml) was added 4-[2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazol-1-yl]ethyl]morpholine (**42**) (0.24 g, 0.78 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (45 mg, 0.06 mmol), and aqueous potassium carbonate (1 ml, 1 M). The reaction mixture was stirred at 80 °C for five hours, then partitioned between ethyl acetate, washed with brine, and dried under anhydrous sodium sulfate. After removal of drying agent and solvent, the residue was purified by flash chromatography to provide compound **43** as a pale yellow solid (0.21 g, 67% yield). MS (ESI) [M+H+]+ = 350.15.

[0334] Step 2 – Synthesis of tert-butyl 4-[6-[1-(2-morpholinoethyl)pyrazol-4-yl]thieno[3,2-d]pyrimidin-4-yl]piperazine-1-carboxylate (44): A mixture of 4-[2-[4-(4-chlorothieno[3,2-d]pyrimidin-6-yl)pyrazol-1-yl]ethyl]morpholine (**43**) (0.21g, 0.6 mmol), tert-butyl piperazine-1-carboxylate (0.13 g, 0.7 mmol), and N,N-diisopropylethylamine (0.1 mL, 0.717 mmol) in acetonitrile (5 mL) was stirred at 60 °C for two hours and then was stirred at 50 °C overnight. The reaction mixture was partitioned between ethyl acetate, washed with brine, and dried under anhydrous sodium sulfate. After removal of drying agent and solvent, the residue was purified by flash chromatography on silica gel to provide compound **44** as an off-white solid (0.2 g, 66% yield). MS(ESI) [M+H+]+ = 500.00.

[0335] Step 3 – Synthesis of 4-[2-[4-(4-piperazin-1-ylthieno[3,2-d]pyrimidin-6-yl)pyrazol-1-yl]ethyl]morpholine (45): To a solution of tert-butyl 4-[6-[1-(2-morpholinoethyl)pyrazol-4-yl]thieno[3,2-d]pyrimidin-4-yl]piperazine-1-carboxylate (**44**) (0.2 g, 0.4 mmol) in acetonitrile (2 mL) was added hydrochloric acid (5 mL, 2.0 M in ethyl ether). The mixture was stirred at room temperature

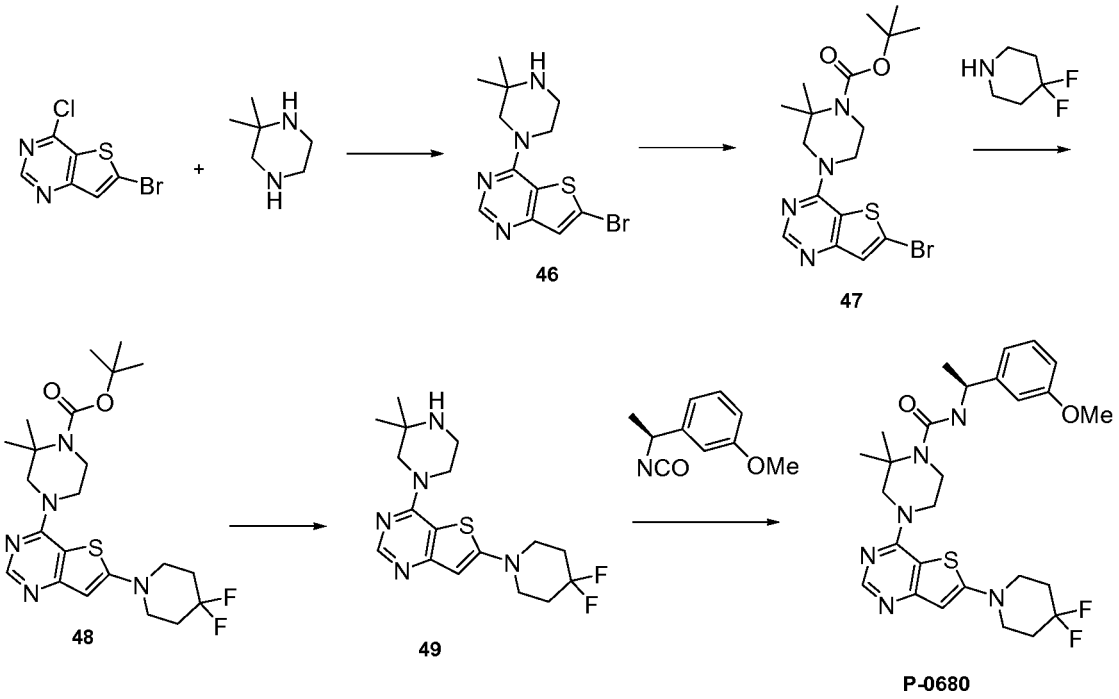
overnight. After removal of solvent, the residue was dried under vacuum to provide hydrochloric acid salt of compound **45** as a brown solid (0.18 g). MS (ESI) [M+H+]+ = 400.25. The compound was used for subsequent reactions without purification.

[0336] Step 4 – Synthesis of N-[(4-fluorophenyl)methyl]-4-[6-[1-(2-morpholinoethyl)pyrazol-4-yl]thieno[3,2-d]pyrimidin-4-yl]piperazine-1-carboxamide (P-0624): To a solution of 4-[2-[4-(4-piperazin-1-ylthieno[3,2-d]pyrimidin-6-yl)pyrazol-1-yl]ethyl]morpholine (**45**) (80%, 69 mg, 0.14 mmol) in acetonitrile (5 mL) was added 1-fluoro-4-(isocyanatomethyl)benzene (37 mg, 0.24 mmol) and N,N-diisopropylethylamine (0.1 mL). The mixture was stirred at room temperature overnight. The reaction mixture was concentrated and the residue was purified by flash chromatography on silica gel followed by preparative HPLC to provide compound **P-0624** as a pale yellow solid (48 mg, 63% yield). The data from the ^{1}H NMR spectrum were consistent with the structure of the compound. MS (ESI) [M+H+]+ = 551.0.

[0337] Compounds (2R)-4-[6-(1,3-dimethylpyrazol-4-yl)thieno[3,2-d]pyrimidin-4-yl]-N-[(1R)-1-(3-methoxyphenyl)ethyl]-2-methyl-piperazine-1-carboxamide (P-0608) and (2R)-4-[6-(1,3-dimethylpyrazol-4-yl)thieno[3,2-d]pyrimidin-4-yl]-N-[(1R)-1-(4-fluorophenyl)ethyl]-2-methyl-piperazine-1-carboxamide (P-0609) were prepared according to the synthetic protocols set forth in Examples 17 and Scheme 14. The data from the ^{1}H NMR and mass spectroscopy data were consistent with the structures of the compounds.

Example 18: Preparation of 4-[6-(4,4-difluoro-1-piperidyl)thieno[3,2-d]pyrimidin-4-yl]-N-[(1S)-1-(3-methoxyphenyl)ethyl]-2,2-dimethyl-piperazine-1-carboxamide (P-0680):

Scheme 15.



[0338] Step 1 – Synthesis of 6-bromo-4-(3,3-dimethylpiperazin-1-yl)thieno[3,2-d]pyrimidine (46): To 6-bromo-4-chloro-thieno[3,2-d]pyrimidine (1.75 g, 7.0 mmol) in acetonitrile (25 ml) was added 2,2-dimethylpiperazine (0.86 g, 7.6 mmol) in acetonitrile (10 ml) and triethylamine (2.4 mL). The reaction mixture was stirred at 50 °C for four hours and concentrated. The residue was washed with a mixture of ethyl acetate and hexanes to provide compound **46** (2.3 g, 95% yield). The ^{1}HNMR spectrum was consistent with the structure of the desired product. It was used for subsequent reactions without further purification.

[0339] Step 2 – Synthesis of tert-butyl 4-(6-bromothieno[3,2-d]pyrimidin-4-yl)-2,2-dimethyl-piperazine-1-carboxylate (47): To a round bottom flask tetrahydrofuran (15 mL, 0.6 mol) was added to 6-bromo-4-(3,3-dimethylpiperazin-1-yl)thieno[3,2-d]pyrimidine (**46**) (1.5 g, 4.58 mmol), followed by di-tert-butyldicarbonate (1.16 ml, 0.01 mol) and 4-dimethylaminopyridine (0.02 g, 0 mol) and N,N-diisopropylethylamine (2 ml, 0.01 mol) under an atmosphere of nitrogen. The reaction mixture was stirred at room temperature overnight. The reaction mixture was concentrated, extracted with ethyl acetate, washed with saturated sodium bicarbonate, and dried with anhydrous sodium sulfate. After removal of drying agent and solvent, the residue was purified by flash column chromatography on silica gel to

provide compound **47** (1.8 g, 92% yield). The ^{1}HNMR spectrum was consistent with the structure of the desired product.

[0340] Step 3 – Synthesis of tert-butyl 4-[6-(4,4-difluoro-1-piperidyl)thieno[3,2-d]pyrimidin-4-yl]-2,2-dimethyl-piperazine-1-carboxylate (48): To a microwave vessel were added *tert*-butyl 4-(6-bromothieno[3,2-d]pyrimidin-4-yl)-2,2-dimethyl-piperazine-1-carboxylate (**47**) (0.16 g, 0.37 mmol), 4,4-difluoropiperidine (0.1 g, 0.83 mmol), and an appropriate amount of tris(dibenzylideneacetone)dipalladium(0) and (1,1′-binaphthalene-2,2′-diyl)bis(diphenylphosphine). To the mixture was added toluene (4 mL). The mixture was stirred at room temperature for five minutes and cesium carbonate (0.07 ml, 0.82 mmol) was added. The mixture was irradiated by microwave at 145 °C for 15 minutes and was concentrated. The residue was purified by chromatography on silica gel to provide compound **48** (0.15 g, 85.6% yield). MS ESI $[M+H^+]^+ = 468.15$

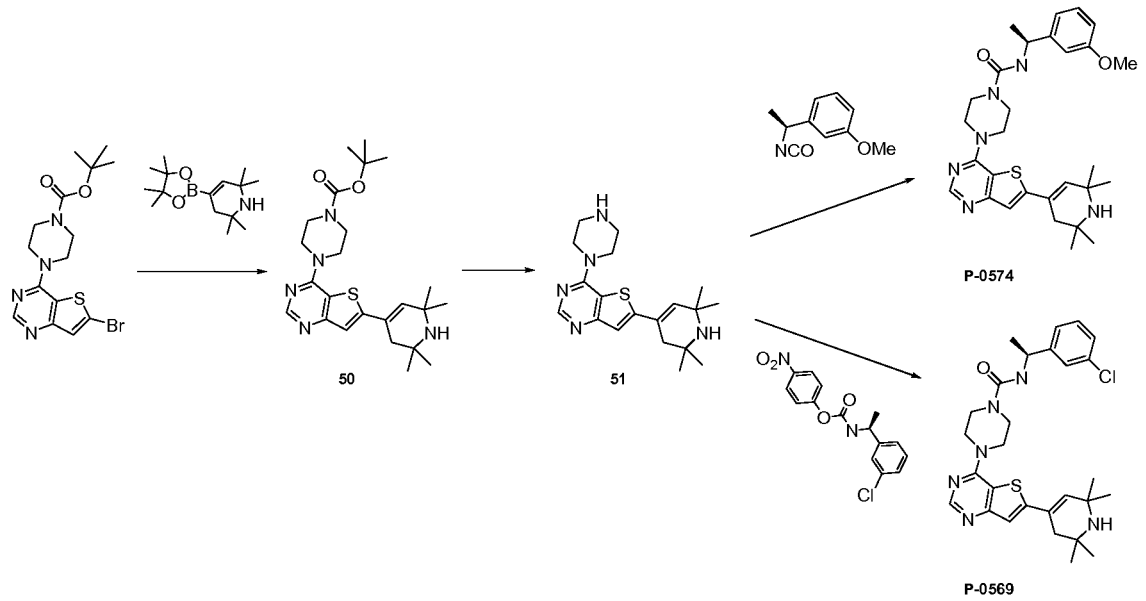
[0341] Step 4 – Preparation of 6-(4,4-difluoro-1-piperidyl)-4-(3,3-dimethylpiperazin-1-yl)thieno[3,2-d]pyrimidine hydrochloride (49): To *tert*-butyl 4-[6-(4,4-difluoro-1-piperidyl)thieno[3,2-d]pyrimidin-4-yl]-2,2-dimethyl-piperazine-1-carboxylate (**48**) (0.15 g, 0.3 mmol) in methylene chloride (5 mL) was added hydrochloric acid in 1,4-dioxane (2 mL, 4 M). The mixture was stirred at room temperature overnight. The resulting reaction mixture was concentrated and dried under vacuum to provide a hydrochloric acid salt of compound **49** (0.12 g, 92% yield). MS ESI [M+H+]+ = 367.95.

[0342] Step 5 – Synthesis of 4-[6-(4,4-difluoro-1-piperidyl)thieno[3,2-d]pyrimidin-4-yl]-N-[(1S)-1-(3-methoxyphenyl)ethyl]-2,2-dimethyl-piperazine-1-carboxamide (P-0680): To 6-(4,4-difluoro-1-piperidyl)-4-(3,3-dimethylpiperazin-1-yl)thieno[3,2-d]pyrimidine (**49**) (0.11 g, 0.3 mmol) in N,N-dimethylformamide (5 ml) was added 1-[(1S)-1-isocyanatoethyl]-3-methoxy-benzene (0.05 g, 0.3 mmol), followed by N,N-diisopropylethylamine (0.1 ml). The reaction was stirred at room temperature for two hours. The reaction mixture was concentrated and the residue was purified by silica gel chromatography to provide compound (**P-0680**) (10 mg, 6% yield). The ^{1}HNMR spectrum was consistent with the structure of the compound. MS ESI $[M+H^+]^+ = 545.4$.

[0343] Compound ethyl 4-[4-[4-[[(1S)-1-(3-methoxyphenyl)ethyl]carbamoyl]-3,3-dimethyl-piperazin-1-yl]thieno[3,2-d]pyrimidin-6-yl]piperazine-1-carboxylate (P-0681) was prepared according to the synthetic protocol set forth in Example 18 and Scheme 15. The data from the ^{1}H NMR and mass spectroscopy data were consistent with the structure of the compound.

Example 19: **Preparations of N-[(1S)-1-(3-methoxyphenyl)ethyl]-4-[6-(2,2,6,6-tetramethyl-1,3-dihydropyridin-4-yl)thieno[3,2-d]pyrimidin-4-yl]piperazine-1-carboxamide (P-0574) and *N*-[(1S)-1-(3-chlorophenyl)ethyl]-4-[6-(2,2,6,6-tetramethyl-1,3-dihydropyridin-4-yl)thieno[3,2-d]pyrimidin-4-yl]piperazine-1-carboxamide (P-0569)**

Scheme 16.



[0344] Step 1 – Synthesis of tert-butyl 4-[6-(2,2,6,6-tetramethyl-1,3-dihydropyridin-4-yl)thieno[3,2-d]pyrimidin-4-yl]piperazine-1-carboxylate (50): To *tert*-butyl 4-(6-bromothieno[3,2-d]pyrimidin-4-yl)piperazine-1-carboxylate (0.2 g, 0.5 mmol; prepared by the procedure described in scheme 10) in acetonitrile (5 ml) was added 2,2,6,6-tetramethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3-dihydropyridine (0.15 g, 0.57 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (35 mg, 0.046 mmol), and aqueous potassium carbonate (2 ml, 1 M). The reaction mixture was irradiated by microwave at 100 °C for 20 minutes. The reaction mixture was concentrated, partitioned between ethyl acetate, washed with brine, and dried under anhydrous sodium sulfate. After removal of drying agent and solvent, the residue was dried under vacuum to provide compound **50** as a yellow solid (0.15 g, 65% yield). MS (ESI) $[M+H^+]^+$ = 458.00. It was used for subsequent reaction without further purification.

[0345] Step 2 – Synthesis of 4-piperazin-1-yl-6-(2,2,6,6-tetramethyl-1,3-dihydropyridin-4-yl)thieno[3,2-d]pyrimidine (51): To *tert*-butyl 4-[6-(2,2,6,6-tetramethyl-1,3-dihydropyridin-4-yl)thieno[3,2-d]pyrimidin-4-yl]piperazine-1-carboxylate (0.2 g, 0.44 mmol) in acetonitrile (5 ml) was added hydrochloric acid in 1,4-dioxane (5 ml, 4 M). The reaction mixture was stirred at room temperature overnight. After removal of solvent, the residue was washed with ethyl acetate to provide hydrochloric acid salt of compound **51** as an off-white solid (0.14 g, 89% yield). MS (ESI) $[M+H^+]^+$ = 358.05. It was used for subsequent reaction without purification.

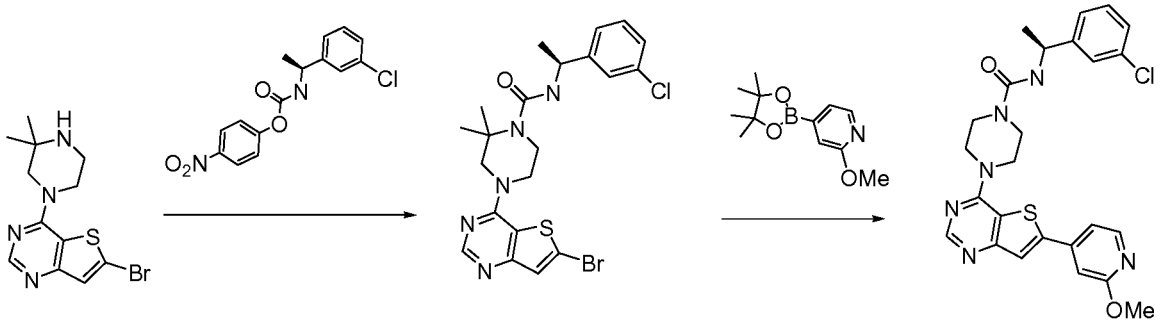
[0346] Step 3a – Synthesis of N-[(1S)-1-(3-methoxyphenyl)ethyl]-4-[6-(2,2,6,6-tetramethyl-1,3-dihydropyridin-4-yl)thieno[3,2-d]pyrimidin-4-yl]piperazine-1-carboxamide (P-0574): To 4-piperazin-1-yl-6-(2,2,6,6-tetramethyl-1,3-dihydropyridin-4-yl)thieno[3,2-d]pyrimidine (27 mg, 0.08 mmol) in acetonitrile (3 ml) was added 1-[(1S)-1-isocyanatoethyl]-3-methoxy-benzene (16 mg, 0.09 mmol), followed by N,N-diisopropylethylamine (0.1 mL). The reaction mixture was stirred at room temperature for eight hours. The reaction mixture was concentrated, partitioned between ethyl acetate, washed with brine, and dried under anhydrous sodium sulfate. After removal of drying agent and solvent, the residue was purified by column chromatography followed by preparative HPLC to provide compound **P-0574** as a white solid (5 mg, 12% yield). The ^{1}HNMR spectrum was consistent with the structure of the compound. MS(ESI) $[M+H^{+}]^{+}$ = 535.1.

[0347] Step 3b – Synthesis of N-[(1S)-1-(3-chlorophenyl)ethyl]-4-[6-(2,2,6,6-tetramethyl-1,3-dihydropyridin-4-yl)thieno[3,2-d]pyrimidin-4-yl]piperazine-1-carboxamide (P-0569): To 4-piperazin-1-yl-6-(2,2,6,6-tetramethyl-1,3-dihydropyridin-4-yl)thieno[3,2-d]pyrimidine (72 mg, 0.23 mmol) in acetonitrile (3 ml) was added (4-nitrophenyl) N-[(1S)-1-(3-chlorophenyl)ethyl]carbamate (108 mg, 0.34 mmol), followed by N,N-diisopropylethylamine (0.1 mL). The reaction mixture was irradiated by microwave at 100 °C for 20 minutes. The reaction mixture was concentrated, partitioned between ethyl acetate, washed with brine, and dried under anhydrous sodium sulfate. After removal of drying agent and solvent, the residue was purified by column chromatography followed by preparative HPLC to provide compound **P-0569** as a white solid (2 mg, 1.6% yield). The ^{1}HNMR spectrum was consistent with the structure of the compound. MS(ESI) $[M+H^{+}]^{+}$ = 539.0

[0348] Compounds (2R)-N-[(1S)-1-(3-chlorophenyl)ethyl]-4-[6-(1,3-dimethylpyrazol-4-yl)thieno[3,2-d]pyrimidin-4-yl]-2-methyl-piperazine-1-carboxamide (P-0591), (2R)-4-[6-(1,3-dimethylpyrazol-4-yl)thieno[3,2-d]pyrimidin-4-yl]-N-[(1S)-1-(3-methoxyphenyl)ethyl]-2-methyl-piperazine-1-carboxamide (P-0598), (2R)-4-[6-(1,3-dimethylpyrazol-4-yl)thieno[3,2-d]pyrimidin-4-yl]-N-[(1S)-1-(4-fluorophenyl)ethyl]-2-methyl-piperazine-1-carboxamide (P-0599), (2R)-4-[6-(1,3-dimethylpyrazol-4-yl)thieno[3,2-d]pyrimidin-4-yl]-N-[(1S)-1-(3-fluorophenyl)ethyl]-2-methyl-piperazine-1-carboxamide (P-0584), (2R)-N-[(1S)-1-[3-(difluoromethoxy)phenyl]ethyl]-4-[6-(1,3-dimethylpyrazol-4-yl)thieno[3,2-d]pyrimidin-4-yl]-2-methyl-piperazine-1-carboxamide (P-0587), (2R)-4-[6-(1,3-dimethylpyrazol-4-yl)thieno[3,2-d]pyrimidin-4-yl]-N-[(1R)-1-(3-methoxyphenyl)ethyl]-2-methyl-piperazine-1-carboxamide (P-0608), and (2R)-4-[6-(1,3-dimethylpyrazol-4-yl)thieno[3,2-d]pyrimidin-4-yl]-N-[(1R)-1-(4-fluorophenyl)ethyl]-2-methyl-piperazine-1-carboxamide (P-0609) were prepared according to the synthetic protocols set forth in Example 19 and Scheme 16. The data from the ^{1}H NMR and mass spectroscopy data were consistent with the structures of the compounds.

Example 20: **Preparation of N-[(1S)-1-(3-chlorophenyl)ethyl]-4-[6-(2-methoxy-4-pyridyl)thieno[3,2-d]pyrimidin-4-yl]-2,2-dimethyl-piperazine-1-carboxamide (P-0556)**

Scheme 17.



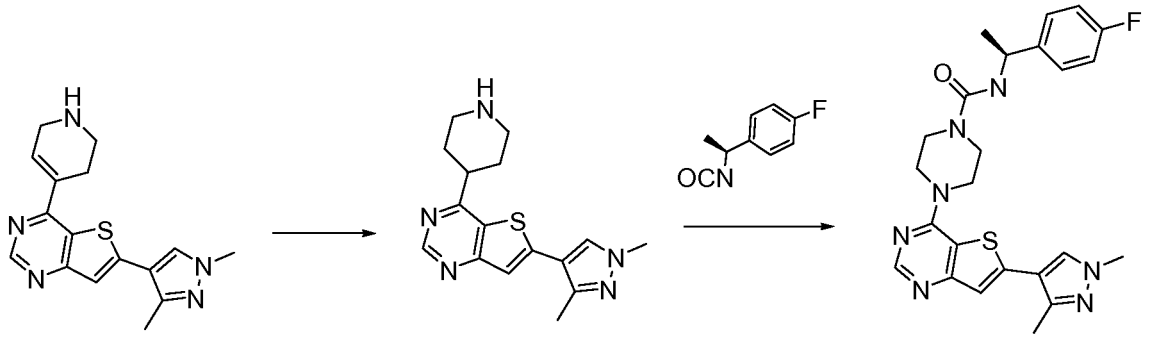
[0349] Step 1 – Synthesis of 4-(6-bromothieno[3,2-d]pyrimidin-4-yl)-N-[(1S)-1-(3-chlorophenyl)ethyl]-2,2-dimethyl-piperazine-1-carboxamide (52): To a mixture of 6-bromo-4-(3,3-dimethylpiperazin-1-yl)thieno[3,2-d]pyrimidine (0.98 g, 2.98 mmol; prepared by the procedure described in Example 18) and (4-nitrophenyl) N-[(1S)-1-(3-chlorophenyl)ethyl]carbamate (2.38 g, 5.97 mmol) in acetonitrile (12 mL) was added triethylamine (1.2 mL). The reaction was heated to 100 °C for 30 minutes by microwave. The reaction mixture was concentrated and the residue was quenched with water, extracted with ethyl acetate, washed with brine, and dried under anhydrous sodium sulfate. After removal of drying agent and solvent, the residue was purified by column chromatography to provide compound **52** (1.24 g, 81% yield).

[0350] Step 2 – Synthesis of N-[(1S)-1-(3-chlorophenyl)ethyl]-4-[6-(2-methoxy-4-pyridyl)thieno[3,2-d]pyrimidin-4-yl]-2,2-dimethyl-piperazine-1-carboxamide (P-0556): To 4-(6-bromothieno[3,2-d]pyrimidin-4-yl)-N-[(1S)-1-(3-chlorophenyl)ethyl]-2,2-dimethyl-piperazine-1-carboxamide (**52**) (35 mg, 0.07 mmol) in acetonitrile (3 ml) was added 2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (21 mg, 0.09 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (9 mg, 0.012 mmol), and an aqueous potassium carbonate (1 ml, 1 M) solution. The reaction mixture was stirred at 35 °C for two hours and then at 40 °C overnight. The reaction mixture was partitioned between ethyl acetate, washed with brine, and dried under anhydrous sodium sulfate. After removal of drying agent and solvent, the residue was purified by preparative HPLC to provide compound **P-0556** as an off-white solid (4 mg, 9% yield). MS (ESI) $[M+H^+]^+ = 537.0$.

[0351] Compound N-[(1S)-1-(3-chlorophenyl)ethyl]-4-[6-(2,4-dimethylthiazol-5-yl)thieno[3,2-d]pyrimidin-4-yl]-2,2-dimethyl-piperazine-1-carboxamide (P-0557) was prepared according to the synthetic protocol set forth in Example 20 and Scheme 17. The data from the ^1H NMR and mass spectroscopy data were consistent with the structure of the compound.

Example 21: **Preparations of 6-(1,3-dimethylpyrazol-4-yl)-4-(4-piperidyl)thieno[3,2-d]pyrimidine (P-0607) and 4-[6-(1,3-dimethylpyrazol-4-yl)thieno[3,2-d]pyrimidin-4-yl]-N-[(1S)-1-(4-fluorophenyl)ethyl]piperidine-1-carboxamide (P-0603).**

Scheme 18.



P-0607 P-0603

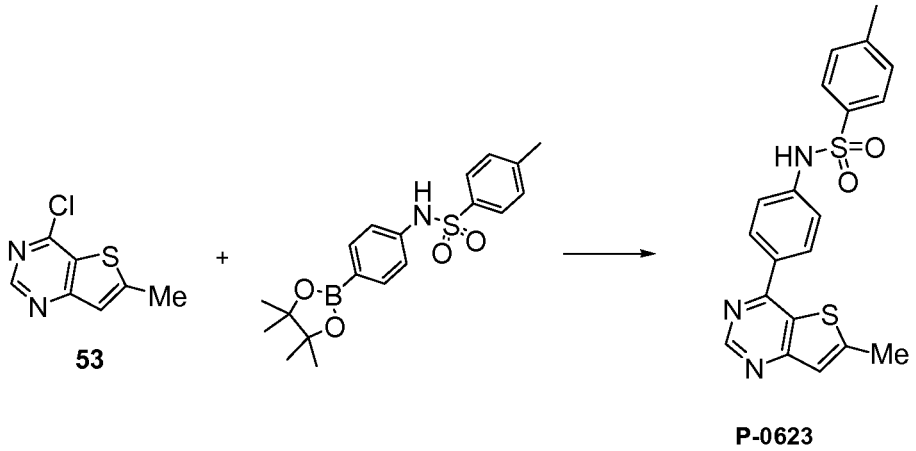
[0352] Step 1 – Synthesis of 6-(1,3-dimethylpyrazol-4-yl)-4-(4-piperidyl)thieno[3,2-d]pyrimidine (P-0607): To 6-(1,3-dimethylpyrazol-4-yl)-4-(1,2,3,6-tetrahydropyridin-4-yl)thieno[3,2-d]pyrimidine (0.15 g, 0.48 mmol; prepared by the procedure described at Example 11 and Scheme 11) in methanol (4 ml) and tetrahydrofuran (4 mL) was added palladium on carbon (10%, wet, 25 mg). The mixture was reacted under a hydrogen atmosphere (40 psi) for two hours. After removal of catalyst and solvent, the residue was dried under vacuum to provide compound **P-607** as a pale yellow solid (0.14 g, 83% yield). The data from the ^{1}H NMR spectrum were consistent with the structure of the compound. MS(ESI) $[M+H^+]^+$ = 314.0.

[0353] Step 2 – Synthesis of 4-[6-(1,3-dimethylpyrazol-4-yl)thieno[3,2-d]pyrimidin-4-yl]-N-[(1S)-1-(4-fluorophenyl)ethyl]piperidine-1-carboxamide (P-0603): To 6-(1,3-dimethylpyrazol-4-yl)-4-(1,2,3,6-tetrahydropyridin-4-yl)thieno[3,2-d]pyrimidine (**P-0607**) (15 mg, 0.048 mmol) in acetonitrile (3 ml) was added 1-fluoro-4-[(1S)-1-isocyanatoethyl]benzene (16 mg, 0.1 mmol) followed by triethylamine (0.1 mL). The reaction mixture was stirred at room temperature for four hours. The reaction mixture was concentrated, partitioned between ethyl acetate, washed with brine, and dried under anhydrous sodium sulfate. After removal of drying agent and solvent, the residue was purified by column chromatography on silica gel followed by preparative HPLC to provide compound **P-0603** as an off-white solid (4 mg, 17% yield). The data from the ^{1}H NMR spectrum were consistent with the structure of the compound. MS(ESI) $[M+H^+]^+$ = 479.0.

[0354] Compound 4-[6-(1,3-dimethylpyrazol-4-yl)thieno[3,2-d]pyrimidin-4-yl]-N-[(4-fluorophenyl)methyl]piperidine-1-carboxamide (P-0604) was prepared according to the synthetic protocol set forth in Example 21 and Scheme 18. The data from the ^{1}H NMR and mass spectroscopy data were consistent with the structure of the compound.

Example 22: Preparation of 4-methyl-N-[4-(6-methylthieno[3,2-d]pyrimidin-4-yl)phenyl]benzenesulfonamide (P-0623)

Scheme 19.

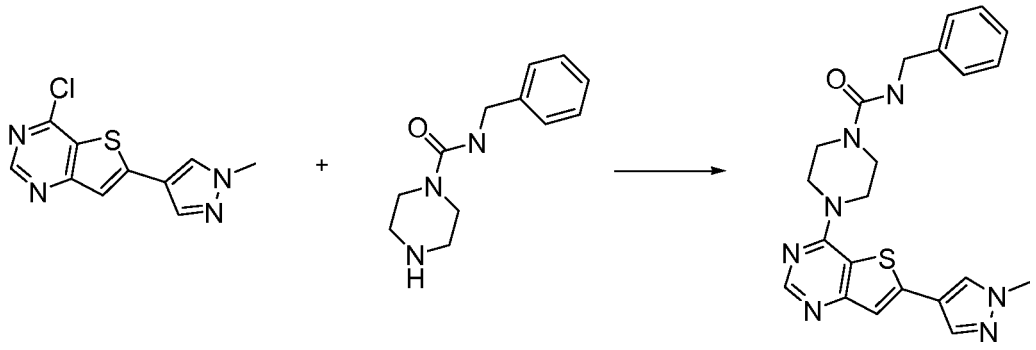


[0355] To 4-chloro-6-methyl-thieno[3,2-d]pyrimidine (45 mg, 0.24 mmol) in acetonitrile (3 ml) was added 4-methyl-N-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]benzenesulfonamide (94 mg, 0.25 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (12 mg, 0.06 mmol), and aqueous potassium carbonate (1 ml, 1 M). The reaction mixture was stirred at 80 °C for nine hours. The reaction mixture was partitioned between ethyl acetate, washed with brine, and dried under anhydrous sodium sulfate. After removal of drying agent and solvent, the residue was purified by flash chromatography on silica gel to provide compound (**P-0623**) as an off-white solid (28 mg, 29% yield). The data from the ^{1}H NMR spectrum were consistent with the structure of the compound. MS (ESI) $[M+H^+]^+ = 396.1$.

[0356] Compound N-[4-(6-methylthieno[3,2-d]pyrimidin-4-yl)phenyl]methanesulfonamide (P-0622) was prepared according to the synthetic protocol set forth in Example 22 and Scheme 19. The ^{1}H NMR and mass spectroscopy data were consistent with the structure of the compound.

Example 23: **Preparation of N-benzyl-4-[6-(1-methylpyrazol-4-yl)thieno[3,2-d]pyrimidin-4-yl]piperazine-1-carboxamide (P-0626).**

Scheme 20.



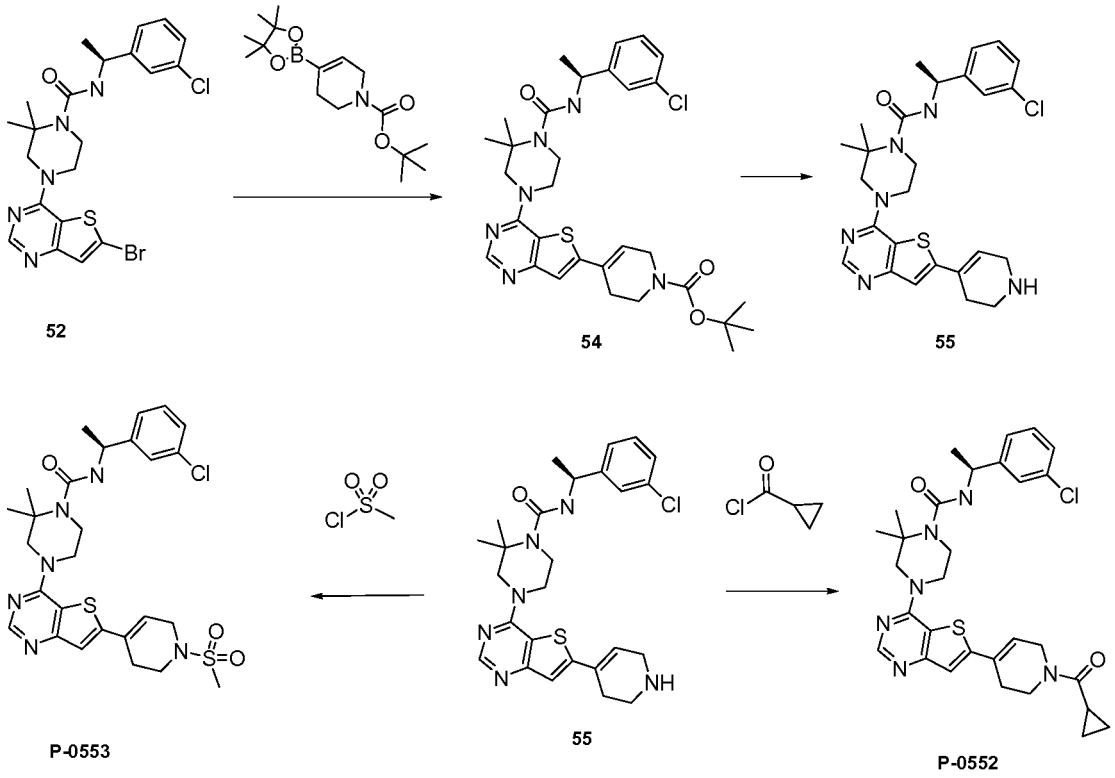
P-0626

[0357] A solution of 4-chloro-6-(1-methylpyrazol-4-yl)thieno[3,2-d]pyrimidine (42 mg, 0.17 mmol; prepared by the procedure described in Example 11 and Scheme 11), N-benzylpiperazine-1-carboxamide (41 mg, 0.19 mmol; prepared by the procedure described in Example 9 and Scheme 9) and N,N-diethylethanamine (0.1 mL, 0.717 mmol) in acetonitrile (5 mL) was stirred at 50 °C for five hours. The reaction mixture was concentrated and the residue was purified by flash chromatography on silica gel to provide compound **P-0626** as a light brown solid (35 mg, 48% yield). The data from the ^{1}H NMR spectrum were consistent with the structure of the compound. MS (ESI) $[M+H^+]^+ = 434.3$.

[0358] Compounds 4-[6-(1-methylpyrazol-4-yl)thieno[3,2-d]pyrimidin-4-yl]-N-phenyl-piperazine-1-carboxamide (P-0627) and N-phenyl-4-[6-[4-(p-tolylsulfonylamino)phenyl]thieno[3,2-d]pyrimidin-4-yl]piperazine-1-carboxamide (P-0625) were prepared according to the synthetic protocol set forth in Example 23 and Scheme 20. The ^{1}H NMR and mass spectroscopy data were consistent with the structure of the compound. The observed mass spectroscopic data are shown in Table 5.

Example 24: Preparations of N-[(1S)-1-(3-chlorophenyl)ethyl]-2,2-dimethyl-4-[6-(1-methylsulfonyl-3,6-dihydro-2H-pyridin-4-yl)thieno[3,2-d]pyrimidin-4-yl]piperazine-1-carboxamide (P-0553) and N-[(1S)-1-(3-chlorophenyl)ethyl]-4-[6-[1-(cyclopropanecarbonyl)-3,6-dihydro-2H-pyridin-4-yl]thieno[3,2-d]pyrimidin-4-yl]-2,2-dimethyl-piperazine-1-carboxamide (P-0552).

Scheme 21.



[0359] Step 1 – Synthesis of tert-butyl 4-[4-[4-[[(1S)-1-(3-chlorophenyl)ethyl]carbamoyl]-3,3-dimethyl-piperazin-1-yl]thieno[3,2-d]pyrimidin-6-yl]-3,6-dihydro-2H-pyridine-1-carboxylate (54): To 4-(6-bromothieno[3,2-d]pyrimidin-4-yl)-N-[(1S)-1-(3-chlorophenyl)ethyl]-2,2-dimethyl-piperazine-1-carboxamide (**52**) (194 mg, 0.38 mmol), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (117.88 mg, 0.38 mmol), and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (24 mg, 0.03 mmol) in 1,4 dioxane was added potassium carbonate (1M aq, 1.2 mL). The reaction mixture was stirred at 35 °C for four hours. The reaction was quenched with water and extracted with ethyl acetate. The organic layer was washed with brine and dried with anhydrous sodium sulfate. After removal of drying agent and solvent, the residue was purified by silica gel chromatography to provide compound **54**.

[0360] Step 2 – Synthesis of N-[(1S)-1-(3-chlorophenyl)ethyl]-2,2-dimethyl-4-[6-(1,2,3,6-tetrahydropyridin-4-yl)thieno[3,2-d]pyrimidin-4-yl]piperazine-1-carboxamide hydrochloride (55): To *tert*-butyl 4-[4-[4-[[(1S)-1-(3-chlorophenyl)ethyl]carbamoyl]-3,3-dimethyl-piperazin-1-yl]thieno[3,2-d]pyrimidin-6-yl]-3,6-dihydro-2H-pyridine-1-carboxylate (**54**) (163 mg, 0.27 mmol) in 1,4 dioxane was added hydrochloric acid in dioxane (0.7 mL, 4M). The reaction mixture was stirred at room temperature for three hours. After removal of solvent, the residue was dried under vacuum to provide compound **55**. It was used for subsequent reaction without purification.

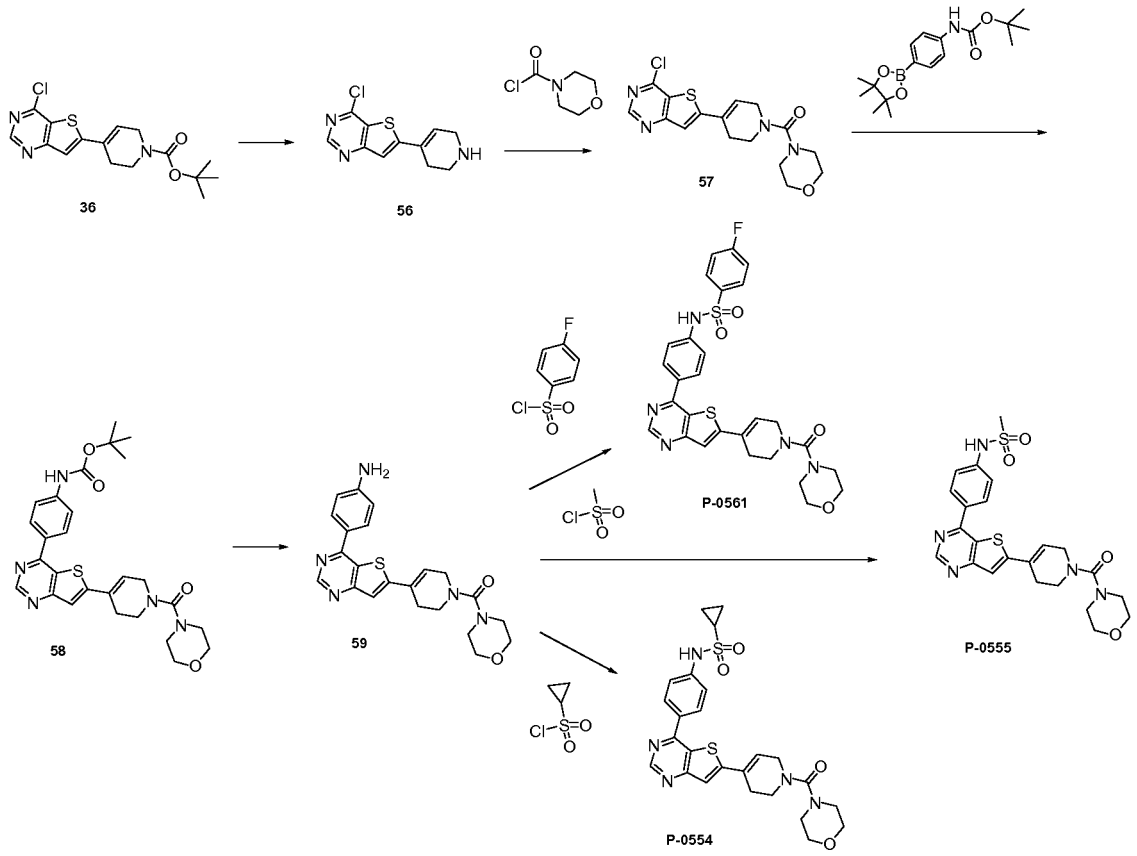
[0361] Step 3a – Synthesis of N-[(1S)-1-(3-chlorophenyl)ethyl]-2,2-dimethyl-4-[6-(1-methylsulfonyl-3,6-dihydro-2H-pyridin-4-yl)thieno[3,2-d]pyrimidin-4-yl]piperazine-1-carboxamide (P-0553): To N-[(1S)-1-(3-chlorophenyl)ethyl]-2,2-dimethyl-4-[6-(1,2,3,6-tetrahydropyridin-4-yl)thieno[3,2-d]pyrimidin-4-yl]piperazine-1-carboxamide (**55**) (49 mg, 0.1 mmol) in acetonitrile was added methanesulfonyl chloride (21.97 mg, 0.19 mmol), followed by N,N-diisopropylethylamine (0.05 ml, 0.29 mmol). The reaction mixture was stirred at room temperature overnight. After removal of solvent, the residue was purified by preparative HPLC to provide compound **P-0553** (5 mg, 8.6% yield). The data from the ^{1}H NMR were consistent with the structure of the compound. MS (ESI) [M+H+]+ = 589.7.

[0362] Step 3b – Synthesis of N-[(1S)-1-(3-chlorophenyl)ethyl]-4-[6-[1-(cyclopropanecarbonyl)-3,6-dihydro-2H-pyridin-4-yl]thieno[3,2-d]pyrimidin-4-yl]-2,2-dimethyl-piperazine-1-carboxamide (P-0552): To N-[(1S)-1-(3-chlorophenyl)ethyl]-2,2-dimethyl-4-[6-(1,2,3,6-tetrahydropyridin-4-yl)thieno[3,2-d]pyrimidin-4-yl]piperazine-1-carboxamide hydrochloride (**55**) (49 mg, 0.1 mmol) in acetonitrile was added cyclopropanecarbonyl chloride (20.04 mg, 0.19 mmol), followed by N-diisopropylethylamine (0.05 ml, 0.29 mmol). The reaction mixture was stirred at room temperature overnight. After removal of solvent, the residue was purified by preparative HPLC to provide compound **P-0552** as a fluffy white solid (11 mg, 20% yield). The data from the ^{1}H NMR were consistent with the structure of the compound. MS (ESI) [M+H+]+ = 579.3.

[0363] Compounds N-[(4-fluorophenyl)methyl]-4-[6-(1-methylsulfonyl-3,6-dihydro-2H-pyridin-4-yl)thieno[3,2-d]pyrimidin-4-yl]piperazine-1-carboxamide (P-0568), N-[(4-fluorophenyl)methyl]-4-[6-(1,2,3,6-tetrahydropyridin-4-yl)thieno[3,2-d]pyrimidin-4-yl]piperazine-1-carboxamide (P-0615) and tert-butyl 4-[4-[4-[(4-fluorophenyl)methylcarbamoyl]piperazin-1-yl]thieno[3,2-d]pyrimidin-6-yl]-3,6-dihydro-2H-pyridine-1-carboxylate (P-0616) were prepared according to the synthetic protocols set forth in Example 24 and Scheme 21. The ^{1}H NMR and mass spectroscopy data were consistent with the structures of the compounds. The observed mass spectroscopic data are shown in Table 5.

Example 25: Preparations of 4-fluoro-N-[4-[6-[1-(morpholine-4-carbonyl)-3,6-dihydro-2H-pyridin-4-yl]thieno[3,2-d]pyrimidin-4-yl]phenyl]benzenesulfonamide (P-0561), N-[4-[6-[1-(morpholine-4-carbonyl)-3,6-dihydro-2H-pyridin-4-yl]thieno[3,2-d]pyrimidin-4-yl]phenyl]methanesulfonamide (P-0555) and N-[4-[6-[1-(morpholine-4-carbonyl)-3,6-dihydro-2H-pyridin-4-yl]thieno[3,2-d]pyrimidin-4-yl]phenyl]cyclopropanesulfonamide (P-0554).

Scheme 22.



[0364] Step 1 – Synthesis of 4-chloro-6-(1,2,3,6-tetrahydropyridin-4-yl)thieno[3,2-d]pyrimidine hydrochloride (56): A solution of *tert*-butyl 4-(4-chlorothieno[3,2-d]pyrimidin-6-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (**36**) (865 mg, 2.46 mmol, prepared by the procedure described in Example 12 and Scheme 12) in acetonitrile was degassed and flushed with argon. To this solution was added hydrochloric acid in 1,4-dioxane (6 mL, 4 M). It was stirred at room temperature for three hours. The precipitate was collected and was dried under vacuum to provide hydrochloric acid salt of compound **56** as white solid. It was used for subsequent reaction without purification.

[0365] Step 2 – Synthesis of [4-(4-chlorothieno[3,2-d]pyrimidin-6-yl)-3,6-dihydro-2H-pyridin-1-yl]-morpholino-methanone (57): A solution of 4-chloro-6-(1,2,3,6-tetrahydropyridin-4-yl)thieno[3,2-d]pyrimidine hydrochloride (**56**) (0.11 g, 0.36 mmol) in acetonitrile was degassed and flushed with argon.

To this solution was added morpholine-4-carbonyl chloride (0.11 g, 0.73 mmol), followed by N,N-diisopropylethylamine (0.19 ml, 1.09 mmol). It was stirred at room temperature overnight. The precipitate was triturated with ethyl acetate and then dried under vacuum to provide compound **57**. This material was used for subsequent reaction without purification.

[0366] Step 3 – Synthesis of tert-butyl N-[4-[6-[1-(morpholine-4-carbonyl)-3,6-dihydro-2H-pyridin-4-yl]thieno[3,2-d]pyrimidin-4-yl]phenyl]carbamate (58): To a mixture of [4-(4-chlorothieno[3,2-d]pyrimidin-6-yl)-3,6-dihydro-2H-pyridin-1-yl]-morpholino-methanone (**57**) (0.2 g, 0.53 mmol), tert-butyl N-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]carbamate (0.2 g, 0.64 mmol), dichloro(1,1-bis(diphenylphosphino)ferrocene)palladium(ii) acetone adduct (0.03 g, 0.04 mmol) in acetonitrile was added aqueous potassium carbonate (3 mL, 1M). The mixture was degassed and flushed with argon. It was stirred at 80°C for three hours. The reaction mixture was cooled in ice/water bath. The precipitate was collected and dried under vacuum to provide compound **58** as gray solid (200 mg, 64% yield). This material was used for subsequent reaction without purification.

[0367] Step 4 – Synthesis of [4-[4-(4-aminophenyl)thieno[3,2-d]pyrimidin-6-yl]-3,6-dihydro-2H-pyridin-1-yl]-morpholino-methanone (59): To *tert*-butyl N-[4-[6-[1-(morpholine-4-carbonyl)-3,6-dihydro-2H-pyridin-4-yl]thieno[3,2-d]pyrimidin-4-yl]phenyl]carbamate (**58**) (0.2 g, 0.38 mmol) in 1,4-dioxane was added hydrochloric acid in dioxane (10 mL, 4 M). It was stirred at room temperature for two days. The precipitate was collected and dried under vacuum to provide the hydrochloric acid salt of compound **59**. This material was used for subsequent reaction without purification.

[0368] Step 5 – Synthesis of 4-fluoro-N-[4-[6-[1-(morpholine-4-carbonyl)-3,6-dihydro-2H-pyridin-4-yl]thieno[3,2-d]pyrimidin-4-yl]phenyl]benzenesulfonamide (P-0561): To [4-[4-(4-aminophenyl)thieno[3,2-d]pyrimidin-6-yl]-3,6-dihydro-2H-pyridin-1-yl]-morpholino-methanone (**59**) (69.5 mg, 0.16 mmol) in pyridine was added 4-fluorobenzenesulfonyl chloride (32.09 mg, 0.16 mmol). The reaction was stirred at room temperature overnight under argon. After removal of solvent, the residue was purified by preparative HPLC to provide compound **P-0561** (7 mg, 7% yield). The data from the ^{1}H NMR were consistent with the structure of the compound. MS (ESI) $[M+H^+]^+ = 579.8$.

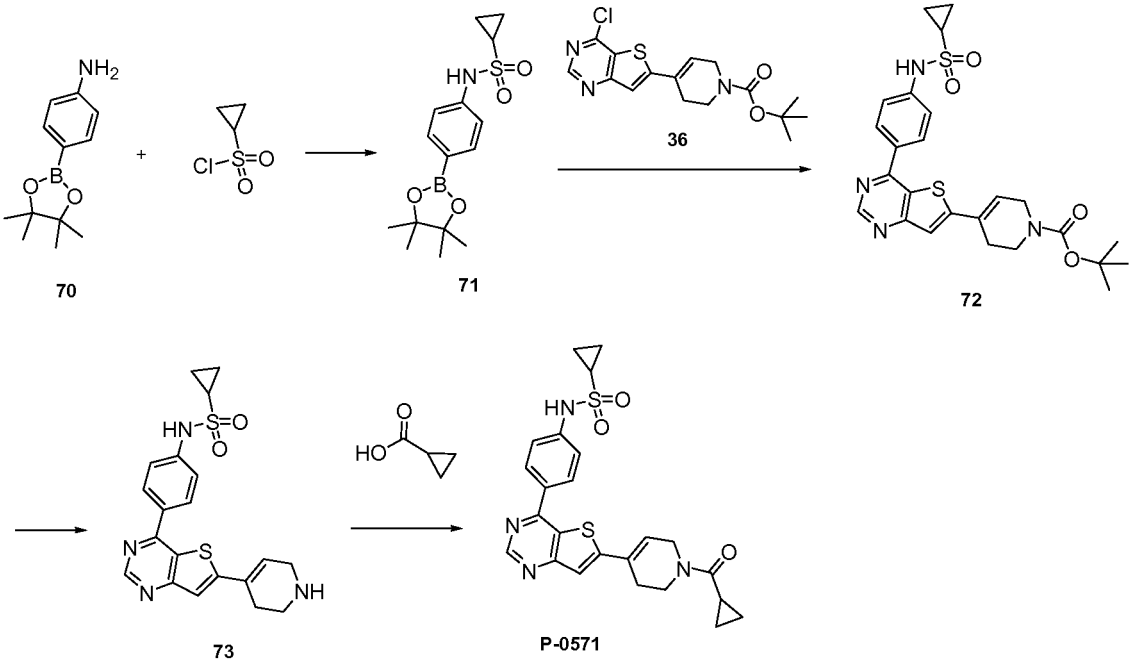
[0369] Step 6 – Synthesis of N-[4-[6-[1-(morpholine-4-carbonyl)-3,6-dihydro-2H-pyridin-4-yl]thieno[3,2-d]pyrimidin-4-yl]phenyl]methanesulfonamide (P-0555): To [4-[4-(4-aminophenyl)thieno[3,2-d]pyrimidin-6-yl]-3,6-dihydro-2H-pyridin-1-yl]-morpholino-methanone (**59**) (88 mg, 0.21 mmol) in pyridine (4 mL) was added methanesulfonyl chloride (0.03 ml, 0.42 mmol). The reaction was stirred at room temperature overnight under argon. After removal of solvent, the residue was purified by preparative HPLC to provide compound **P-0555** (14 mg, 13% yield). The data from the ^{1}H NMR spectrum were consistent with the structure of the compound. MS (ESI) $[M+H^+]^+ = 499.9$.

[0370] Step 7 – Synthesis of N-[4-[6-[1-(morpholine-4-carbonyl)-3,6-dihydro-2H-pyridin-4-yl]thieno[3,2-d]pyrimidin-4-yl]phenyl]cyclopropanesulfonamide (P-0554): To [4-[4-(4-aminophenyl)thieno[3,2-d]pyrimidin-6-yl]-3,6-dihydro-2H-pyridin-1-yl]-morpholino-methanone (**59**) (88 mg, 0.21 mmol) in pyridine (4 mL) was added cyclopropanesulfonyl chloride (0.04 ml, 0.42 mmol). The reaction was stirred at room temperature overnight under argon. After removal of solvent, the residue was purified by preparative HPLC to provide compound **P-0554** (2.5 mg, 2% yield). The data from the ^{1}H NMR spectrum were consistent with the structure of the compound. MS (ESI) $[M+H^+]^+$ = 525.9.

[0371] Compounds N-[4-[6-[1-(cyclopropanecarbonyl)-3,6-dihydro-2H-pyridin-4-yl]thieno[3,2-d]pyrimidin-4-yl]phenyl]cyclopropanesulfonamide (P-0571), N-[4-[6-[1-(cyclopropanecarbonyl)-3,6-dihydro-2H-pyridin-4-yl]thieno[3,2-d]pyrimidin-4-yl]phenyl]-4-fluoro-benzenesulfonamide (P-0570), 4-methyl-N-[4-[6-[1-(morpholine-4-carbonyl)-3,6-dihydro-2H-pyridin-4-yl]thieno[3,2-d]pyrimidin-4-yl]phenyl]benzenesulfonamide (P-0590) and 4-methyl-N-[4-[6-(4-piperidyl)thieno[3,2-d]pyrimidin-4-yl]phenyl]benzenesulfonamide (P-0592) were prepared according to the synthetic protocols set forth in Example 25 and Scheme 22. The ^{1}H NMR and mass spectroscopy data were consistent with the structures of the compounds. The observed mass spectroscopic data are shown in Table 5.

Example 26: **Preparation of N-[4-[6-[1-(cyclopropanecarbonyl)-3,6-dihydro-2H-pyridin-4-yl]thieno[3,2-d]pyrimidin-4-yl]phenyl]cyclopropanesulfonamide (P-0571).**

Scheme 23.



[0372] Step 1 – Synthesis of N-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]cyclopropanesulfonamide (71): To 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline

(**70**) (710 mg, 3.24 mmol) in pyridine (4 mL) was added cyclopropanesulfonyl chloride (0.82 ml, 8.1 mmol). The reaction was stirred at room temperature for two and half hours. The reaction mixture was concentrated twice after addition of toluene. The residue was purified by silica gel chromatography to provide compound **71** as an off-white solid. MS (ESI) $[M+H^+]^+$ = 324.15 and MS (ESI) $[M-H^+]^-$ = 322.15.

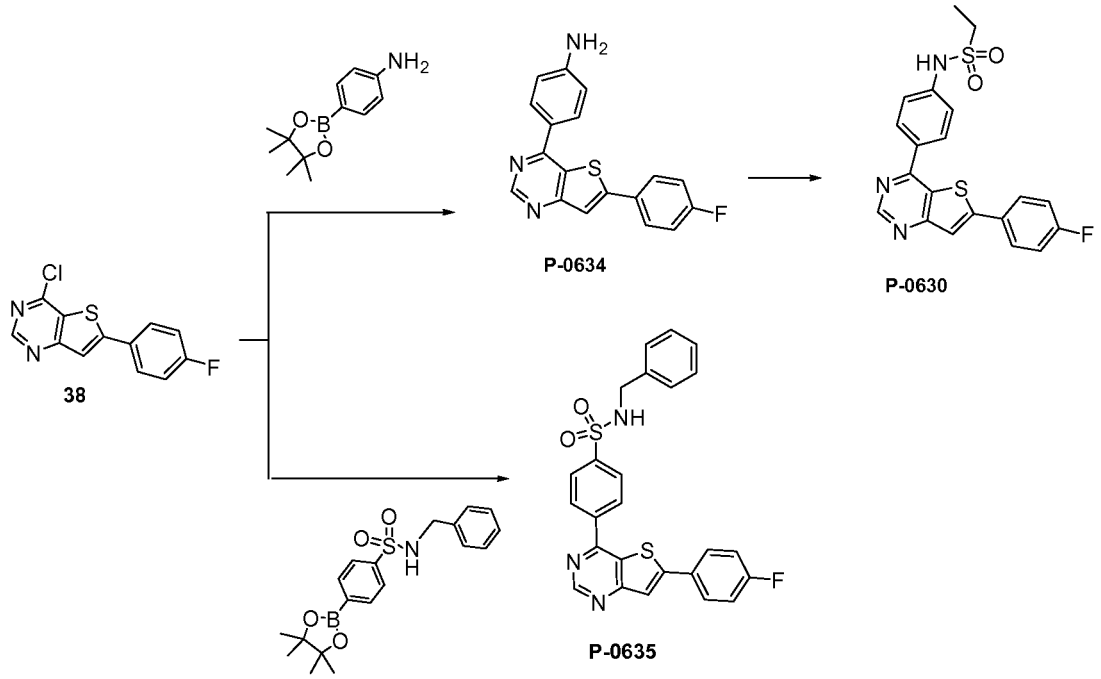
[0373] Step 2 – Synthesis of tert-butyl 4-[4-[4-(cyclopropylsulfonylamino)phenyl]thieno[3,2-d]pyrimidin-6-yl]-3,6-dihydro-2H-pyridine-1-carboxylate (72): To *tert*-butyl 4-(4-chlorothieno[3,2-d]pyrimidin-6-yl)-3,6-dihydro-2H-pyridine-1-carboxylate and N-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]cyclopropanesulfonamide in acetonitrile was added 1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) and aqueous potassium carbonate (2 mL, 1M). The reaction mixture was irradiated by microwave at 120 °C for 20 minutes in the microwave reactor. The reaction mixture was partitioned between water and 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 chromatography to provide compound **72**. MS (ESI) $[M+H^+]^+$ = 513.0.

[0374] Step 3 – Synthesis of N-[4-[6-(1,2,3,6-tetrahydropyridin-4-yl)thieno[3,2-d]pyrimidin-4-yl]phenyl]cyclopropanesulfonamide hydrochloride (73): To tert-butyl 4-[4-[4-(cyclopropylsulfonylamino)phenyl]thieno[3,2-d]pyrimidin-6-yl]-3,6-dihydro-2H-pyridine-1-carboxylate (**72**) (0.2 g, 0.39 mmol) in acetonitrile was added hydrochloric acid in 1,4-dioxane (1 mL, 4 M). The mixture was stirred at room temperature for two hours. After removal of solvent, the residue was dried under vacuum to provide hydrochloric acid salt of compound **73**. This material was used for subsequent reaction without purification.

[0375] Step 4 – Synthesis of N-[4-[6-[1-(cyclopropanecarbonyl)-3,6-dihydro-2H-pyridin-4-yl]thieno[3,2-d]pyrimidin-4-yl]phenyl]cyclopropanesulfonamide (P-0571): A mixture of cyclopropanecarboxylic acid (0.01 ml, 0.09 mmol) and O-benzotriazol-1-yl-tetramethyluronium (0.07 g, 0.18 mmol) in acetonitrile was stirred at room temperature for 30 minutes. To this mixture was then added N-[4-[6-(1,2,3,6-tetrahydropyridin-4-yl)thieno[3,2-d]pyrimidin-4-yl]phenyl]cyclopropanesulfonamide hydrochloride (**73**) (0.04 g, 0.09 mmol) and N,N-diisopropylethylamine (0.03 ml, 0.18 mmol). The reaction was stirred at room temperature for two hours. After removal of solvent, the residue was purified preparative HPLC to provide compound **P-0571** as a pale yellow solid (15 mg, 35% yield). The data from the ^{1}H NMR spectrum were consistent with the structure of the compound. MS (ESI) $[M+H^+]^+$ = 481.0.

Example 27: Preparations of 4-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]aniline (P-0634), N-[4-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]phenyl]ethanesulfonamide (P-0630), and N-benzyl-4-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]benzenesulfonamide (P-0635):

Scheme 24.



[0376] Step 1 – Synthesis of 4-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]aniline (P-0634): To 4-chloro-6-(4-fluorophenyl)thieno[3,2-d]pyrimidine (**38**) (0.12 g, 0.45 mmol) in acetonitrile (2.5 ml), were added 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.12 g, 0.55 mmol), 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (0.05 g, 0.06 mmol) and potassium carbonate (1.2 ml, 13.37 mmol) in water. The reaction mixture was heated at 170 °C for 15 minutes. The reaction mixture was poured into water, and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated, and purified with column chromatography on silica gel to provide compound **P-0634** (0.075 g, 51% yield). The data from the ^{1}H NMR spectrum were consistent with the structure of the compound. MS (ESI) $[M+H^+]^+ = 321.8$.

[0377] Step 2 – Synthesis of N-[4-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]phenyl]ethanesulfonamide (P-0630): To 4-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]aniline (**P-0634**) (0.03 g, 0.09 mmol) in dichloroethane (2 ml) were added pyridine (0.01 g, 0 mol), and ethanesulfonyl chloride (0.05 g, 0.39 mmol). The reaction was stirred at room temperature overnight. The reaction mixture was poured into water, and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated and dried

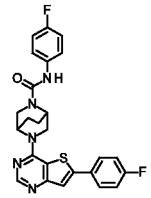
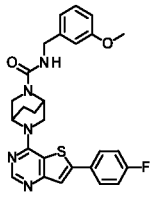
under vacuum to provide compound **P-0630** (0.016 g, 40% yield). The data from the ^{1}H NMR spectrum were consistent with the structure of the compound. MS (ESI) $[M+H^+]^+$ = 413.8.

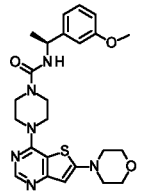
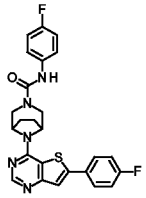
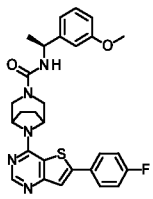
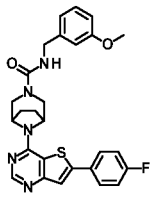
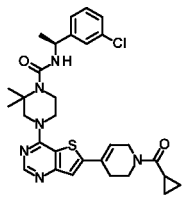
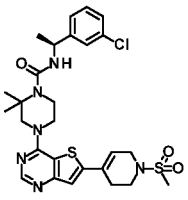
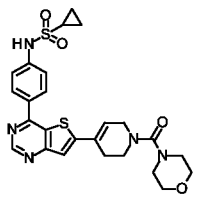
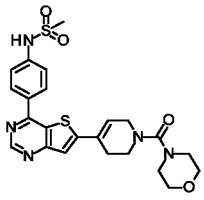
[0378] Synthesis of N-benzyl-4-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]benzenesulfonamide (P-0635): To 4-chloro-6-(4-fluorophenyl)thieno[3,2-d]pyrimidine (0.03 g, 0.11 mmol) in acetonitrile (2.5 ml), were added N-benzyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide (0.05 g, 0.13 mmol), 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (0.05 g, 0.06 mmol) and potassium carbonate (1.2 ml, 13.37 mmol) in water. The reaction was heated at 170 °C for 15 minutes. The reaction mixture was poured into water, and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated, and purified with column chromatography to provide compound **P-0635** (29 mg, 53% yield). The data from the ^{1}H NMR spectrum were consistent with the structure of the compound. MS (ESI) $[M+H^+]+$ = 475.9.

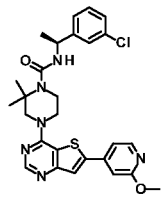
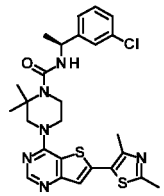
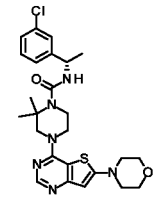
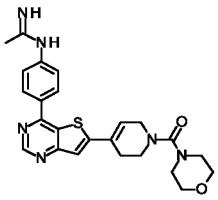
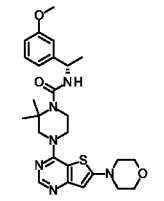
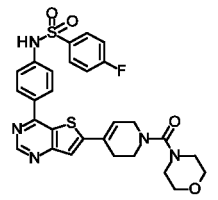
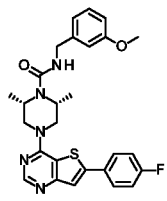
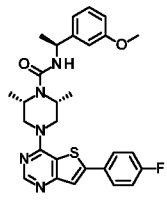
[0379] Compounds N-[4-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]phenyl]-4-methyl-benzenesulfonamide (P-0636), 1-[(4-fluorophenyl)methyl]-3-[4-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]phenyl]urea (P-0633), N-[4-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]phenyl]acetamide (P-0632) and N-[4-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]phenyl]benzamide (P-0631) were prepared according to the synthetic protocols set forth in Example 27 and Scheme 24. The ^{1}H NMR and mass spectroscopy data were consistent with the structures of the compounds. The observed mass spectroscopic data are shown in Table 5.

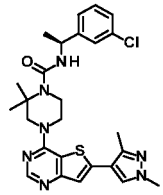
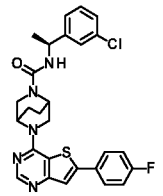
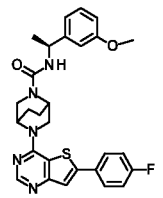
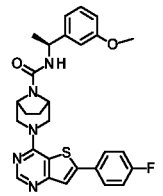
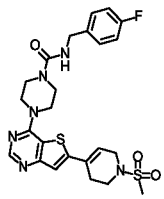
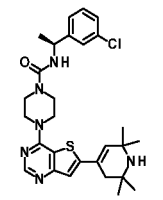
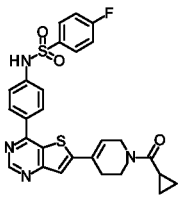
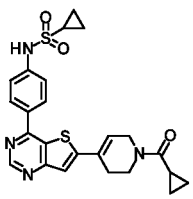
[0380] Compounds listed in Table 5 (P-0546 to P-0640, P-0677 to P-0682, P-0703, P-0704 and P-0709) were prepared according to the procedures set forth in Examples 9-27 and Schemes 9-24 above.

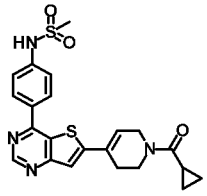
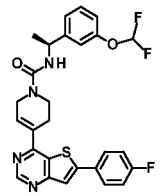
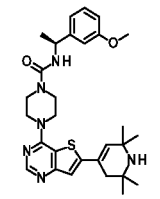
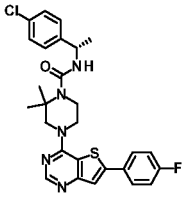
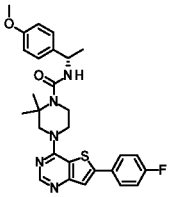
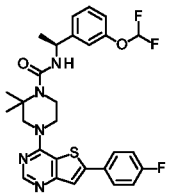
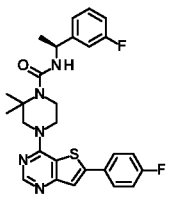
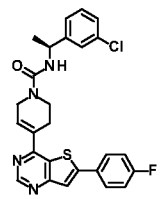
TABLE 5

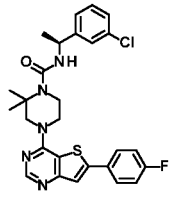
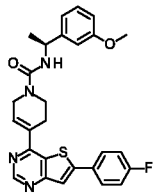
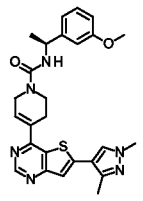
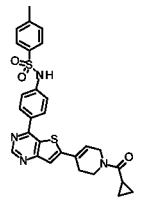
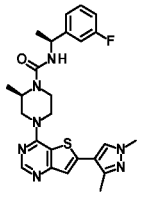
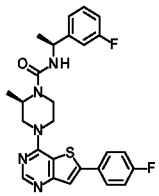
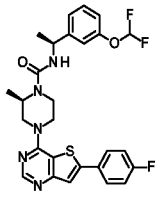
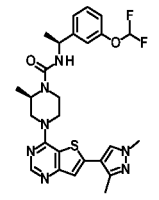
No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0546		N-(4-fluorophenyl)-5-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]-2,5-diazabicyclo[2.2.2]octane-2-carboxamide	478.3
P-0547		5-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]-N-[(3-methoxyphenyl)methyl]-2,5-diazabicyclo[2.2.2]octane-2-carboxamide	504.3

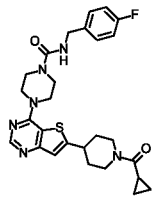
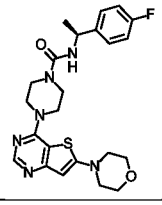
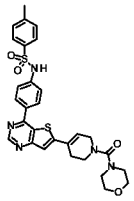
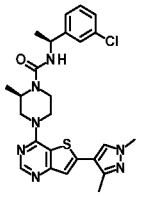
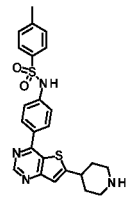
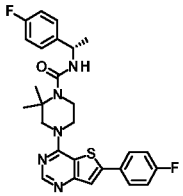
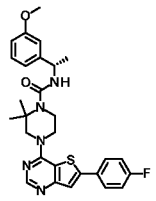
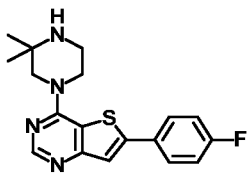
No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0548		N-[(1S)-1-(3-methoxyphenyl)ethyl]-4-(6-morpholinothieno[3,2-d]pyrimidin-4-yl)piperazine-1-carboxamide	483.3
P-0549		N-(4-fluorophenyl)-8-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxamide	478.8
P-0550		8-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]-N-[(1S)-1-(3-methoxyphenyl)ethyl]-3,8-diazabicyclo[3.2.1]octane-3-carboxamide	518.8
P-0551		8-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]-N-[(3-methoxyphenyl)methyl]-3,8-diazabicyclo[3.2.1]octane-3-carboxamide	504.8
P-0552		N-[(1S)-1-(3-chlorophenyl)ethyl]-4-[6-[1-(cyclopropanecarbonyl)-3,6-dihydro-2H-pyridin-4-yl]thieno[3,2-d]pyrimidin-4-yl]-2,2-dimethyl-piperazine-1-carboxamide	579.3
P-0553		N-[(1S)-1-(3-chlorophenyl)ethyl]-2,2-dimethyl-4-[6-(1-methylsulfonyl-3,6-dihydro-2H-pyridin-4-yl)thieno[3,2-d]pyrimidin-4-yl]piperazine-1-carboxamide	589.8
P-0554		N-[4-[6-[1-(morpholine-4-carbonyl)-3,6-dihydro-2H-pyridin-4-yl]thieno[3,2-d]pyrimidin-4-yl]phenyl]cyclopropanesulfonamide	525.9
P-0555		N-[4-[6-[1-(morpholine-4-carbonyl)-3,6-dihydro-2H-pyridin-4-yl]thieno[3,2-d]pyrimidin-4-yl]phenyl]methanesulfonamide	499.9

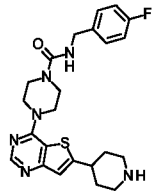
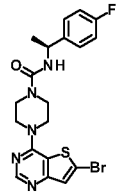
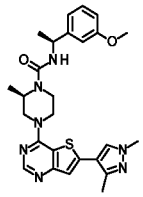
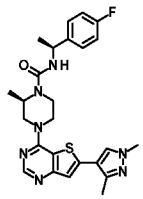
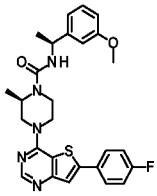
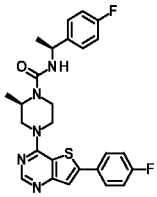
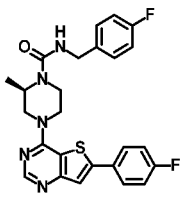
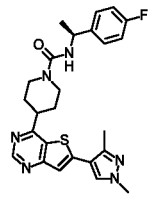
No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0556		N-[(1S)-1-(3-chlorophenyl)ethyl]-4-[6-(2-methoxy-4-pyridyl)thieno[3,2-d]pyrimidin-4-yl]-2,2-dimethyl-piperazine-1-carboxamide	537.0
P-0557		N-[(1S)-1-(3-chlorophenyl)ethyl]-4-[6-(2,4-dimethylthiazol-5-yl)thieno[3,2-d]pyrimidin-4-yl]-2,2-dimethyl-piperazine-1-carboxamide	541.2
P-0558		N-[(1S)-1-(3-chlorophenyl)ethyl]-2,2-dimethyl-4-(6-morpholinothieno[3,2-d]pyrimidin-4-yl)piperazine-1-carboxamide	515.4
P-0559		N-[4-[6-[1-(morpholine-4-carbonyl)-3,6-dihydro-2H-pyridin-4-yl]thieno[3,2-d]pyrimidin-4-yl]phenyl]acetamidine	462.9
P-0560		N-[(1S)-1-(3-methoxyphenyl)ethyl]-2,2-dimethyl-4-(6-morpholinothieno[3,2-d]pyrimidin-4-yl)piperazine-1-carboxamide	511.0
P-0561		4-fluoro-N-[4-[6-[1-(morpholine-4-carbonyl)-3,6-dihydro-2H-pyridin-4-yl]thieno[3,2-d]pyrimidin-4-yl]phenyl]benzenesulfonamide	579.8
P-0562		(2R,6S)-4-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]-N-[(3-methoxyphenyl)methyl]-2,6-dimethyl-piperazine-1-carboxamide	506.3
P-0563		(2R,6S)-4-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]-N-[(1S)-1-(3-methoxyphenyl)ethyl]-2,6-dimethyl-piperazine-1-carboxamide	520.8

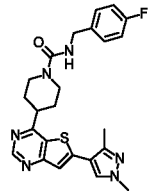
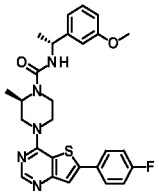
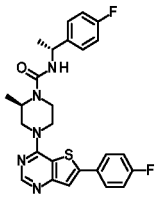
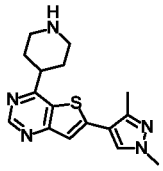
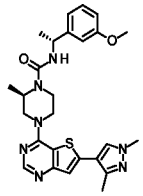
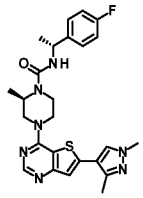
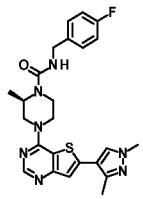
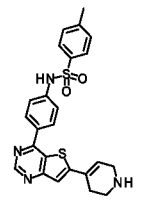
No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0564		N-[(1S)-1-(3-chlorophenyl)ethyl]-4-[6-(1,3-dimethylpyrazol-4-yl)thieno[3,2-d]pyrimidin-4-yl]-2,2-dimethyl-piperazine-1-carboxamide	524.8
P-0565		N-[(1S)-1-(3-chlorophenyl)ethyl]-5-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]-2,5-diazabicyclo[2.2.2]octane-2-carboxamide	523.9
P-0566		5-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]-N-[(1S)-1-(3-methoxyphenyl)ethyl]-2,5-diazabicyclo[2.2.2]octane-2-carboxamide	518.3
P-0567		3-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]-N-[(1S)-1-(3-methoxyphenyl)ethyl]-3,8-diazabicyclo[3.2.1]octane-8-carboxamide	518.4
P-0568		N-[(4-fluorophenyl)methyl]-4-[6-(1-methylsulfonyl-3,6-dihydro-2H-pyridin-4-yl)thieno[3,2-d]pyrimidin-4-yl]piperazine-1-carboxamide	531.2
P-0569		N-[(1S)-1-(3-chlorophenyl)ethyl]-4-[6-(2,2,6,6-tetramethyl-1,3-dihydropyridin-4-yl)thieno[3,2-d]pyrimidin-4-yl]piperazine-1-carboxamide	539.0
P-0570		N-[4-[6-[1-(cyclopropanecarbonyl)-3,6-dihydro-2H-pyridin-4-yl]thieno[3,2-d]pyrimidin-4-yl]phenyl]-4-fluoro-benzenesulfonamide	534.9
P-0571		N-[4-[6-[1-(cyclopropanecarbonyl)-3,6-dihydro-2H-pyridin-4-yl]thieno[3,2-d]pyrimidin-4-yl]phenyl]cyclopropanesulfonamide	481.0

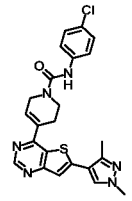
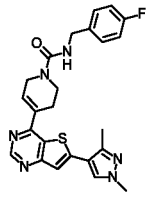
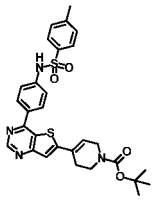
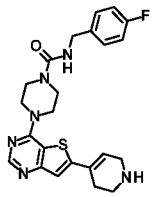
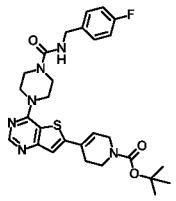
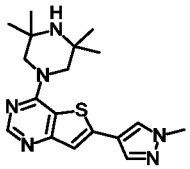
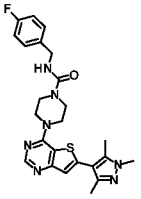
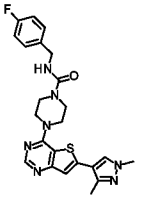
No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0572		N-[4-[6-[1-(cyclopropanecarbonyl)-3,6-dihydro-2H-pyridin-4-yl]thieno[3,2-d]pyrimidin-4-yl]phenyl]methanesulfonamide	455.1
P-0573		N-[(1S)-1-[3-(difluoromethoxy)phenyl]ethyl]-4-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]-3,6-dihydro-2H-pyridine-1-carboxamide	525.2
P-0574		N-[(1S)-1-(3-methoxyphenyl)ethyl]-4-[6-(2,2,6,6-tetramethyl-1,3-dihydropyridin-4-yl)thieno[3,2-d]pyrimidin-4-yl]piperazine-1-carboxamide	535.1
P-0575		N-[(1S)-1-(4-chlorophenyl)ethyl]-4-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]-2,2-dimethyl-piperazine-1-carboxamide	524.3
P-0576		4-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]-N-[(1S)-1-(4-methoxyphenyl)ethyl]-2,2-dimethyl-piperazine-1-carboxamide	520.4
P-0577		N-[(1S)-1-[3-(difluoromethoxy)phenyl]ethyl]-4-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]-2,2-dimethyl-piperazine-1-carboxamide	556.4
P-0578		N-[(1S)-1-(3-fluorophenyl)ethyl]-4-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]-2,2-dimethyl-piperazine-1-carboxamide	508.3
P-0579		N-[(1S)-1-(3-chlorophenyl)ethyl]-4-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]-3,6-dihydro-2H-pyridine-1-carboxamide	492.9

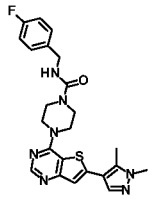
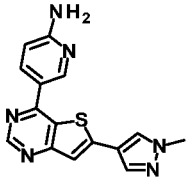
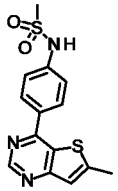
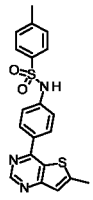
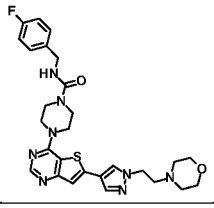
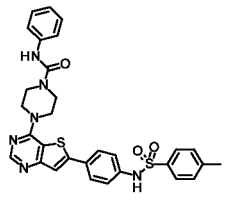
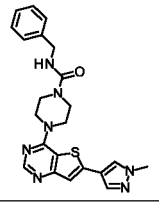
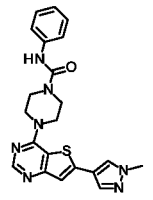
No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0580		N-[(1S)-1-(3-chlorophenyl)ethyl]-4-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]-2,2-dimethyl-piperazine-1-carboxamide	524.0
P-0581		4-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]-N-[(1S)-1-(3-methoxyphenyl)ethyl]-3,6-dihydro-2H-pyridine-1-carboxamide	489.0
P-0582		4-[6-(1,3-dimethylpyrazol-4-yl)thieno[3,2-d]pyrimidin-4-yl]-N-[(1S)-1-(3-methoxyphenyl)ethyl]-3,6-dihydro-2H-pyridine-1-carboxamide	489.0
P-0583		N-[4-[6-[1-(cyclopropanecarbonyl)-3,6-dihydro-2H-pyridin-4-yl]thieno[3,2-d]pyrimidin-4-yl]phenyl]-4-methyl-benzenesulfonamide	530.9
P-0584		(2R)-4-[6-(1,3-dimethylpyrazol-4-yl)thieno[3,2-d]pyrimidin-4-yl]-N-[(1S)-1-(3-fluorophenyl)ethyl]-2-methyl-piperazine-1-carboxamide	494.4
P-0585		(2R)-N-[(1S)-1-(3-fluorophenyl)ethyl]-4-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]-2-methyl-piperazine-1-carboxamide	494.4
P-0586		(2R)-N-[(1S)-1-[3-(difluoromethoxy)phenyl]ethyl]-4-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]-2-methyl-piperazine-1-carboxamide	542.4
P-0587		(2R)-N-[(1S)-1-[3-(difluoromethoxy)phenyl]ethyl]-4-[6-(1,3-dimethylpyrazol-4-yl)thieno[3,2-d]pyrimidin-4-yl]-2-methyl-piperazine-1-carboxamide	542.4

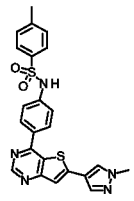
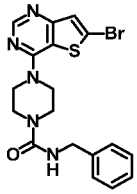
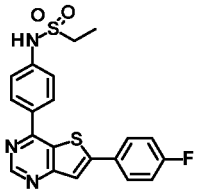
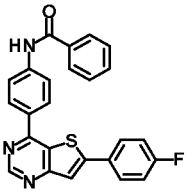
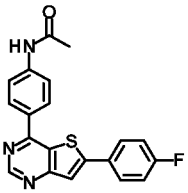
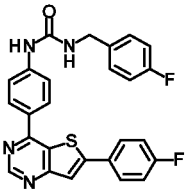
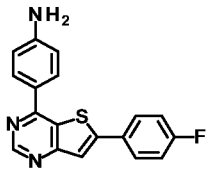
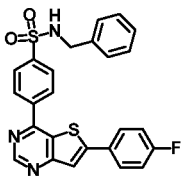
No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0588		4-[6-[1-(cyclopropanecarbonyl)-4-piperidyl]thieno[3,2-d]pyrimidin-4-yl]-N-[(4-fluorophenyl)methyl]piperazine-1-carboxamide	523.0
P-0589		N-[(1S)-1-(4-fluorophenyl)ethyl]-4-(6-morpholinothieno[3,2-d]pyrimidin-4-yl)piperazine-1-carboxamide	471.5
P-0590		4-methyl-N-[4-[6-[1-(morpholine-4-carbonyl)-3,6-dihydro-2H-pyridin-4-yl]thieno[3,2-d]pyrimidin-4-yl]phenyl]benzenesulfonamide	575.9
P-0591		(2R)-N-[(1S)-1-(3-chlorophenyl)ethyl]-4-[6-(1,3-dimethylpyrazol-4-yl)thieno[3,2-d]pyrimidin-4-yl]-2-methyl-piperazine-1-carboxamide	510.0
P-0592		4-methyl-N-[4-[6-(4-piperidyl)thieno[3,2-d]pyrimidin-4-yl]phenyl]benzenesulfonamide	464.9
P-0593		N-[(1S)-1-(4-fluorophenyl)ethyl]-4-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]-2,2-dimethyl-piperazine-1-carboxamide	508.3
P-0594		4-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]-N-[(1S)-1-(3-methoxyphenyl)ethyl]-2,2-dimethyl-piperazine-1-carboxamide	520.4
P-0595		4-(3,3-dimethylpiperazin-1-yl)-6-(4-fluorophenyl)thieno[3,2-d]pyrimidine	343.2

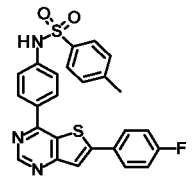
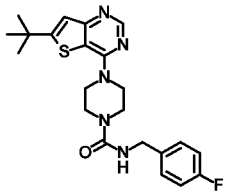
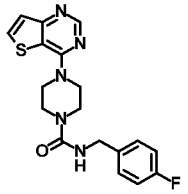
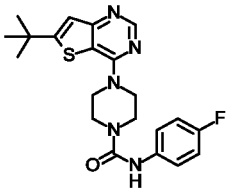
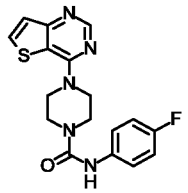
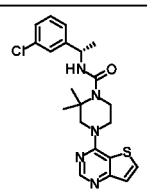
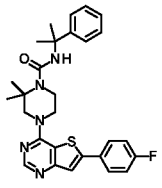
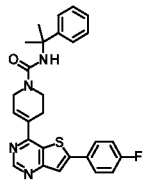
No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0596		N-[(4-fluorophenyl)methyl]-4-[6-(4-piperidyl)thieno[3,2-d]pyrimidin-4-yl]piperazine-1-carboxamide	455.0
P-0597		4-(6-bromothieno[3,2-d]pyrimidin-4-yl)-N-[(1S)-1-(4-fluorophenyl)ethyl]piperazine-1-carboxamide	465.2
P-0598		(2R)-4-[6-(1,3-dimethylpyrazol-4-yl)thieno[3,2-d]pyrimidin-4-yl]-N-[(1S)-1-(3-methoxyphenyl)ethyl]-2-methyl-piperazine-1-carboxamide	506.6
P-0599		(2R)-4-[6-(1,3-dimethylpyrazol-4-yl)thieno[3,2-d]pyrimidin-4-yl]-N-[(1S)-1-(4-fluorophenyl)ethyl]-2-methyl-piperazine-1-carboxamide	494.5
P-0600		(2R)-4-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]-N-[(1S)-1-(3-methoxyphenyl)ethyl]-2-methyl-piperazine-1-carboxamide	506.4
P-0601		(2R)-N-[(1S)-1-(4-fluorophenyl)ethyl]-4-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]-2-methyl-piperazine-1-carboxamide	494.5
P-0602		(2R)-N-[(4-fluorophenyl)methyl]-4-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]-2-methyl-piperazine-1-carboxamide	480.5
P-0603		4-[6-(1,3-dimethylpyrazol-4-yl)thieno[3,2-d]pyrimidin-4-yl]-N-[(1S)-1-(4-fluorophenyl)ethyl]piperidine-1-carboxamide	479.0

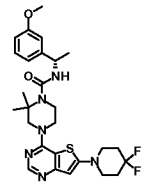
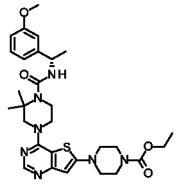
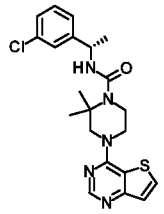
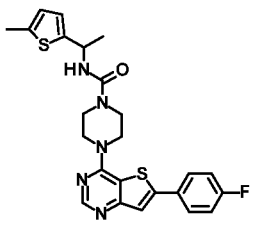
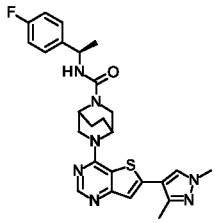
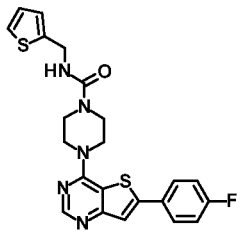
No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0604		4-[6-(1,3-dimethylpyrazol-4-yl)thieno[3,2-d]pyrimidin-4-yl]-N-[(4-fluorophenyl)methyl]piperidine-1-carboxamide	465.0
P-0605		(2R)-4-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]-N-[(1R)-1-(3-methoxyphenyl)ethyl]-2-methyl-piperazine-1-carboxamide	506.6
P-0606		(2R)-N-[(1R)-1-(4-fluorophenyl)ethyl]-4-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]-2-methyl-piperazine-1-carboxamide	494.4
P-0607		6-(1,3-dimethylpyrazol-4-yl)-4-(4-piperidyl)thieno[3,2-d]pyrimidine	314.0
P-0608		(2R)-4-[6-(1,3-dimethylpyrazol-4-yl)thieno[3,2-d]pyrimidin-4-yl]-N-[(1R)-1-(3-methoxyphenyl)ethyl]-2-methyl-piperazine-1-carboxamide	506.8
P-0609		(2R)-4-[6-(1,3-dimethylpyrazol-4-yl)thieno[3,2-d]pyrimidin-4-yl]-N-[(1R)-1-(4-fluorophenyl)ethyl]-2-methyl-piperazine-1-carboxamide	494.8
P-0610		(2R)-4-[6-(1,3-dimethylpyrazol-4-yl)thieno[3,2-d]pyrimidin-4-yl]-N-[(4-fluorophenyl)methyl]-2-methyl-piperazine-1-carboxamide	480.7
P-0611		4-methyl-N-[4-[6-(1,2,3,6-tetrahydropyridin-4-yl)thieno[3,2-d]pyrimidin-4-yl]phenyl]benzenesulfonamide	461.0

No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0612		N-(4-chlorophenyl)-4-[6-(1,3-dimethylpyrazol-4-yl)thieno[3,2-d]pyrimidin-4-yl]-3,6-dihydro-2H-pyridine-1-carboxamide	464.9
P-0613		4-[6-(1,3-dimethylpyrazol-4-yl)thieno[3,2-d]pyrimidin-4-yl]-N-[(4-fluorophenyl)methyl]-3,6-dihydro-2H-pyridine-1-carboxamide	463.2
P-0614		tert-butyl 4-[4-[4-(p-tolylsulfonylamino)phenyl]thieno[3,2-d]pyrimidin-6-yl]-3,6-dihydro-2H-pyridine-1-carboxylate	563.0
P-0615		N-[(4-fluorophenyl)methyl]-4-[6-(1,2,3,6-tetrahydropyridin-4-yl)thieno[3,2-d]pyrimidin-4-yl]piperazine-1-carboxamide	453.0
P-0616		tert-butyl 4-[4-[4-[(4-fluorophenyl)methylcarbamoyl]piperazin-1-yl]thieno[3,2-d]pyrimidin-6-yl]-3,6-dihydro-2H-pyridine-1-carboxylate	553.0
P-0617		6-(1-methylpyrazol-4-yl)-4-(2,2,6,6-tetramethyl-1,3-dihydropyridin-4-yl)thieno[3,2-d]pyrimidine	353.9
P-0618		N-[(4-fluorophenyl)methyl]-4-[6-(1,3,5-trimethylpyrazol-4-yl)thieno[3,2-d]pyrimidin-4-yl]piperazine-1-carboxamide	480.7
P-0619		4-[6-(1,3-dimethylpyrazol-4-yl)thieno[3,2-d]pyrimidin-4-yl]-N-[(4-fluorophenyl)methyl]piperazine-1-carboxamide	466.4

No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0620		4-[6-(1,5-dimethylpyrazol-4-yl)thieno[3,2-d]pyrimidin-4-yl]-N-[(4-fluorophenyl)methyl]piperazine-1-carboxamide	466.0
P-0621		5-[6-(1-methylpyrazol-4-yl)thieno[3,2-d]pyrimidin-4-yl]pyridin-2-amine	309.1
P-0622		N-[4-(6-methylthieno[3,2-d]pyrimidin-4-yl)phenyl]methanesulfonamide	320.0
P-0623		4-methyl-N-[4-(6-methylthieno[3,2-d]pyrimidin-4-yl)phenyl]benzenesulfonamide	396.1
P-0624		N-[(4-fluorophenyl)methyl]-4-[6-[1-(2-morpholinoethyl)pyrazol-4-yl]thieno[3,2-d]pyrimidin-4-yl]piperazine-1-carboxamide	551.0
P-0625		N-phenyl-4-[6-[4-(p-tolylsulfonylamino)phenyl]thieno[3,2-d]pyrimidin-4-yl]piperazine-1-carboxamide	584.9
P-0626		N-benzyl-4-[6-(1-methylpyrazol-4-yl)thieno[3,2-d]pyrimidin-4-yl]piperazine-1-carboxamide	434.3
P-0627		4-[6-(1-methylpyrazol-4-yl)thieno[3,2-d]pyrimidin-4-yl]-N-phenyl-piperazine-1-carboxamide	420.3

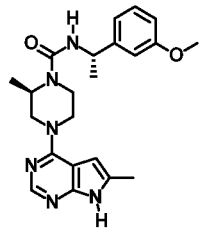
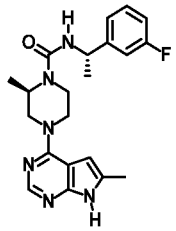
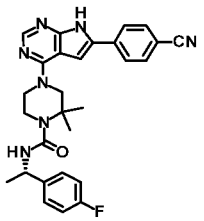
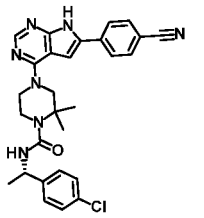
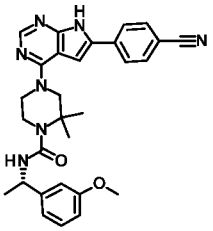
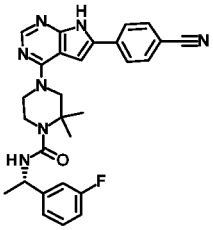
No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0628		4-methyl-N-[4-[6-(1-methylpyrazol-4-yl)thieno[3,2-d]pyrimidin-4-yl]phenyl]benzenesulfonamide	461.9
P-0629		N-benzyl-4-(6-bromothieno[3,2-d]pyrimidin-4-yl)piperazine-1-carboxamide	433.6
P-0630		N-[4-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]phenyl]ethanesulfonamide	413.8
P-0631		N-[4-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]phenyl]benzamide	425.9
P-0632		N-[4-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]phenyl]acetamide	363.8
P-0633		1-[(4-fluorophenyl)methyl]-3-[4-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]phenyl]urea	473.0
P-0634		4-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]aniline	321.8
P-0635		N-benzyl-4-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]benzenesulfonamide	475.9

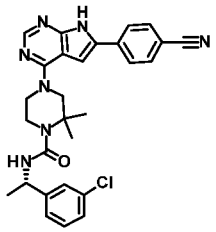
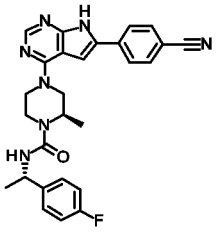
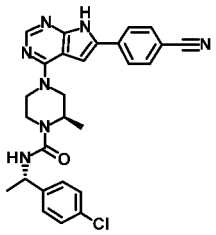
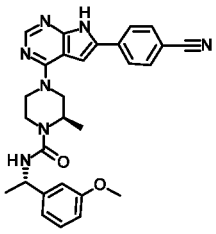
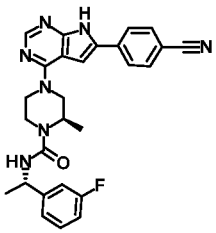
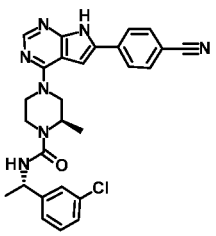
No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0636		N-[4-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]phenyl]-4-methyl-benzenesulfonamide	475.9
P-0637		4-(6-tert-butylthieno[3,2-d]pyrimidin-4-yl)-N-[(4-fluorophenyl)methyl]piperazine-1-carboxamide	428.0
P-0638		N-[(4-fluorophenyl)methyl]-4-thieno[3,2-d]pyrimidin-4-yl-piperazine-1-carboxamide	372.2
P-0639		4-(6-tert-butylthieno[3,2-d]pyrimidin-4-yl)-N-(4-fluorophenyl)piperazine-1-carboxamide	413.9
P-0640		N-(4-fluorophenyl)-4-thieno[3,2-d]pyrimidin-4-yl-piperazine-1-carboxamide	358.1
P-0677		N-[(1S)-1-(3-chlorophenyl)ethyl]-2,2-dimethyl-4-thieno[3,2-d]pyrimidin-4-yl-piperazine-1-carboxamide	430.2
P-0678		4-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]-2,2-dimethyl-N-(1-methyl-1-phenyl-ethyl)piperazine-1-carboxamide	504.3
P-0679		4-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]-N-(1-methyl-1-phenyl-ethyl)-3,6-dihydro-2H-pyridine-1-carboxamide	472.9

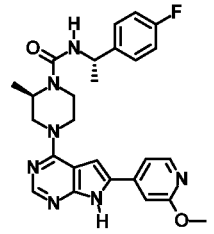
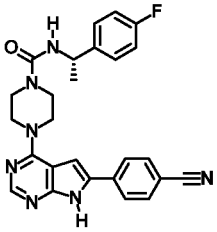
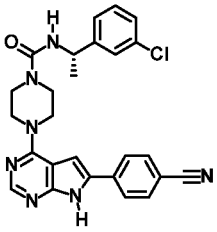
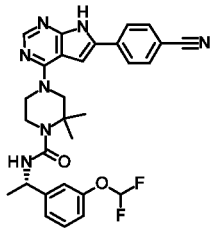
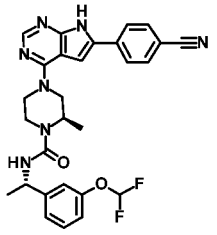
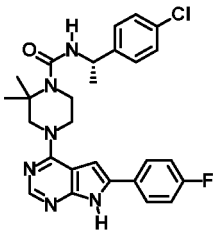
No.	Compound	Name	MS(ESI) $[M+H^+]^+$ observed
P-0680		4-[6-(4,4-difluoro-1-piperidyl)thieno[3,2-d]pyrimidin-4-yl]-N-[(1S)-1-(3-methoxyphenyl)ethyl]-2,2-dimethyl-piperazine-1-carboxamide	545.35
P-0681		ethyl 4-[4-[4-[[(1S)-1-(3-methoxyphenyl)ethyl]carbamoyl]-3,3-dimethyl-piperazin-1-yl]thieno[3,2-d]pyrimidin-6-yl]piperazine-1-carboxylate	582.45
P-0682		N-[(1S)-1-(3-chlorophenyl)ethyl]-2,2-dimethyl-4-thieno[3,2-d]pyrimidin-4-yl-piperazine-1-carboxamide	430.2
P-0703		4-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]-N-[1-(5-methyl-2-thienyl)ethyl]piperazine-1-carboxamide	482.35
P-0704		5-[6-(1,3-dimethylpyrazol-4-yl)thieno[3,2-d]pyrimidin-4-yl]-N-[(1R)-1-(4-fluorophenyl)ethyl]-2,5-diazabicyclo[2.2.2]octane-2-carboxamide	506.5
P-0709		4-[6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl]-N-(2-thienylmethyl)piperazine-1-carboxamide	453.95

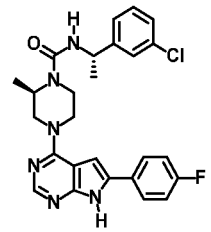
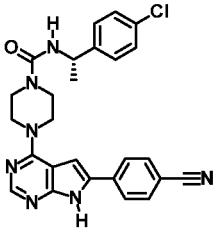
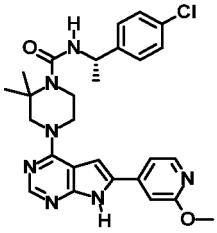
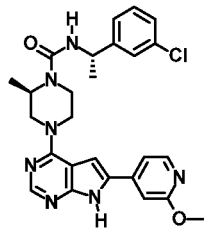
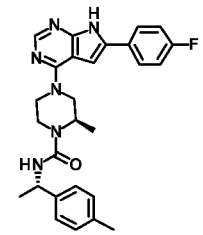
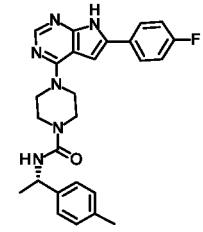
[0381] Compounds listed in Table 6 below, e.g., compounds P-0683 to P-0725 and P-0731 were prepared according to the protocols set forth in Examples 1-3 and Schemes 1-3. The ^{1}H NMR and mass spectroscopy data were consistent with the structures of the compounds.

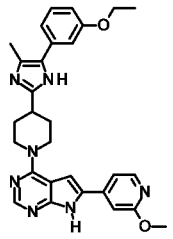
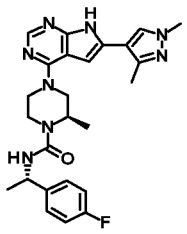
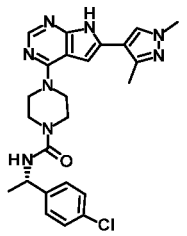
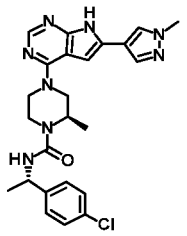
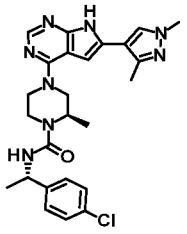
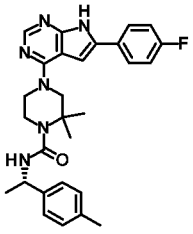
TABLE 6

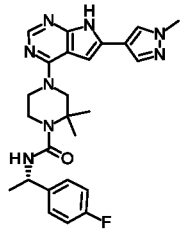
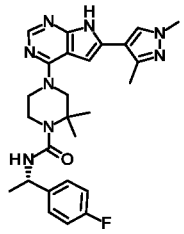
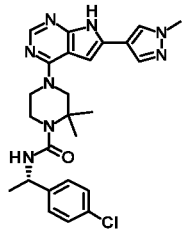
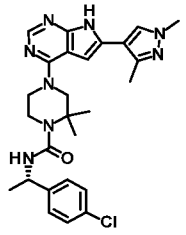
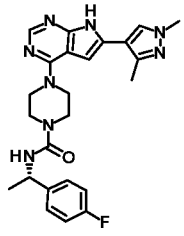
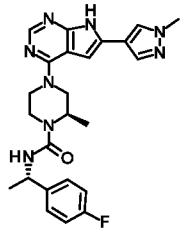
No.	Compound	Name	
P-0683		(2R)-N-[(1S)-1-(3-methoxyphenyl)ethyl]-2-methyl-4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperazine-1-carboxamide	409.4
P-0684		(2R)-N-[(1S)-1-(3-fluorophenyl)ethyl]-2-methyl-4-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperazine-1-carboxamide	397.4
P-0685		4-[6-(4-cyanophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[(1S)-1-(4-fluorophenyl)ethyl]-2,2-dimethyl-piperazine-1-carboxamide	498.5
P-0686		N-[(1S)-1-(4-chlorophenyl)ethyl]-4-[6-(4-cyanophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-2,2-dimethyl-piperazine-1-carboxamide	515.3
P-0687		4-[6-(4-cyanophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[(1S)-1-(3-methoxyphenyl)ethyl]-2,2-dimethyl-piperazine-1-carboxamide	510.8
P-0688		4-[6-(4-cyanophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[(1S)-1-(3-fluorophenyl)ethyl]-2,2-dimethyl-piperazine-1-carboxamide	498.8

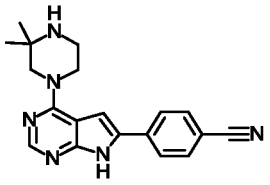
No.	Compound	Name	
P-0689		N-[(1S)-1-(3-chlorophenyl)ethyl]-4-[6-(4-cyanophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-2,2-dimethyl-piperazine-1-carboxamide	515
P-0690		(2R)-4-[6-(4-cyanophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[(1S)-1-(4-fluorophenyl)ethyl]-2-methyl-piperazine-1-carboxamide	484.8
P-0691		(2R)-N-[(1S)-1-(4-chlorophenyl)ethyl]-4-[6-(4-cyanophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-2-methyl-piperazine-1-carboxamide	500.9
P-0692		(2R)-4-[6-(4-cyanophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[(1S)-1-(3-methoxyphenyl)ethyl]-2-methyl-piperazine-1-carboxamide	496.8
P-0693		(2R)-4-[6-(4-cyanophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[(1S)-1-(3-fluorophenyl)ethyl]-2-methyl-piperazine-1-carboxamide	484.7
P-0694		(2R)-N-[(1S)-1-(3-chlorophenyl)ethyl]-4-[6-(4-cyanophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-2-methyl-piperazine-1-carboxamide	501

No.	Compound	Name	
P-0695		(2R)-N-[(1S)-1-(4-fluorophenyl)ethyl]-4-[6-(2-methoxy-4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-2-methyl-piperazine-1-carboxamide	490.9
P-0696		4-[6-(4-cyanophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[(1S)-1-(4-fluorophenyl)ethyl]piperazine-1-carboxamide	470.5
P-0697		N-[(1S)-1-(3-chlorophenyl)ethyl]-4-[6-(4-cyanophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	486.4
P-0698		4-[6-(4-cyanophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[(1S)-1-[3-(difluoromethoxy)phenyl]ethyl]-2,2-dimethyl-piperazine-1-carboxamide	546.7
P-0699		(2R)-4-[6-(4-cyanophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[(1S)-1-[3-(difluoromethoxy)phenyl]ethyl]-2-methyl-piperazine-1-carboxamide	532.8
P-0700		N-[(1S)-1-(4-chlorophenyl)ethyl]-4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-2,2-dimethyl-piperazine-1-carboxamide	508

No.	Compound	Name	
P-0701		(2R)-N-[(1S)-1-(3-chlorophenyl)ethyl]-4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-2-methyl-piperazine-1-carboxamide	493.9
P-0702		N-[(1S)-1-(4-chlorophenyl)ethyl]-4-[6-(4-cyanophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	486.05
P-0710		N-[(1S)-1-(4-chlorophenyl)ethyl]-4-[6-(2-methoxy-4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-2,2-dimethyl-piperazine-1-carboxamide	520.1
P-0711		(2R)-N-[(1S)-1-(3-chlorophenyl)ethyl]-4-[6-(2-methoxy-4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-2-methyl-piperazine-1-carboxamide	507
P-0712		(2R)-4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-2-methyl-N-[(1S)-1-(p-tolyl)ethyl]piperazine-1-carboxamide	473.4
P-0713		4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[(1S)-1-(p-tolyl)ethyl]piperazine-1-carboxamide	459.35

No.	Compound	Name	
P-0714		4-[4-[5-(3-ethoxyphenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-(2-methoxy-4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine	508.3*
P-0715		(2R)-4-[6-(1,3-dimethylpyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[(1S)-1-(4-fluorophenyl)ethyl]-2-methyl-piperazine-1-carboxamide	477.4
P-0716		N-[(1S)-1-(4-chlorophenyl)ethyl]-4-[6-(1,3-dimethylpyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	479.4
P-0717		(2R)-N-[(1S)-1-(4-chlorophenyl)ethyl]-2-methyl-4-[6-(1-methylpyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	479.3
P-0718		(2R)-N-[(1S)-1-(4-chlorophenyl)ethyl]-4-[6-(1,3-dimethylpyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-2-methyl-piperazine-1-carboxamide	493.3
P-0719		4-[6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-2,2-dimethyl-N-[(1S)-1-(p-tolyl)ethyl]piperazine-1-carboxamide	487.4

No.	Compound	Name	
P-0720		N-[(1S)-1-(4-fluorophenyl)ethyl]-2,2-dimethyl-4-[6-(1-methylpyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	477.4
P-0721		4-[6-(1,3-dimethylpyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[(1S)-1-(4-fluorophenyl)ethyl]-2,2-dimethyl-piperazine-1-carboxamide	491.4
P-0722		N-[(1S)-1-(4-chlorophenyl)ethyl]-2,2-dimethyl-4-[6-(1-methylpyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	493.4
P-0723		N-[(1S)-1-(4-chlorophenyl)ethyl]-4-[6-(1,3-dimethylpyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-2,2-dimethyl-piperazine-1-carboxamide	507.4
P-0724		4-[6-(1,3-dimethylpyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-N-[(1S)-1-(4-fluorophenyl)ethyl]piperazine-1-carboxamide	463.4
P-0725		(2R)-N-[(1S)-1-(4-fluorophenyl)ethyl]-2-methyl-4-[6-(1-methylpyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]piperazine-1-carboxamide	463.4

No.	Compound	Name	
P-0731		4-[4-(3,3-dimethylpiperazin-1-yl)-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	333.3

The asterisk * in Table 6 indicates the observed MS (ESI) $[M-H^+]^-$ molecular weight.

Example 28: Compound Properties

[0382] While the inhibitory activity of the compounds on any c-kit kinase and mutants thereof is important to their activity in treating of disease, the compounds described herein show favorable properties that provide advantages as a pharmaceutical as well.

[0383] The compounds described herein are useful for treating disorders related to c-kit and mutants thereof, e.g., diseases related to unregulated kinase signal transduction, including cell proliferative disorders, fibrotic disorders and metabolic disorders, among others. As described in more detail below and in Lipson et al., U.S. 20040002534 (U.S. application 10/600, 868, filed June 23, 2003) which is incorporated herein by reference in its entirety, cell proliferative disorders which can be treated by the present disclosure include cancers, and mast cell proliferative disorders.

[0384] The presence of c-kit or mutant(s) of c-kit has also been associated with a number of different types of cancers. In addition, the association between abnormalities in c-kit and disease are not restricted to cancer. As such, c-kit has been associated with malignancies, including mast cell tumors, small cell lung cancer, testicular cancer, gastrointestinal stromal tumors (GISTs), glioblastoma, astrocytoma, neuroblastoma, carcinomas of the female genital tract, sarcomas of neuroectodermal origin, colorectal carcinoma, carcinoma in situ, Schwann cell neoplasia associated with neurofibromatosis, acute myelocytic leukemia, acute lymphocytic leukemia, chronic myelogenous leukemia, mastocytosis, melanoma, and canine mast cell tumors, and inflammatory diseases, including asthma, rheumatoid arthritis, allergic rhinitis, multiple sclerosis, inflammatory bowel syndrome, transplant rejection, and hypereosinophilia.

Exemplary c-kit biochemical assay

[0385] Assays for biochemical cell-based activity of c-kit kinase are known in the art, for example, as described in US Patent Nos. 7498342 and 7846941, the disclosures of which are hereby incorporated by reference as it relates to such assays. The c-kit (or kinase domain thereof) is an active kinase in AlphaScreen. IC_{50} values are determined with respect to inhibition of c-Kit kinase activity, where

inhibition of phosphorylation of a peptide substrate is measured as a function of compound concentration. Compounds to be tested were dissolved in DMSO to a concentration of 20 mM. These were diluted 30 µl into 120 µl of DMSO (4 mM) and 1 µl was added to an assay plate. These were then serially diluted 1:3 (50 µl to 100 µl DMSO) for a total of 8 points. Plates were prepared such that each kinase reaction is 20 µl in 1x kinase buffer (50 mM HEPES, pH 7.2, 5 mM $MgCl_2$, 5 mM $MnCl_2$, 0.01% NP-40, 0.2% BSA), 5% DMSO and 10 µM ATP. Substrate was 100 nM biotin-(E4Y)3 (Open Source Biotech, Inc.). C-kit kinase was at 0.1 ng per sample. After incubation of the kinase reaction for 1 hour at room temperature, 5 µl of donor beads (Streptavidin coated beads (Perkin Elmer Life Science) final concentration 1 µg/ml) in stop buffer (50 mM EDTA in 1x kinase buffer) was added, the sample was mixed and incubated for 20 minutes at room temperature before adding 5 µl of acceptor beads (PY20 coated beads (Perkin Elmer Life Science) final concentration 1 µg/ml) in stop buffer. The samples were incubated for 60 minutes at room temperature and the signal per well was read on AlphaQuest reader. Phosphorylated substrate results in binding of the PY20 antibody and association of the donor and acceptor beads such that signal correlates with kinase activity. The signal vs. compound concentration was used to determine the IC_{50}.

[0386] Compounds were also tested using a similar assay with a 10-fold higher ATP concentration. For these samples, compounds to be tested were dissolved in DMSO to a concentration of 20 mM. These were diluted 30 µl into 120 µl of DMSO (4 mM) and 1 µl was added to an assay plate. These were then serially diluted 1:3 (50 µl to 100 µl DMSO) for a total of 8 points. Plates were prepared such that each kinase reaction is 20 µl in 1x kinase buffer (25 mM HEPES, pH 7.5, 2 mM $MgCl_2$, 2 mM $MnCl_2$, 0.01% Tween-20, 1 mM DTT, and 0.001% BSA), 5% DMSO and 100 µM ATP. Substrate was 30 nM biotin-(E4Y)10 (Upstate Biotech, Cat# 12-440). C-kit kinase was at 1 ng per sample. After incubation of the kinase reaction for 1 hour at room temperature, 5 µl of donor beads (Streptavidin coated beads (Perkin Elmer Life Science) final concentration 10 µg/ml) in stop buffer (25 mM HEPES pH 7.5, 100 mM EDTA, 0.3% BSA) was added, the sample was mixed and incubated for 20 minutes at room temperature before adding 5 µl of acceptor beads (PY20 coated beads (Perkin Elmer Life Science) final concentration 10 µg/ml) in stop buffer. The samples were incubated for 60 minutes at room temperature and the signal per well was read on AlphaQuest or Envision reader (Perkin Elmer Life Science). Phosphorylated substrate results in binding of the PY20 antibody and association of the donor and acceptor beads such that signal correlates with kinase activity. The signal vs. compound concentration was used to determine the IC_{50}.

[0387] The c-kit enzyme used in the above assay was either obtained from Cell Signaling Technology (Cat. #7754) or was prepared as follows: A plasmid encoding kit (DNA and encoded protein sequences shown below) was engineered using common polymerase chain reaction (PCR) methods. Complementary DNA cloned from various human tissues were purchased from Invitrogen, and these were used as substrates in the PCR reactions. Specific custom synthetic oligonucleotide primers were

designed to initiate the PCR product, and also to provide the appropriate restriction enzyme cleavage sites for ligation with the plasmids. The entire sequence encoding the enzyme was made through a gene synthesis procedure, using custom synthetic oligonucleotides covering the entire coding sequence (Invitrogen, see below).

[0388] The plasmid used for ligation with the kinase-encoding inserts was derivative of pET (Novagen) for expression using E. coli. The Kit kinase was engineered to include a Histidine tag for purification using metal affinity chromatography. The kinase-encoding plasmid was engineered as bicistronic mRNA to co-express a second protein that modifies the kinase protein during its expression in the host cell. Protein tyrosine phosphatase 1B (PTP), was co-expressed for dephosphorylation of the phospho-Tyrosines.

[0389] For protein expression, the plasmid containing the Kit gene was transformed into *E.coli* strains BL21(DE3)RIL and transformants selected for growth on LB agar plates containing appropriate antibiotics. Single colonies were grown overnight at 37°C in 200 ml TB (Terrific broth) media. 16x1L of fresh TB media in 2.8L flasks were inoculated with 10 ml of overnight culture and grown with constant shaking at 37°C. Once cultures reached an absorbance of 1.0 at 600 nm, IPTG was added and cultures were allowed to grow for a further 12 to 18 hrs at temperatures ranging from 12-30°C. Cells were harvested by centrifugation and pellets frozen at –80°C until ready for lysis.

[0390] For protein Purification; frozen *E.coli* cell pellets were resuspended in lysis buffer and lysed using standard mechanical methods. Protein was purified via poly-Histidine tags using immobilized metal affinity purification IMAC. The Kit kinase was purified using a 3 step purification process utilizing; IMAC, size exclusion chromatography and ion exchange chromatography. The poly-Histidine tag was removed using Thrombin (Calbiochem).

[0391] Compounds were assayed using a similar assay to that described above, using in a final reaction volume of 25 µl: c-Kit (h) (5-10 mU) in 8 mM MOPS pH 7.0, 0.2 mM EDTA, 10 mM $MnCl_2$, 0.1 mg/ml poly (Glu, Tyr) 4:1, 10 mM MgAcetate and γ-^{33}P-ATP (approximately 500 cpm/pmol), with appropriate concentrations of compound. Incubated for 40 minutes at room temperature and stopped by addition of 5 µl of 3% phosphoric acid. Spotted 10 µl of each sample onto Filtermat A and washed 3x with 75 mM phosphoric acid, once with methanol, dried and measured on scintillation counter (performed at Upstate USA, Charlottesville, VA).

Exemplary c-kit mutant biochemical assay

[0392] The c-kit mutant D816V (or kinase domain thereof) is an active kinase in AlphaScreen. IC_{50} values are determined with respect to inhibition of c-Kit mutant D816V kinase activity, where inhibition of phosphorylation of a peptide substrate is measured as a function of compound concentration.

Compounds to be tested were dissolved in DMSO to a concentration of 20 mM. These were diluted 30 µl into 120 µl of DMSO (4 mM) and 1 µl was added to an assay plate. These were then serially diluted 1:3 (50 µl to 100 µl DMSO) for a total of 8 points. Plates were prepared such that each kinase reaction is 20 µl in 1x kinase buffer (25 mM HEPES, pH 7.2, 8 mM $MgCl_2$, 2 mM $MnCl_2$, 50 mM NaCl, 0.01% Brij, 1 mM DTT, 0.01% BSA), 5% DMSO and 10 µM ATP. Substrate was 30 nM biotin-(E4Y)10 (EMD Millipore, Cat# 12-440). C-kit mutant D816V kinase was at 0.75 ng per sample. After incubation of the kinase reaction for 30 minutes at room temperature, 5 µl of donor beads (Streptavidin coated beads (Perkin Elmer Life Science) final concentration 7.5 µg/ml) in stop buffer (25 mM Hepes pH 7.5, 100 mM EDTA, 0.01% BSA) was added, the sample was mixed and incubated for 20 minutes at room temperature before adding 5 µl of acceptor beads (PY20 coated beads (Perkin Elmer Life Science) final concentration 7.5 ug/ml) in stop buffer. The samples were incubated for 60 minutes at room temperature and the signal per well was read on EnVision reader. Phosphorylated substrate results in binding of the PY20 antibody and association of the donor and acceptor beads such that signal correlates with kinase activity. The signal vs. compound concentration was used to determine the IC_{50}.

Protein Expression and Purification

[0393] Recombinant c-kit mutant D816V (residues 551-934, kinase insertion domain residues 694-753 deleted) with a 6x-histidine N-terminal tag was expressed in *E. coli* Arctic Express (DE3) RIL (Stratagene). Cells were grown in Terrific Broth (TB) media to an OD_{600} of 0.6 at 37°C at which temperature was reduced to 10°C, protein was induced with 1.0 mM IPTG for 18 hours and harvested by centrifugation at 8000 x g for 20 minutes. Cells were re-suspended in 0.1M KPO_4 pH 8.0, 250 mM NaCl, 10% Glycerol, 0.75% NP-40, 25 mM Imidazole, 5 mM BME with 0.2 mg/ml Lysosyme, 2.0 mM PMSF, 25µg/ml DNAse I, incubated in ice for 30 minutes and lysed with a cell disruptor (MicroFluidics). The lysate was clarified by centrifugation at 20,000 x g for 2 hours. The protein was captured with Talon resin (Clontech). Contaminating proteins were washed off with 25 mM Tris-HCl pH 8.3, 250 mM NaCl, 15% Glycerol, 1% Triton X-100, and protein eluted using 100 mM EDTA. The protein was further purified using Gel Filtration column 26/600 Superdex 200 (GE) in 50 mM Tris-HCl, pH 8.0, 250 mM NaCl, 15% Glycerol, 5 mM BME. The protein was aliquoted and flash-frozen in liquid Nitrogen.

Exemplary cell-based assays of c-kit mutant kinase activity

[0001] The c-Kit mutant D816V inhibitors were assessed using an engineered BaF3-FL KIT D816V or BaF3-FL KIT V560G/D816V cell line. The BaF3-FL KIT D816V cell lines were created by introduction of KIT mutant (D816V) full length constructs that render the cells dependent on the introduced kinase for growth. Inhibitors of c-Kit mutant D816V kinase reduce or eliminate the mediated c-kit mutant D816V kinase activation, resulting in reduced cell proliferation of the BaF3-FL Kit mutant D816V cells. This

inhibition is measured by the effect of compound concentration on cell growth to assess IC_{50} values. BaF3-FL KIT D816V 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 of RPMI Medium 1X (Invitrogen #11875-093) supplemented with 10% FBS (Invitrogen #10438), 1% Non Essential Amino Acids(Invitrogen #11140), 1% Penicillin Streptomycin (Invitrogen #15140), 1% L-Glutamine (Invitrogen #25030-081). Compounds were dissolved in DMSO at a concentration of 5 mM and were serially diluted 1:3 for a total of eight points and added to the cells to a final maximum concentration of 10 µM in 100 µl cell culture medium (final concentration 0.2% DMSO). Cells were also treated with Dasatinib as a positive control. The cells were incubated at 37 °C, 5% CO_2 for three days. ATPlite Buffer (Perkin Elmer #6016739) and substrate were equilibrated to room temperature, and enzyme/substrate Recombinant Firefly Luciferase/D- Luciferin was reconstituted. The cell plates were equilibrated to room temperature for 30 minutes, then lysed by addition of 25 uL per well of the ATPlite Reagent. The plate was mixed for 5 minutes on a plate shaker to lyse the cells. The plates were read on a Tecan Safire 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 is used to determine the IC_{50} value.

[0001] Plasmids P75635 and P75565 were engineered for mammalian cell expression. In both plasmids, full-length human v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog gene (NCBI accession NM_000222, KIT, residues M1-V976) was subcloned into the pCI-Neo vector (Promega E1841). Plasmid P75635 contains the mutation of residue Aspartic acid 816 to Valine. Plasmid P75565 contains the double mutation of residues Valine 560 to Glycine and Aspartic acid 816 to Valine. The pCI-neo Mammalian Expression Vector carries the human cytomegalovirus (CMV) immediate-early enhancer/promoter region to promote constitutive expression of KIT and contains the neomycin phosphotransferase gene, a selectable marker.

[0394] It is understood that the results of these assays may vary as assay conditions are varied. Inhibition levels determined under the conditions described herein represent a relative activity for the compounds tested under the specific conditions employed. The cell based assays are likely to show variability due to the complexity of the system and the sensitivity thereof to any changes in the assay conditions. As such, some level of inhibition in the cell based assays is indicative of the compounds having some inhibitory activity for those cells, whereas lack of inhibition below the threshold of the highest concentration tested does not necessarily indicate that the compound has no inhibitory activity on the cells, only that under the conditions tested, no inhibition is observed. In some instances, the compounds were not tested in all of the assays, or assay results were not valid.

[0395] The following table provides data indicating the c-kit and c-kit D816V biochemical inhibitory activity for exemplary compounds as described herein. In the table below, activity in the kit and kit

mutant assays is provided as follows: +++ = 0.0001 < IC_{50} < 1 μM; ++ = 1 μM < IC_{50} < 10 μM , + = 10 μM < IC_{50} < 200 μM.

Compound number	Biochemical activity (IC_{50} μM)	Biochemical activity (IC_{50} μM)
	Kit	Kit D816V
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-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	++	+++
P-0100	+++	++
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	+	++
P-0129		+++
P-0130	+	++
P-0131	++	++
P-0132	++	
P-0133	+++	++
P-0134	+++	++
P-0137	+	++
P-0138		+++
P-0139		++
P-0140		++
P-0142		+
P-0143		++
P-0144	++	+++
P-0145		+
P-0146		+
P-0147		++
P-0148		+
P-0149	+	+
P-0150	+	+

P-0151	+	+
P-0152		+++
P-0153		+
P-0154	+	++
P-0155	++	+++
P-0156	++	+++
P-0157	+	+
P-0158	+	
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-0173	+	
P-0174		+
P-0175	+	
P-0177	+	+++
P-0178	+	
P-0179		++
P-0180	+	
P-0181	+	+
P-0182	+	+
P-0183	++	+
P-0187		+++
P-0188	++	+++
P-0190	+	
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-0209	++	
P-0210	+	

P-0211		+++
P-0212	++	+++
P-0213	+	+
P-0214	+++	+++
P-0215	+	+
P-0216	+	
P-0217	++	+
P-0218	+	++
P-0219	+	++
P-0220	+++	+++
P-0221	++	+++
P-0222	++	++
P-0223	+++	+++
P-0224	+++	+++
P-0225	+	++
P-0226	++	+
P-0227	+	+
P-0228		++
P-0229	++	+++
P-0230	++	++
P-0231		++
P-0232	+	+
P-0233	+	+
P-0234	+	+
P-0235	+	++
P-0236	++	+
P-0237	+++	++
P-0238		+
P-0239	+++	++
P-0240	+	
P-0241	++	+++
P-0242	+++	++
P-0244	++	
P-0247	++	+++
P-0248	+	++
P-0249	++	+++
P-0250	+++	+++
P-0251	+	+++
P-0252	+	+++
P-0253	++	+++
P-0254	++	+++
P-0255	+++	+++
P-0256	+++	+++
P-0257	++	+++
P-0258	++	+++
P-0259	++	+++
P-0260	++	+++
P-0261	+++	+++
P-0262	+++	+++
P-0263	+	+++
P-0264	+	+++

P-0265	+	+
P-0266	++	++
P-0267	+	+++
P-0268	++	+++
P-0269	+	+++
P-0270	+	+++
P-0271	++	+++
P-0272		+++
P-0273		+++
P-0274		++
P-0275		++
P-0276	++	
P-0277	+	
P-0278	+	
P-0279	+	
P-0280	+	
P-0281	+	+++
P-0282	++	+++
P-0283	+	++
P-0284	+	++
P-0285	++	+++
P-0286	++	+++
P-0287	+	++
P-0288	+	++
P-0289	+	+++
P-0290	++	+++
P-0291	++	+++
P-0292	++	+++
P-0293	++	+++
P-0294	+	+++
P-0295	++	+++
P-0296	++	+++
P-0297	+	++
P-0298	+	++
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P-0729	+++	+++
P-0730	+++	+++

[0396] Compounds P-0001 to P-0731, i.e., compounds 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-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, P-0100, 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-0125, P-0126, P-0127, P-0128, P-0129, P-0130, P-0131, P-0132, P-0134, P-0135, P-0136, P-0137, P-0138, P-0139, P-0140, P-0141, P-0142, P-0143, P-0144, P-0145, P-0146, P-0147, P-0148, P-0149, P-0150, P-0151, P-0152, P-0153, P-0154, P-0156, P-0157, P-0158, P-0159, P-0160, P-0161, P-0163, P-0164, P-0165, P-0167, P-0168, P-0169, P-0170, P-0171, P-0172, P-0173, P-0174, P-0175, P-0176, P-0179, P-0180, P-0181, P-0182, P-0183, 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, P-0212, P-0213, P-0214, P-0215, P-0216, P-0217, P-0218, P-0219, P-0220, P-0221, P-0222, P-0223, P-0224, P-0225, P-0226, P-0227, P-0228, P-0229, P-0230, P-0231, P-0232, P-0233, P-0234, P-0235, P-0236, P-0237, P-0238, P-0239, P-0240, P-0241, P-0242, P-0243, P-0244, P-0245, P-0247, P-0248, P-0249, P-0250, P-0251, P-0252, P-0253, P-0254, P-0255, P-0256, P-0257, P-0258, P-0259, P-0260, P-0261, P-0262, P-0263, P-0264, P-0265, P-0266, P-0267, P-0268, P-0269, P-0270, P-0271, P-0272, P-0273, P-0274, P-0275, P-0276, P-0277, P-0278, P-0279, P-0280, P-0281, P-0282, P-0283, P-0284, P-0285, P-0286, P-0287, P-0288, P-0289, P-0290, P-0291, P-0292, P-0293, P-0294, P-0295, P-0296, P-0297, P-0298, P-0299, P-0300, P-0301, P-0302, P-0303, P-0304, P-0305, P-0306, P-0307, P-0308, P-0309, P-0310, P-0311, P-0312, P-0313, P-0314, P-0315, P-0316, P-0317, P-0318, P-0319, P-0320, P-0321, P-0322, P-0323, P-0324, P-0325, P-0326, P-0327, P-0328,

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[0397] Pharmacokinetic properties of compounds as described herein (including any solid forms or formulations thereof) are assessed in male Sprague Dawley rats or male Beagle dogs. Rats are dosed daily with compound either by IV injections via surgically implanted jugular catheters or by oral gavage (PO). Each compound is prepared as a 20 mg/mL stock solution in dimethyl sulfoxide, which is further diluted to provide the dosing stock at the desired concentration for the IV or PO formulations. For IV dosing, the dosing stock is diluted into a 1:1:8 mixture of Solutol ®:ethanol:water. For PO dosing, the dosing stock is diluted into 1% methylcellulose. In a cassette format (or each compound, solid form thereof or formulation thereof is done individually), compounds are diluted to 0.5 mg/mL each for IV dosing and 0.4 mg/mL each for PO dosing and dosed at 1 mg/kg (2 mL/kg) or 2 mg/kg (5 mL/kg), respectively. For IV dosed animals, tail vein blood samples are collected with lithium heparin anticoagulant at 5, 15, 30, and 60 minutes and 4, 8, and 24 hours post dosing each day. For PO dosed animals, tail vein blood samples are collected with lithium heparin anticoagulant at 30 minutes, 1, 2, 4, 8 and 24 hours post dosing each day. Dogs are dosed daily by oral capsules in a suitable formulation at 50 mg/mL. Cephalic vein blood samples are collected with lithium heparin anticoagulant at 30 minutes, 1, 2, 4, 8 and 24 hours post dosing each day. All samples are processed to plasma and frozen for later analysis of each compound by LC/MS/MS. Plasma levels as a function of time are plotted to assess the AUC (ng*hr/mL). Compounds according to the present disclosure preferably show improved pharmacokinetic properties relative to previously described compounds, i.e. they have substantially higher values for one or more of AUC, Cmax and half-life relative to previously described compounds.

[0398] All patents, patent applications and other references cited in the specification 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.

[0399] 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 preferred embodiments are exemplary and are not intended as limitations on the scope of 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.

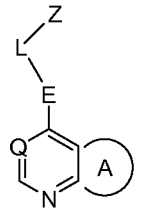
[0400] While this disclosure has been disclosed with reference to specific embodiments, it is apparent that other embodiments and variations of this disclosure may be devised by others skilled in the art without departing from the true spirit and scope of the disclosure.

[0401] In addition, where features or aspects of the disclosure are described in terms of Markush groups or other 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 Markush group or other group.

[0402] Also, unless indicated to the contrary, where various numerical values are provided for embodiments, additional embodiments are described by taking any two different values as the endpoints of a range. Such ranges are also within the scope of the described disclosure.

WHAT IS CLAIMED IS:

1. A compound of Formula (I):



I

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

wherein:

ring A is an optionally substituted 5-membered fused heterocyclic aromatic ring having from 1-2 heteroatoms as ring members selected from O, N or S; or an optionally substituted fused benzene ring; or when ring A is substituted with two or more substituents, two adjacent substituents together with the atoms to which they are attached optionally form a fused 5- or 6-membered ring;

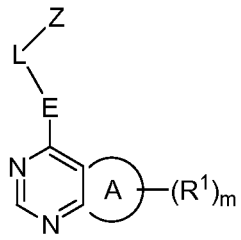
E is optionally substituted arylene, optionally substituted heteroarylene, optionally substituted heterocyclylene or optionally substituted cycloalkylene, wherein two substituents together with the atom or atoms to which they attach form an optionally substituted 3- to 6-membered monocyclic ring or an optionally substituted 7- to 9-membered bicyclic ring;

L is selected from a bond, $-N(R^a)SO_2-$, $-SO_2N(R^a)-$, $-N(R^a)SO_2N(R^a)-$, $-N(R^a)C(O)-$, $-C(O)N(R^a)-$, $-C(O)N(R^a)SO_2-$, $-SO_2-$, $-C(O)O-$, $-C(O)-$, $-N(R^a)C(O)N(R^a)-$, or $-C(=NR^a)N(R^a)-$, wherein R^a is independently H, C_{1-4}alkyl or C_{1-4} haloalkyl;

Q is N or CH;

Z is selected from H, optionally substituted aryl, optionally substituted aryl-C_{1-4}alkyl, optionally substituted heteroaryl, optionally substituted heteroaryl-C_{1-4} alkyl, optionally substituted heterocycloalkyl, optionally substituted C_{1-6}alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkyl-C_{1-4}alkyl, optionally substituted heterocyclyl or optionally substituted heterocyclyl-C_{1-4}alkyl; or when Z is a substituted aromatic ring having two or more substituents, two adjacent substituents on the aromatic ring taken together with the atoms to which they are attached optionally form a fused 5- or 6-membered ring.

2. The compound of claim 1, wherein the compound has Formula II:



II

wherein:

ring A is 5-membered fused heterocyclic aromatic ring having from 1-2 heteroatoms as ring members selected from O, N or S; or a fused benzene ring;

E is arylene, heteroarylene, heterocyclylene or cycloalkylene, each of which is optionally substituted with from 1-4 R^m substituents, wherein each R^m is independently selected from C_{1-4} alkyl, C_{1-4}alkoxy, halogen, -CN, C_{1-4}haloalkyl or C_{1-4}haloalkoxy; or two R^m substituents on the heterocyclylene are taken together to form a $-(CH_2)_n-$ bridging linkage, which together with the atoms to which they are attached forms a 7- to 9-membered bicyclic ring, wherein n is 1, 2 or 3 and wherein the bicyclic ring is optionally substituted with from 1-2 R^n substituents independently selected from C_{1-4} alkyl, halogen, $-OCH_3$, CF_3, CN, $-OCF_3$, $-CHF_2$ or $-OCHF_2$; or two R^m substituents when attaching to the same carbon atom of the heterocyclylene taken together with the atom to which they attach form a 3- to 6-membered monocyclic ring, which is optionally substituted with 1-2 R^n substituents; or two R^m substituents when attaching to the same carbon atom of the cycloalkylene or heterocyclylene are optionally taken together with the atom to which they attach form a –C(=O)- linkage;

L is selected from a bond, $-N(R^a)SO_2-$, $-SO_2N(R^a)-$, $-N(R^a)SO_2N(R^a)-$, $-N(R^a)C(O)-$, $-C(O)N(R^a)-$, $-C(O)N(R^a)SO_2-$, $-SO_2-$, -C(O)O-, -C(O)-, $-N(R^a)C(O)N(R^a)-$, or $-C(=NR^a)N(R^a)-$, wherein R^a, is independently H or C_{1-4}alkyl;

Z is selected from H, aryl, aryl-C_{1-4}alkyl, heteroaryl, heteroaryl-C_{1-4} alkyl, heterocycloalkyl, C_{1-6}alkyl, C_{3-6}cycloalkyl, $-N(R^b)(R^c)$, cycloalkyl-C_{1-4}alkyl, heterocyclyl or heterocyclyl-C_{1-4}alkyl, wherein the aliphatic or aromatic portion of Z is each independently optionally substituted with from 1-3 R^d groups, wherein each R^d is independently selected from C_{1-6}alkyl, C_{1-6} haloalkyl, halogen, C_{1-6}alkoxy, C_{1-6} haloalkoxy, C_{3-6}cycloalkyl, heterocycloalkyl, heteroaryl, or R^2; or two adjacent R^d substituents on an aromatic ring are taken together to form a 5 or 6-membered ring; wherein each R^d group is optionally further substituted with from 1-2 R^e members selected from C_{1-6}alkyl, C_{1-6} haloalkyl, halogen, C_{1-6}alkoxy, C_{1-6} haloalkoxy, NO_2, CN, -OH, $-NH_2$, -C(O)OH, -C(S)OH, $-C(O)NH_2$, $-C(S)NH_2$, $-S(O)_2NH_2$, $-NHC(O)NH_2$, $-NHS(O)_2NH_2$, $-C(NH)NH_2$, $-OR^f$, $-SR^f$, $-OC(O)R^f$, $-OC(S)R^f$, $-C(O)R^f$, $-C(O)OR^f$, $-C(S)OR^f$, $-S(O)R^f$, $-S(O)_2R^f$, $-C(O)NHR^f$, $-C(S)NHR^f$, $-C(O)NR^fR^f$, $-S(O)_2NHR^f$, $-S(O)_2NR^fR^f$, $-C(NH)NHR^f$, $-C(NH)NR^fR^f$, $-NHC(O)R^f$, $-NHC(S)R^f$, $-NR^fC(O)R^f$, $-NHS(O)_2R^f$, $-NR^fS(O)_2R^f$ or $-NHC(O)NHR^f$, wherein R^f is C_{1-6}alkyl or aryl; and wherein R^b and R^c are each independently C_{1-6}alkyl or R^b and R^c together with the nitrogen atom to which they are attached form a 5 or 6-membered ring, which is optionally substituted with 1-3 R^e; and wherein R^2 is halogen, CN, -OH, $-NH_2$, $-NO_2$, -C(O)OH, -C(S)OH, $-C(O)NH_2$, $-C(S)NH_2$, $-S(O)_2NH_2$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHS(O)_2NH_2$, $-C(NH)NH_2$, $-OR^g$, $-SR^g$, $-OC(O)R^g$, $-OC(S)R^g$, $-C(O)R^g$, $-C(S)R^g$, $-C(O)OR^g$, $-C(S)OR^g$, $-S(O)R^g$, $-S(O)_2R^g$, $-C(O)NHR^g$, $-C(S)NHR^g$, $-C(O)NR^gR^g$, $-C(S)NR^gR^g$, $-S(O)_2NHR^g$, $-S(O)_2NR^gR^g$, $-C(NH)NHR^g$, $-C(NH)NR^gR^g$, $-NHC(O)R^g$, $-NHC(S)R^g$, $-NR^gC(O)R^g$, $-NR^gC(S)R^g$, $-NHS(O)_2R^g$, $-NR^gS(O)_2R^g$, $-NHC(O)NHR^g$, $-NHC(S)NHR^g$, $-NR^gC(O)NH_2$, $-NR^gC(S)NH_2$, $-NR^gC(O)NHR^g$, $-NR^gC(S)NHR^g$,

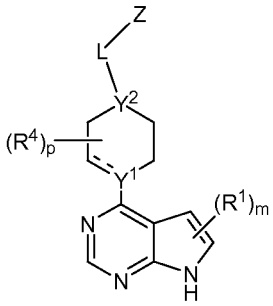
-NHC(O)NR^{g}R^g, -NHC(S)NR^{g}R^g, -NR^{g}C(O)NR^{g}R^g, -NR^{g}C(S)NR^{g}R^g, -NHS(O)$_2$NHR^g, -NR^{g}S(O)$_2$NH$_2$, -NR^{g}S(O)$_2$NHR^g, -NHS(O)$_2$NR^{g}R^g, -NR^{g}S(O)$_2$NR^{g}R^g, -NHR^g or -NR^{g}R^g, wherein each R^g is independently C$_{1-6}$alkyl, aryl, aryl-C$_{1-2}$alkyl, C$_{3-6}$cycloalkyl, C$_{3-6}$cycloalkyl-C$_{1-4}$alkyl, heteroaryl, heteroaryl-C$_{1-4}$alkyl, heterocycloalkyl or heterocycloalkyl-C$_{1-4}$alkyl, wherein each R^g is further optionally substituted with 1-3 R^h substituents independently selected from C$_{1-6}$alkyl, C$_{1-6}$alkoxy, halogen, C$_{1-6}$ haloalkyl or C$_{1-6}$ haloalkoxy;

each R^1 is independently selected from C$_{1-6}$alkyl, C$_{1-6}$alkoxy, C$_{2-6}$alkenyl, C$_{2-6}$alkynyl, -X^1-aryl, aryl-C$_{1-4}$alkyl-X^1-, heteroaryl-X^1-, heteroaryl-C$_{1-4}$ alkyl-X^1-, C$_{3-6}$cycloalkyl-X^1-, C$_{3-6}$cycloalkyl-C$_{1-4}$alkyl-X^1-, C$_{3-6}$cycloalkenyl-X^1-, CH$_2$=CH-X^1, C$_{3-6}$cycloalkyl-C$_{2-4}$alkenyl-X^1, C$_{3-6}$cycloalkyl-C$_{2-4}$alkynyl-X^1, heterocyclyl-X^1-, heterocyclyl-C$_{1-4}$alkyl-X^1- or R^2, wherein X^1 is a bond or –C(O)- and wherein the aliphatic or aromatic portion of R^1 is optionally substituted with from 1-5 R^3 members selected from halogen, -CH=CH$_2$, CN, -OH, -NH$_2$, -NO$_2$, -C(O)OH, -C(S)OH, -C(O)NH$_2$, -C(S)NH$_2$, -S(O)$_2$NH$_2$, -NHC(O)NH$_2$, -NHC(S)NH$_2$, -NHS(O)$_2$NH$_2$, -C(NH)NH$_2$, -OR^i, -SR^i, -OC(O)R^i, -OC(S)R^i, -C(O)R^i, -C(S)R^i, -C(O)OR^i, -C(S)OR^i, -S(O)R^i, -S(O)$_2$R^i, -C(O)NHR^i, -C(S)NHR^i, -C(O)NR^{i}R^i, -C(S)NR^{i}R^i, -S(O)$_2$NHR^i, -S(O)$_2$NR^{i}R^i, -C(NH)NHR^i, -C(NH)NR^{i}R^i, -NHC(O)R^i, -NHC(S)R^i, -NR^{i}C(O)R^i, -NR^{i}C(S)R^i, -NHS(O)$_2$R^i, -NR^{i}S(O)$_2$R^i, -NHC(O)NHR^i, -NHC(S)NHR^i, -NR^{i}C(O)NH$_2$, -NR^{i}C(S)NH$_2$, -NR^{i}C(O)NHR^i, -NR^{i}C(S)NHR^i, -NHC(O)NR^{i}R^i, -NHC(S)NR^{i}R^i, -NR^{i}C(O)NR^{i}R^i, -NR^{i}C(S)NR^{i}R^i, -NHS(O)$_2$NHR^i, -NR^{i}S(O)$_2$NH$_2$, -NR^{i}S(O)$_2$NHR^i, -NHS(O)$_2$NR^{i}R^i, -NR^{i}S(O)$_2$NR^{i}R^i, -NHR^i, R^i or -NR^{i}R^i, wherein R^i is each independently C$_{1-6}$alkyl, aryl, aryl-C$_{1-2}$alkyl, C$_{3-6}$cycloalkyl, C$_{3-6}$cycloalkyl-C$_{1-4}$alkyl, heteroaryl, heteroaryl-C$_{1-4}$alkyl, heterocycloalkyl or heterocycloalkyl-C$_{1-4}$alkyl, wherein each R^i is further optionally substituted with from 1-3 R^j groups independently selected from CN, -OH, -N(R^k)(R^k), -NO$_2$, -C(O)OH, - C(O)NH$_2$, -S(O)$_2$NH$_2$, -NHC(O)NH$_2$, -C(NH)NH$_2$, -OC(O)R^k, -OC(S)R^k, -C(O)R^k, -C(S)R^k, -C(O)OR^k, -S(O)$_2$R^k, -C(O)NHR^k, C$_{1-6}$alkyl, C$_{1-6}$alkoxy, halogen, C$_{1-6}$ haloalkyl or C$_{1-6}$ haloalkoxy, wherein R^k is C$_{1-6}$alkyl; or two adjacent R^1 substituents together with the atom to which they are attached form a 4-, 5- or 6-membered carbocyclic ring or heterocyclic ring having from 1-2 heteroatoms as ring members selected from O, N or S; and

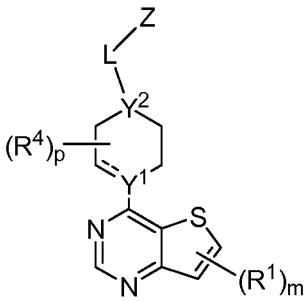
the subscript m is 0, 1 or 2.

3. The compound of claim **2**, wherein m is 1 or 2.

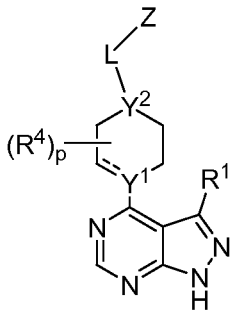
4. The compound of any of claims **1-3**, having Formula IIa, IIb or IIc:



IIa



IIb



IIc

wherein

---- is a single bond or a double bond;

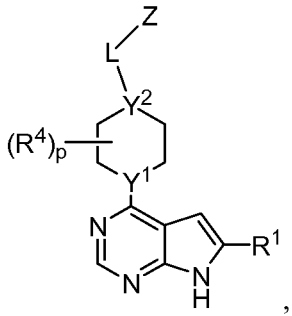
Y^1 and Y^2 are each independently N, C or CH;

each R^4 substituent is independently selected from C_{1-4} alkyl or halogen; or two R^4 substituents are taken together to form a $-(CH_2)_n-$ bridging linkage, which together with the atoms to which they are attached forms a 7- to 9-membered bicyclic ring, wherein n is 1, 2 or 3 and wherein the bicyclic ring is optionally substituted with from 1-2 substituents independently selected from C_{1-4} alkyl or halogen; or two R^4 substituents when attached to the same carbon atom are optionally taken together to form an oxo group;

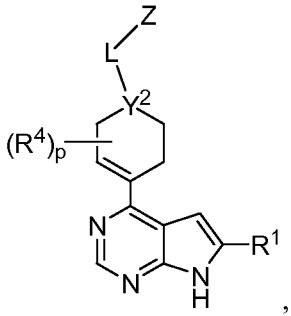
the subscript p is 0, 1, 2, 3 or 4; and

the subscript m is 1 or 2.

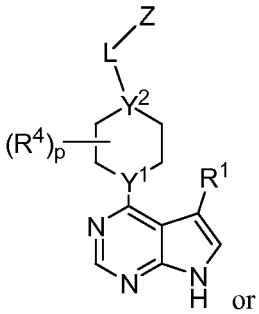
5. The compound of claim **4**, having Formula IIa-1, IIa-2, IIa-3 or IIa-4:



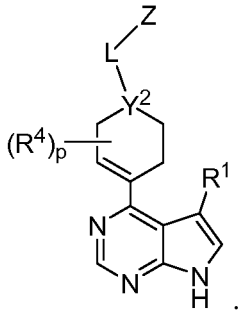
IIa-1 ,



IIa-2 ,

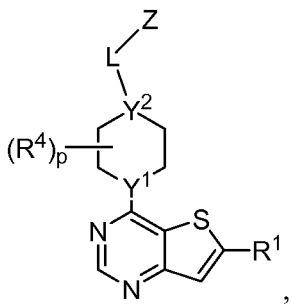


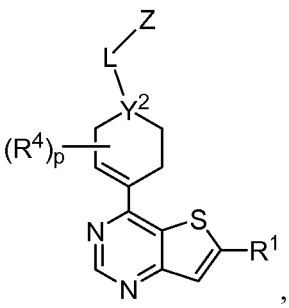
IIa-3 or

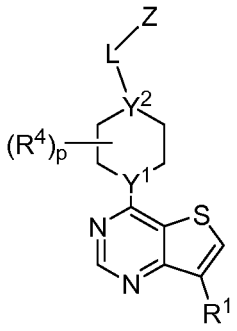


IIa-4 .

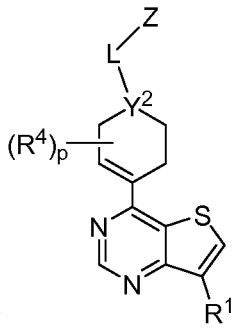
6. The compound of claim **4**, having Formula IIb-1, IIb-2, IIb-3 or IIb-4:


IIb-1

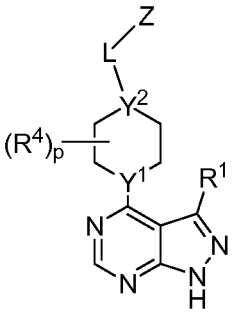

IIb-2


IIb-3

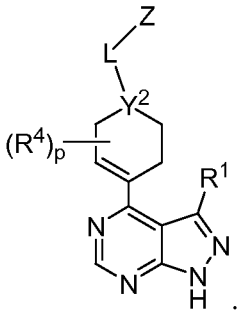
or


IIb-4

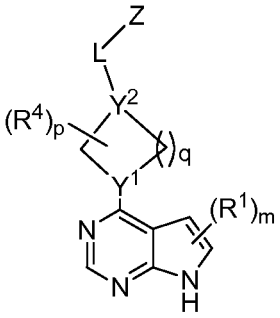
7. The compound of claim **4**, having Formula IIc-1 or IIc-2:

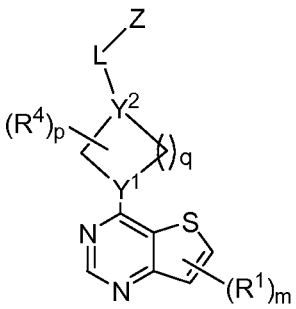

IIc-1

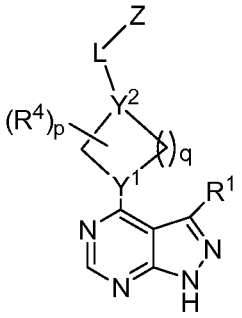
or


IIc-2

8. The compound of any of claims **1-3**, having Formula IId, IIe or IIf:


IId


IIe


IIf

wherein

Y^1 and Y^2 are each independently N or CH;

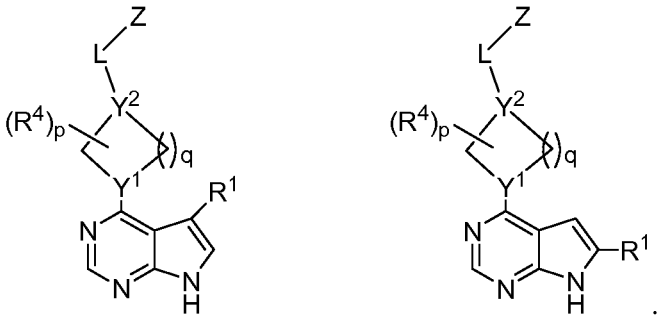
each R^4 substituent is independently selected from C_{1-4} alkyl or halogen; or two R^4 substituents are taken together to form a $-(CH_2)_n-$ bridging linkage, which together with the atoms to which they are attached forms a 5- to 8-membered bicyclic ring, wherein n is 1, 2 or 3 and wherein the bicyclic ring is optionally substituted with from 1-2 substituents independently selected from C_{1-4} alkyl or halogen; or two R^4 substituents when attached to the same carbon atom are optionally taken together to form an oxo group;

the subscript q is 1 or 2;

the subscript p is 0, 1, 2, 3 or 4; and

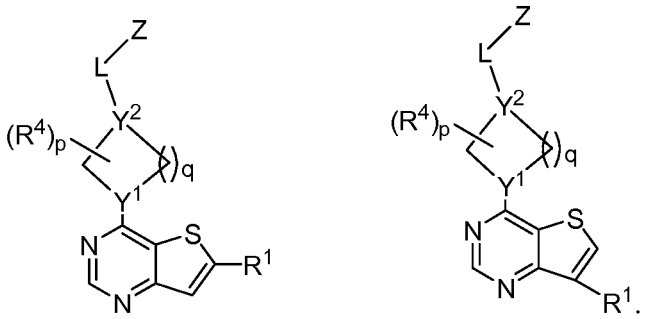
the subscript m is 1 or 2.

9. The compound of claim **8**, having Formula IId-1 or IId-2:



IId-1 IId-2

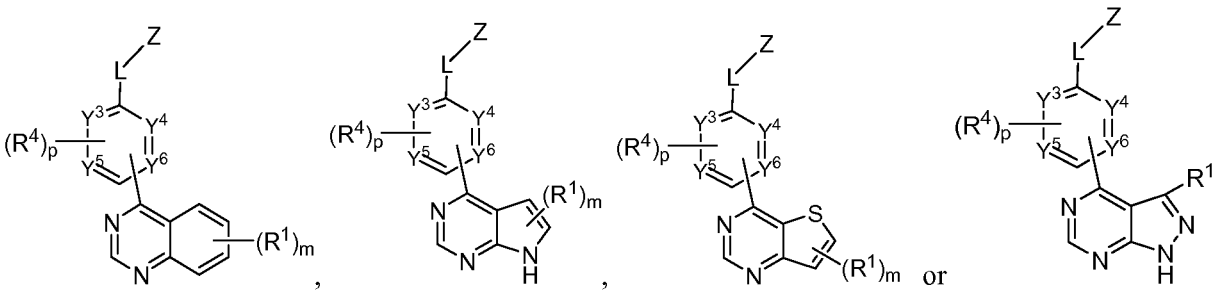
10. The compound of claim **8**, having Formula IIe-1 or IIe-2:



IIe-1 IIe-2

11. The compound of any of claims **4-10**, wherein (i) Y^1 is CH and Y^2 is N; or (ii) Y^1 is N and Y^2 is CH; or (iii) Y^1 and Y^2 are N; or (iv) Y^1 and Y^2 are CH.

12. The compound of any of claims **1-3**, having Formula IIg, IIh, IIj or IIk:



IIg IIh IIj IIk

wherein:

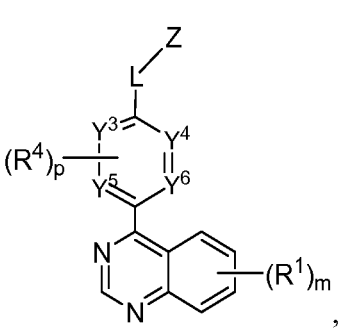
Y^3, Y^4, Y^5 and Y^6 are each independently CH or N with the proviso that Y^3, Y^4, Y^5 and Y^6 are not simultaneously N;

each R^4 substituent is independently selected from C_{1-4} alkyl or halogen;

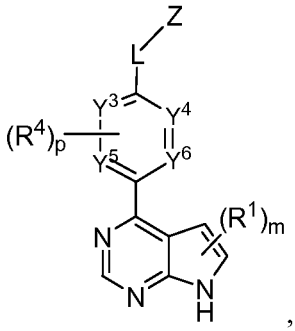
the subscript p is 0, 1, 2, 3 or 4; and

the subscript m is 1 or 2.

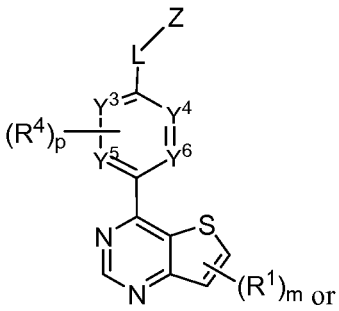
13. The compound of claim **12**, having Formula IIg-1, IIh-1, IIj-1 or IIk-1:



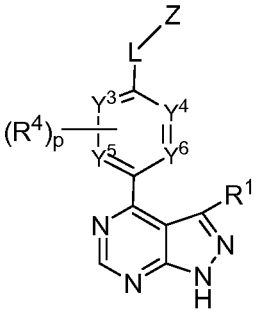
IIg-1



IIh-1

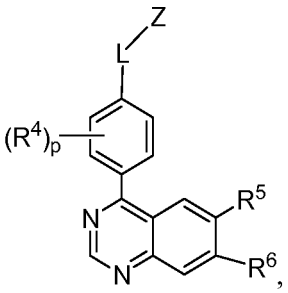


IIj-1 or

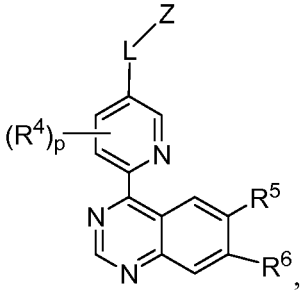


IIk-1

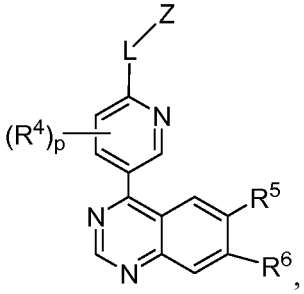
14. The compound of claim **13**, wherein the compound has Formulas IIg-1a to IIg-1g selected from:



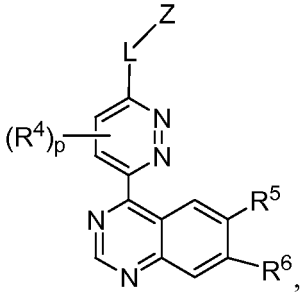
IIg-1a



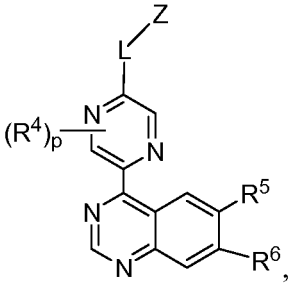
IIg-1b



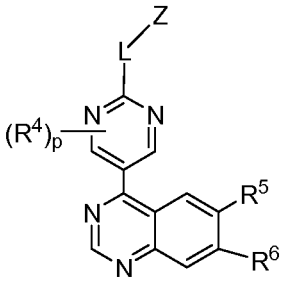
IIg-1c



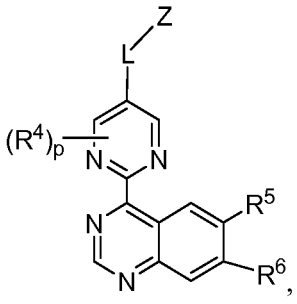
IIg-1d



IIg-1e



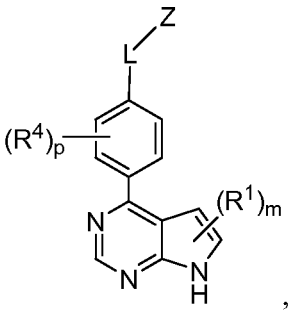
IIg-1f or

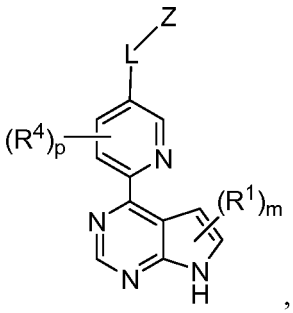


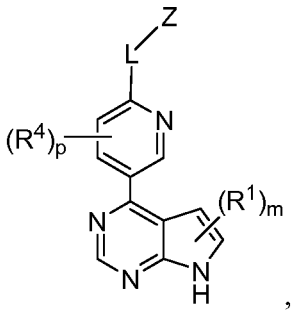
IIg-1g

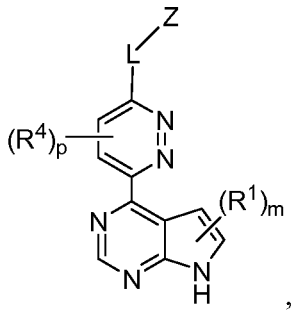
wherein R^5 and R^6 are each independently H or R^1, optionally substituted with 1-5 R^3 substituents; or R^5 and R^6 together with the atom to which they are attached form a 5- or -6-membered carbocyclic or heterocyclic ring.

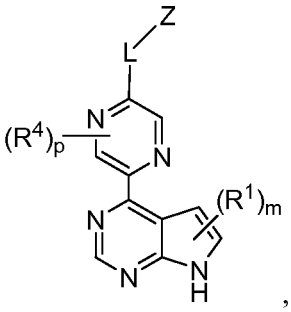
15. The compound of claim **13**, wherein the compound has Formulas IIh-1a to IIh-1g selected from:

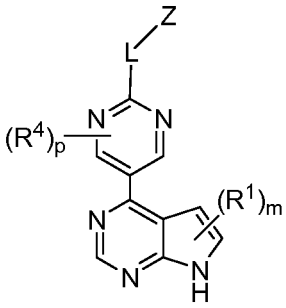

IIh-1a ,

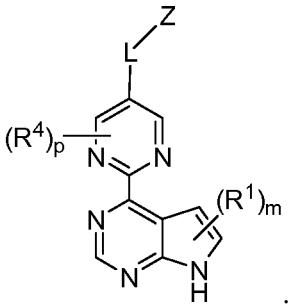

IIh-1b ,


IIh-1c ,

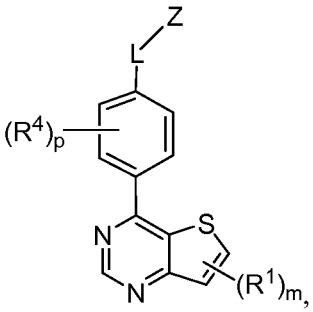

IIh-1d ,

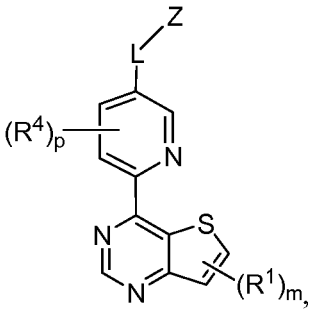

IIh-1e ,

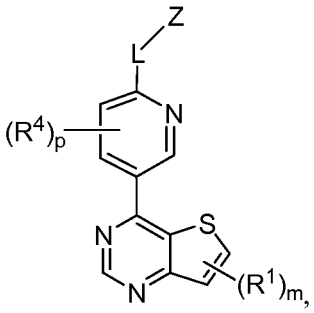

IIh-1f or

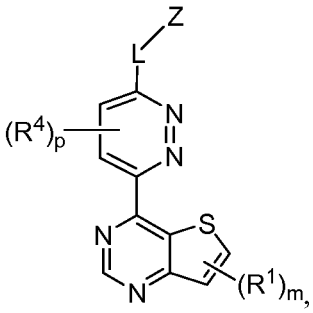

IIh-1g .

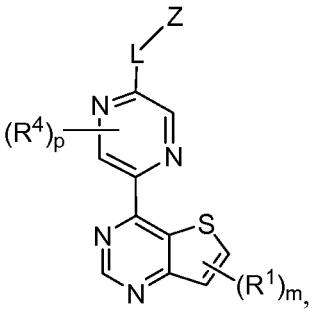
16. The compound of claim **13**, wherein the compound has Formulas IIj-1a to IIj-1g selected from:


IIj-1a

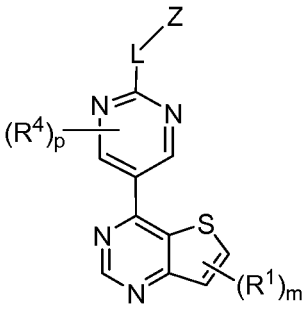

IIj-1b


IIj-1c


IIj-1d

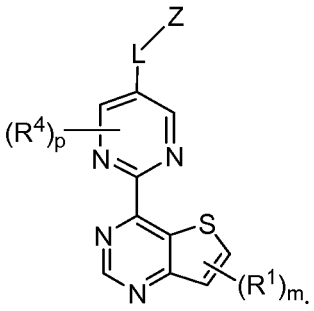


IIj-1e



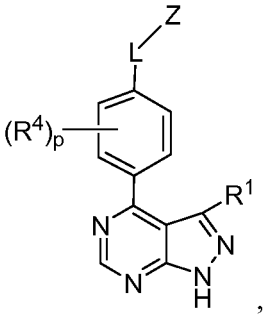
IIj-1f

or

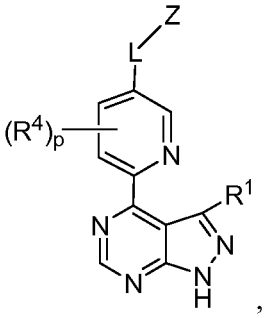


IIj-1g

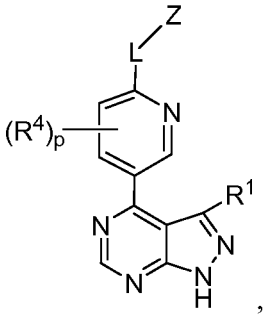
17. The compound of claim **13**, wherein the compound has Formulas IIk-1a to IIk-1g selected from:



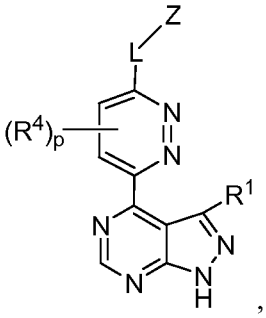
IIk-1a



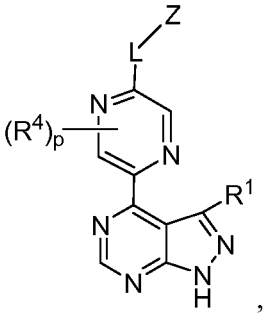
IIk-1b



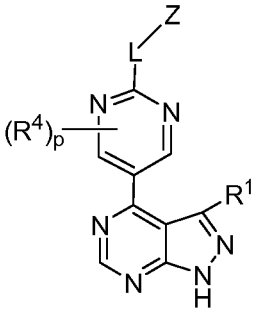
IIk-1c



IIk-1d

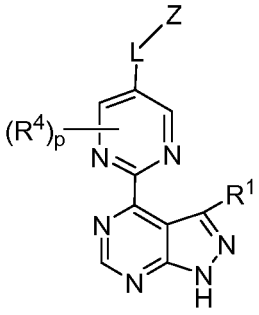


IIk-1e



IIk-1f

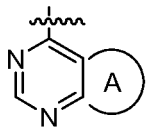
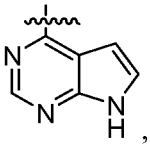
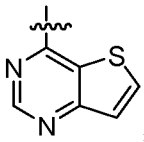
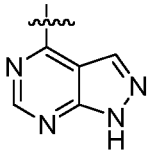
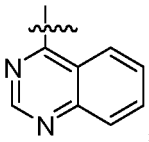
or



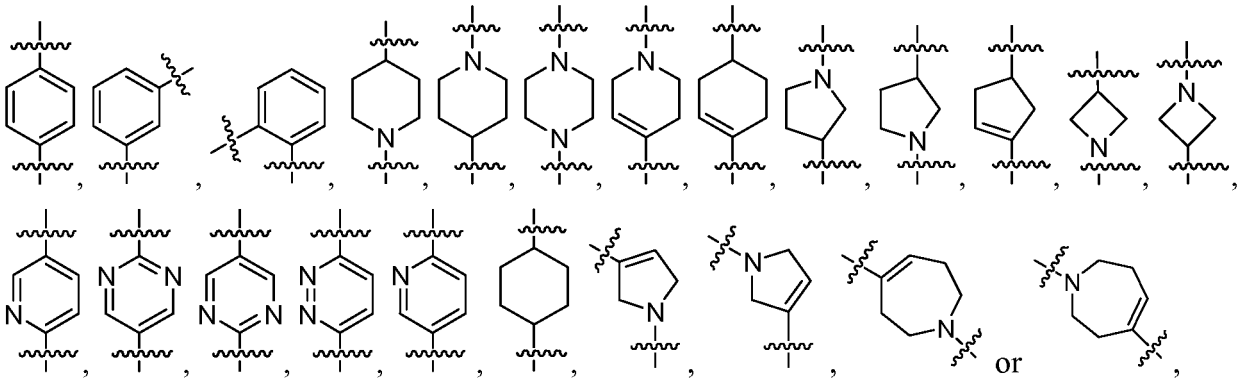
IIk-1g

18. The compound of any of claims **12-13**, wherein (i) Y^3, Y^4, Y^5 and Y^6 are CH; or (ii) Y^3, Y^4 and Y^5 are CH and Y^6 is N; or (iii) Y^3, Y^5 and Y^6 are CH and Y^4 is N; or (iv) Y^3 and Y^5 are CH and Y^4 and Y^6 are N; or (v) Y^3 and Y^6 are N and Y^4 and Y^5 are CH; or (vi) Y^3 and Y^4 are N and Y^5 and Y^6 are CH; or (vii) Y^3 and Y^4 are CH and Y^5 and Y^6 are N.

19. The compound of any of claims **1-3**, wherein


is selected from  ,  ,  or  , each of which is substituted with from 1-2 R^1 groups, wherein each R^1 is optionally substituted with from 1-5 R^3 members, and wherein the wavy line indicates the point of attachment to the rest of the molecule.

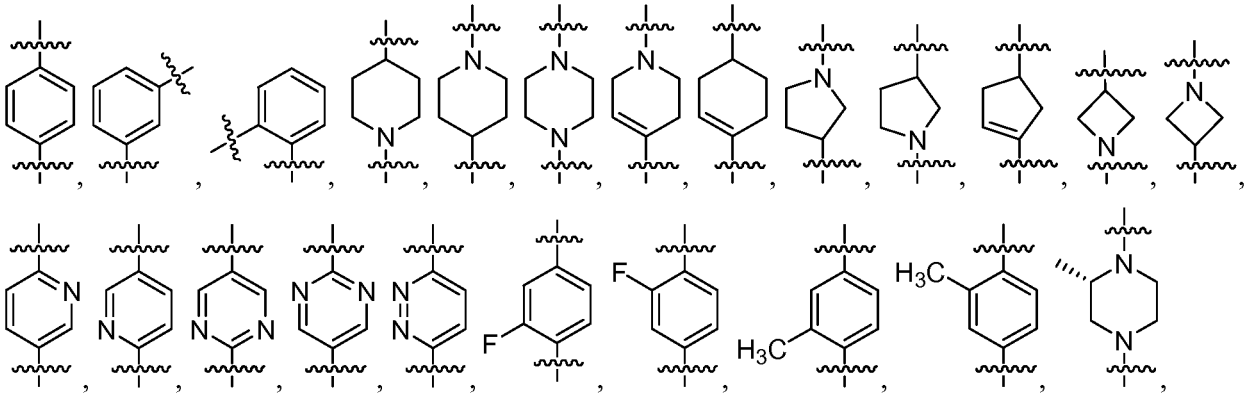
20. The compound of any of claims **1-3**, wherein E is selected from:

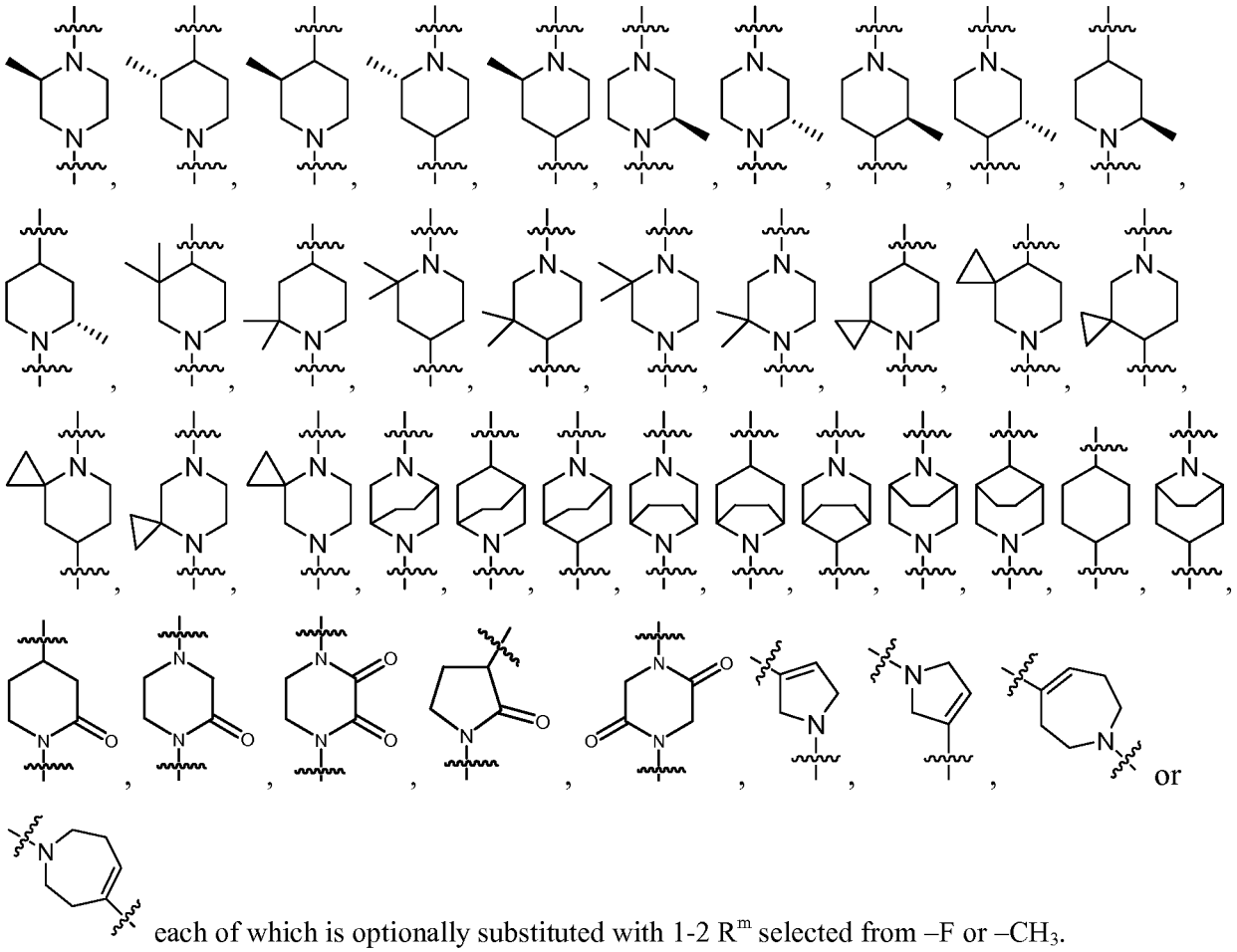

or ,

each of which is optionally substituted with 1-2 R^m substituents, wherein each R^m is independently selected from C_{1-4} alkyl or halogen; or two R^m substituents are taken together to form a $-(CH_2)_n-$ bridging linkage, which together with the atoms to which they are attached forms a 5- to 9-membered bicyclic ring, wherein n is 1, 2 or 3 and wherein the bicyclic ring is optionally substituted with from 1-2 R^n substituents; or two R^m substituents when attaching to the same carbon atom of the heterocyclylene are taken together with the atom to which they attach form a 3- to 6-membered monocyclic ring, which is optionally substituted with R^n; and

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

21. The compound of claim **20**, wherein E is selected from:





each of which is optionally substituted with 1-2 R^m selected from –F or $–CH_3$.

22. The compound of any of claims **1-21**, wherein L is selected from a bond, $–NHSO_2$-, $-SO_2NH$-, -NHC(O)-, -C(O)NH-, $-SO_2$-, -C(O)O-, -C(O)-, -NHC(O)NH- or -C(=NH)NH-.

23. The compound of any of claims **1-21**, wherein Z is selected from H, D, C_{1-6}alkyl, deuterated C_{1-6}alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl-C_{1-4}alkyl, aryl, aryl-C_{1-4}alkyl, heteroaryl, heteroaryl-C_{1-4} alkyl, heterocycloalkyl, heterocyclyl or heterocyclyl-C_{1-4}alkyl, wherein the aliphatic or aromatic portion of Z is optionally substituted with from 1-3 R^d substituents, wherein each R^d is independently selected from CN, NO_2, C_{1-6}alkyl, C_{1-6} haloalkyl, halogen, C_{1-6}alkoxy, deuterated C_{1-6}alkoxy, C_{1-6} haloalkoxy, C_{3-6}cycloalkyl, heterocyclyl, $-NH_2$ or $-N(C_{1-6}alkyl)_2$; or two adjacent R^d substituents on an aromatic ring are taken together to form a 5 or 6-membered ring having from 0-2 heteroatoms selected from O, N or S.

24. The compound of claim **23,** wherein Z is H, CH_3, CD_3, ethyl, butyl, propyl, dimethylamino, phenyl, benzyl, 1-methylbenzyl, 1-ethylbenzyl, benzylmethyl, 1-naphthalenyl, 2-naphthalenyl, 1,3-benzodioxol-4-yl, 1,3-benzodioxol-5-yl, indanyl, 1,2-benzoxazolyl, 1,3-benzoxazolyl, thiophenyl, thiozolyl, benzothiophenyl, pyrazolyl, pyrrolidinyl, pyridyl, cyclopropyl, pyridylmethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, oxazolyl, 2-oxo-pyrrolidinyl, 1,2,4-oxadiazolyl, 1,2,5-

oxadiazolyl, 1,2,3-oxadiazolyl, 1,3,4-oxadiazolyl, 1,3,5-oxadiazolyl or isoxazolyl, each of which is optionally substituted with from 1-3 members independently selected from $-CH_3$, CD_3, ethyl, propyl, butyl, isopropyl, CN, NO_2, NH_2, $-N(CH_3)_2$, halogen, $-OCH_3$, $-OCH(CH_3)_2$, $-OCD_3$, cyclopropyl, CF_3, CHF_2, $-OCF_3$, $-OCHF_2$ or cyclopropylmethyl.

25. The compound of any of claims **2-22**, wherein R^1 is selected from halogen, -CN, C_{1-6}alkyl, C_{1-6}alkoxy, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl-C_{1-4}alkyl, aryl, aryl-C_{1-4}alkyl, heteroaryl, heteroaryl-C_{1-4} alkyl, heterocyclyl, heterocyclyl-C_{1-4}alkyl, $-C(O)-R^g$, $-C(O)NHR^g$, $-C(O)NR^gR^g$, $-NHC(O)R^g$, $-NHC(O)NHR^g$, $-NHC(O)NR^gR^g$, $-NR^gR^g$, $-NHR^g$, $-C(O)OR^g$, $-OC(O)R^g$, $-SO_2R^g$, $-NHSO_2R^g$, $-NHSO_2NHR^g$, $-NHSO_2NR^gR^g$, $-SO_2NHR^g$ or $-SO_2NR^gR^g$, wherein at each occurrence R^1 is optionally substituted with from 1-4 R^3 members, wherein each R^3 is independently selected from halogen, -CN, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{3-6}cycloalkyl, C_{3-6} cycloalkyl-C_{1-4}alkyl, aryl, aryl-C_{1-4}alkyl, heteroaryl, heteroaryl-C_{1-4} alkyl, heterocyclyl, heterocyclyl-C_{1-4}alkyl or R^2; or two adjacent R^3 substituents on an aromatic ring are taken together to form a 5 or 6-membered ring having from 0-2 heteroatoms selected from O, N or S.

26. The compound of claim **25**, wherein R^1 is H, CN, vinyl, deuterated C_{1-6}alkyl, C_{1-6}alkyl, halogen, C_{1-6}alkoxy, 2-cyclopropylethynyl, pyridyl, phenyl, benzyl, pyrazolyl, oxazolyl, thiozolyl, pyrimidinyl, pyrazinyl, pyridazinyl, cyclopropyl, cyclopropylmethyl, cyclopropylcarbonyl, cyclobutyl, cyclobutylmethyl, cyclopentyl, cyclopentylmethyl, cyclohexyl, cyclohexylmethyl, benzoyl, phenylcarbamoyl, piperidinyl, piperazinyl, morpholinyl, cyclopentenyl, cyclohexenyl, 1,2,3,6-tetrahydropyridin-4-yl, 2,3-dihydro-1,4-benzodioxin-5-yl, 1,3-benzodioxol-4-yl, 1,3-benzodioxol-5-yl, indanyl, 1,2-benzoxazolyl, 1,3-benzoxazolyl, each of which is optionally substituted with from 1-4 members independently selected from halogen, $-CH_3$, CD_3, $-OCH_3$, CN, CF_3, CF_3O-, $-CF_2H$, CHF_2O-, $-N(CH_3)_2$, $-NHCH_3$, CH_3CONH-, $NH_2C(O)$-, $CH_3NHC(O)$-, $(CH_3)_2NC(O)$-, cyclopropyl, 1-cyanocyclopropyl, CH_3SO_2NH-, cyclopropyl-SO_2NH-, butyl- SO_2NH-, p-$CH_3C_6H_4SO_2NH$-, NH_2SO_2-, CH_3NHSO_2-, $(CH_3)_2NSO_2$-, morpholinyl, piperidinyl, cyclopropylcarbonyl, cyclobuylcarbonyl, cyclopentylcarbonyl, cyclohexylcarbonyl, 4-morpholinylcarbonyl, piperdinylcarbonyl, piperazinylcarbonyl, t-butoxycarbonyl or 2-(4-morpholinyl)-ethyl.

27. The compound of any of claims **1-26**, wherein the compound is selected from any of compounds P-0001 to P-0731.

28. A pharmaceutical composition comprising a compound of any of claims **1-27** and a pharmaceutically acceptable carrier or excipient.

29. A pharmaceutical composition comprising a compound of any of claims **1-27**, or a composition of claim **28**, and another therapeutic agent.

30. A method for modulating a protein kinase, said method comprising: administering to a subject in need thereof a compound of any of claims **1-27** or a composition of claim **28** or **29**, wherein said protein kinase is a c-kit protein kinase or a mutant c-kit protein kinase.

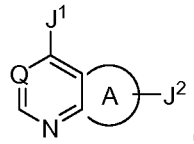
31. A method for treating a subject suffering or at risk of a disease or condition mediated by a protein kinase, said method comprising:

administering to the subject in need thereof an effective amount of a compound of any of claims **1-27**, wherein the protein kinase is a c-kit protein or a mutant c-kit protein kinase.

32. The method of claim **31**, wherein the disease or condition is selected from a cancer, gastrointestinal stromal tumors or mastocytosis.

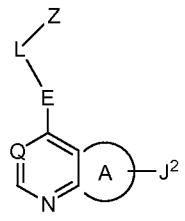
33. A method for preparing a compound of formula (I) of claim **1**, said method comprising:

contacting a compound of formula (III):



(III)

with an agent having formula: G^1-E-L-Z under conditions sufficient to form a compound having formula IIIa:



(IIIa)

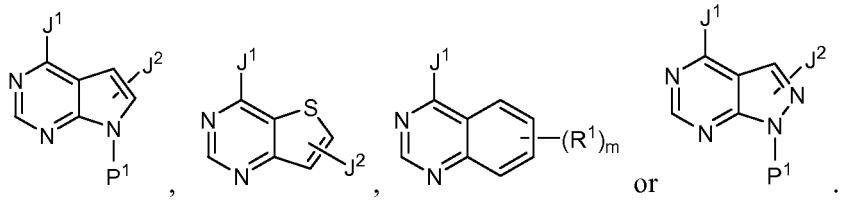
reacting a compound of formula IIIa with an agent having formula: G^2-$(R^1)_m$ under conditions sufficient to form a compound of formula I; and

wherein Q is N or CH;

J^1 and J^2 are each independently selected from halogen, tosylate, mesylate or triflate;

G^1 and G^2 are each independently NH or $-B(OR^{50})_2$; wherein R^{50} is –OH, alkyl or two $-OR^{50}$ substituents together with the boron atom to which they are attached to form an optionally substituted 5 or 6-membered ring.

34. The method of claim **33**, wherein the compound of formula (III) is selected from III-1, III-2, III-3 or III-4:



(III-1) (III-2) (III-3) (III-4)

35. A compound, a composition and a method as described herein.