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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/or mutant c-kit protein kinases.

COMPOUNDS AND METHODS FOR KINASE MODULATION, AND INDICATIONS THEREFOR**CROSS-REFERENCE TO RELATED APPLICATIONS**

[0001] This application claims the benefit under of 35 U.S.C. §119(e) of United States Provisional Application 61/947,980, filed on March 4, 2014, which is hereby incorporated by reference.

FIELD

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

BACKGROUND

[0003] 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.

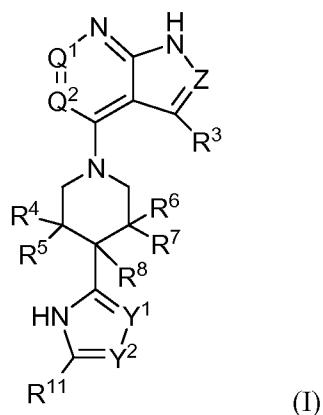
[0004] Stem Cell Factor (SCF) is a protein encoded by the S1 locus, and has also been called kit ligand (KL) and mast cell growth factor (MGF), based on the biological properties used to identify it (reviewed in Tsujimura, *Pathol Int* 1996, **46**:933-938; Loveland, et al., *J. Endocrinol* 1997, **153**:337-344; Vliagostis, et al., *Clin Immunol* 1997, **100**:435-440; Broudy, *Blood* 1997, **90**:1345-1364; Pignon, *Hematol Cell Ther* 1997, **39**:114-116; and Lyman, et al., *Blood* 1998, **91**:1101-1134.). Herein we use the abbreviation SCF to refer to the ligand for the c-Kit RTK (receptor tyrosine kinase).

[0005] SCF is synthesized as a transmembrane protein with a molecular weight of 230 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.

[0006] 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

[0007] In one aspect, the present disclosure provides a compound of formula (I):



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

Z is N or CR¹;

Q^1 is N or CR^2 , wherein R^2 is H, halogen, CH_3 , CH_3O , or CN, wherein CH_3 or CH_3O is optionally substituted with from 1 to 3 halogens;

Q^2 is N or CH;

R^3 is H, F, CH_3 , CH_3O , CHF_2 , CH_2F , CF_3 , CHF_2O , CH_2FO or CF_3O ;

R^4 , R^5 , R^6 and R^7 are each independently H, C_{1-4} alkyl or C_{1-4} haloalkyl;

Y^1 is N or CR⁹, wherein R⁹ is H, C₁₋₄alkyl or C₁₋₄haloalkyl;

Y^2 is N or CB^{10} .

wherein R¹⁰ and R¹¹ are each independently optionally substituted C₁₋₄alkyl, C₁₋₄haloalkyl, optionally substituted C₃₋₆cycloalkyl, optionally substituted aryl or optionally substituted heteroaryl, wherein two adjacent substituents on an aryl or heteroaryl ring are optionally taken together with the atoms to which they

attach to form an optionally substituted fused 5- or 6-membered ring having from 0-2 heteroatoms selected from O, N or S; and

- (i) R¹ is optionally substituted aryl or optionally substituted heteroaryl; and R⁸ is H, C₁₋₄alkyl or C₁₋₄haloalkyl; or
- (ii) R¹ is optionally substituted C₁₋₆alkyl; and R⁸ is C₁₋₄alkyl or C₁₋₄haloalkyl.

[0008] In another aspect, the disclosure provides a composition. The composition includes a compound of any of formulas (I), (II), (IIa), (IIa-1) or (IIa-1a) 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, 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.

[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), (IIa), (IIa-1) or (IIa-1a), 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), (IIa), (IIa-1) or (IIa-1a) 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), (IIa), (IIa-1) or (IIa-1a) 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.* C₁₋₆ 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, C₁₋₆ 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, C₁₋₂ alkyl, C₁₋₄ alkyl, C₂₋₆ alkyl, C₂₋₄ alkyl, C₁₋₆ alkyl, C₂₋₈ alkyl, C₁₋₇ alkyl, C₂₋₇ alkyl and C₃₋₆ 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. As used herein, "deuterated C₁₋₆alkyl" is meant to include partially deuterated or perdeuterated C₁₋₆alkyl groups. Non-limiting examples include -CD₃, CD₃CH₂-, CD₃CD₂-, -CD(CD₃)₂, -CD(CH₃)₂, and the like.

[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.*, C₁₋₆ means one to six carbons; C₁₋₆ alkylene is meant to include methylene, ethylene, propylene, 2-methylpropylene, pentylene, hexylene and the like). C₁₋₄ alkylene includes methylene -CH₂-, ethylene -CH₂CH₂-, propylene -CH₂CH₂CH₂-, and isopropylene -CH(CH₃)CH₂-, -CH₂CH(CH₃)-, -CH₂-(CH₂)₂CH₂-, -CH₂-CH(CH₃)CH₂-,

-CH₂-C(CH₃)₂- , -CH₂-CH₂CH(CH₃)- . 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. In another embodiment, an alkyl group may have 6 or fewer carbon atoms. When a prefix is not included to indicate the number of carbon atoms in an alkylene portion, the alkylene moiety or portion thereof will have 12 or fewer main chain carbon atoms or 8 or fewer main chain carbon atoms, 6 or fewer main chain carbon atoms or 4 or fewer main chain carbon atoms.

[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, (C₂-C₆)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 radical or a branched divalent hydrocarbon radical having the number of carbon atoms indicated in the prefix and containing at least one double bond. For example, i.e., C₂₋₆ means two to six carbons; C₂₋₆ alkenylene is meant to include, but is not limited to, -CH=CH-, -CH₂-CH=CH-, -CH₂-CH=C(CH₃)-, -CH=CH-CH=CH-, and the like. Similarly, the term "alkynylene" refers to a linear bivalent hydrocarbon radical or a branched divalent hydrocarbon radical containing at least one triple bond and having the number of carbon atoms indicated in the prefix. For example, C₂₋₆ means two to six carbons; C₂₋₆ alkynylene is meant to include, but is not limited to, -C≡C-, -C≡CCH₂-, -CH₂-C≡CCH₂-, -C≡CCH(CH₃)-, and the like. When a prefix is not included to indicate the number of carbon atoms in an alkenylene or alkynylene 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", "Carbocyclic" 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., C₃₋₈ 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 ring double or triple bond(s).

[0022] "Cycloalkylene" by itself or as part of another substituent, refers to a divalent 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. 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., cyclopropylmethylen, cyclobutylethylene, cyclobutylmethylen, 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 an unsaturated, 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 unsaturated, 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. 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 “C₁₋₆ 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 -NH₂.

[0032] “Alkylamino” refers to a –NH-alkyl group, where alkyl is as defined herein. Exemplary alkylamino groups include CH₃NH-, 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] “Alkylthio” refers to -S-alkyl, where alkyl is as defined herein. Exemplary alkylthio groups include CH₃S-, ethylthio, and the like. The term “thioalkoxy” refers to a -O-alkylthio group, where the alkylthio group is as defined herein, e.g., thiomethoxy, thioethoxy, and the like.

[0035] “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.

[0036] “Arylene” by itself or as part of another substituent, refers to a divalent 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. Arylene can be a divalent radical of the aryl group as defined herein. Exemplary arylene includes, e.g., phenylene, biphenylene, and the like.

[0037] “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.

[0038] “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, phenethoxy, and the like.

[0039] “Aryloxy” refers to -O-aryl, where the aryl group is as defined herein. Exemplary aryloxy includes, e.g., phenoxy.

[0040] “Arylthio” refers to -S-aryl, where the aryl group is as defined herein. Exemplary arylthio includes, e.g., phenylthio.

[0041] “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, phthalazinyl, benzotriazinyl, benzimidazolyl, benzopyrazolyl, benzotriazolyl, benzisoxazolyl, isobenzofuryl, isoindolyl, indolizinyl, benzotriazinyl, thienopyridinyl, thienopyrimidinyl, pyrazolopyrimidinyl, imidazopyridinyl, benzothiazolyl, benzothienyl, quinolyl, isoquinolyl, indazolyl, pteridinyl and thiadiazolyl. "Nitrogen containing heteroaryl" refers to heteroaryl wherein any of the heteroatoms is N. As used herein, "heterocyclic aromatic ring" is meant to be a heteroaryl ring.

[0042] "Heteroarylene" by itself or as part of another substituent, refers a divalent monocyclic aromatic ring radical containing 5 or 6 ring atoms, or a divalent 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. Heteroarylene can be a divalent radical of heteroaryl group, 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.

[0043] "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.

[0044] "Heterocycloalkyl" refers to a saturated or unsaturated non-aromatic cycloalkyl group that contains from one to five ring 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 polycyclic 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. 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 heterocycloalkyl groups include oxetanyl, azetidinyl, 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, 1-methylpyridin-2-one moiety, 1-methyl-2-oxo-3-pyridyl, 1-methyl-2-oxo-4-pyridyl, 1-methyl-2-oxo-5-pyridyl, 1-methyl-2-oxo-6-pyridyl, 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 piperazine-1,4-diyl, 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, 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, 3-oxomorpholin-2-yl, 3-oxomorpholin-4-yl, 3-oxomorpholin-5-yl, 3-oxomorpholin-6-yl, 2-oxopiperazin-3-yl, 2-oxopiperazin-4-yl, 2-oxopiperazin-5-yl, 2-oxopiperazin-6-yl, 2-oxopiperazin-7-yl, piperazin-1-oxide-2-yl, piperazin-1-oxide-3-yl, piperazin-1-oxide-4-yl, pyridine-2-one-3-yl, pyridine-2-one-4-yl, pyridine-2-one-5-yl, pyridine-2-one-6-yl, pyridine-2-one-7-yl, piperidinyl, morpholinyl, piperazinyl, isoxazolinyl, pyrazolinyl, imidazolinyl, pyrazol-5-one-3-yl, pyrazol-5-one-4-yl, pyrrolidine-2,5-dione-1-yl, pyrrolidine-2,5-dione-3-yl, pyrrolidine-2,5-dione-4-yl, imidazolidine-2,4-dione-1-yl, imidazolidine-2,4-dione-3-yl, imidazolidine-2,4-dione-5-yl, pyrrolidinyl, tetrahydroquinolinyl, decahydroquinolinyl, tetrahydrobenzooxazepinyl, dihydrodibenzooxepinyl, and the like.

[0045] “Heterocycloalkylene” by itself or as part of another substituent, refers to a divalent heterocycloalkyl, where the heterocycloalkyl is as defined herein. Exemplary heterocycloalkyl 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.

[0046] “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 heterocycloalkyl include, e.g., 2-pyridylmethyl, 2-thiazolylethyl, pyrrolidin-1-ylmethyl, 2-piperidinylmethyl, and the like.

[0047] The substituents for alkyl, alkoxy, haloalkyl, haloalkoxy, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heterocycloalkylene, alkylene, alkenylene, or alkynylene include, but are not limited to, R', halogen, -OH, -NH₂, -NO₂, -CN, -C(O)OH, -C(S)OH, -C(O)NH₂, -C(S)NH₂, -S(O)₂NH₂, -NHC(O)NH₂, -NH

C(S)NH₂, -NHS(O)₂NH₂, -C(NH)NH₂, -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)NH₂, -NR'C(S)NH₂, -NHC(O)NR'R'', -NHC(S)NR'R'', -NHS(O)₂NHR', -NR'S(O)₂NH₂, -NR'S(O)₂NHR', -NHC(S)NRR'', -NHC(O)NRR'', -NHS(O)₂NR'R'', -NR'S(O)₂NR'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, C₁₋₈ alkyl, heterocycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, aryl substituted with 1-3 halogens, C₁₋₈ alkoxy, haloalkyl, haloalkoxy or C₁₋₈ thioalkoxy groups, or unsubstituted aryl-C₁₋₄ 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, -NH₂, -NO₂, -CN, -C(O)OH, -C(S)OH, -C(O)NH₂, -C(S)NH₂, -S(O)₂NH₂, -NHC(O)NH₂, -NH C(S)NH₂, -NHS(O)₂NH₂, -C(NH)NH₂, -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)₂R^{a1}, -C(O)NHR^{a1}, -C(S)NHR^{a1}, -C(O)NR^{a1}R^{a2}, -C(S)NR^{a1}R^{a2}, -S(O)₂NHR^{a1}, -S(O)₂NR^{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)₂R^{a1}, -NR^{a1}S(O)₂R^{a2}, -NHC(O)NHR^{a1}, -NHC(S)NHR^{a1}, -NR^{a1}C(O)NH₂, -NR^{a1}C(S)NH₂, -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)₂NHR^{a1}, -NR^{a1}S(O)₂NH₂, -NR^{a1}S(O)₂NHR^{a2}, -NHS(O)₂NR^{a1}R^{a2}, -NR^{a1}S(O)₂NR^{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, C₁₋₈ alkyl, heterocycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, aryl substituted with 1-3 halogens, C₁₋₈ alkoxy, haloalkyl, haloalkoxy or C₁₋₈ thioalkoxy groups, or unsubstituted aryl-C₁₋₄ alkyl groups. R^{a1}, R^{a2} and R^{a3} can be further substituted with R^{b1}, halogen, -OH, -NH₂, -NO₂, -CN, -C(O)OH, -C(S)OH, -C(O)NH₂, -C(S)NH₂, -S(O)₂NH₂, -NHC(O)NH₂, -NH C(S)NH₂, -NHS(O)₂NH₂, -C(NH)NH₂, -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)₂R^{b1}, -C(O)NHR^{b1}, -C(S)NHR^{b1}, -C(O)NR^{b1}R^{b2}, -C(S)NR^{b1}R^{b2}, -S(O)₂NHR^{b1}, -S(O)₂NR^{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)₂R^{b1}, -NR^{b1}S(O)₂R^{b2}, -NHC(O)NHR^{b1}, -NHC(S)NHR^{b1}, -NR^{b1}C(O)NH₂, -NR^{b1}C(S)NH₂, -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^{b1}R^{b2}, -NR^{b1}C(S)NR^{b1}R^{b2}, -NHS(O)₂NHR^{b1}, -NR^{b1}S(O)₂NH₂, -NR^{b1}S(O)₂NHR^{b2}, -NHS(O)₂NR^{b1}R^{b2}, -NR^{b1}S(O)₂NR^{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, C₁₋₈ alkyl, heterocycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, aryl substituted with 1-3 halogens, C₁₋₈ alkoxy, haloalkyl, haloalkoxy or C₁₋₈ thioalkoxy groups, or unsubstituted aryl-C₁₋₄ alkyl groups.

[0048] Substituents for the aryl and heteroaryl groups are varied and are generally selected from: R', halogen, -OH, -NH₂, -NO₂, -CN, -C(O)OH, -C(S)OH, -C(O)NH₂, -C(S)NH₂, -S(O)₂NH₂, -NHC(O)NH₂, -NH C(S)NH₂, -NHS(O)₂NH₂, -C(NH)NH₂, -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)NH₂, -NR'C(S)NH₂, -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)₂NHR', -NR'S(O)₂NH₂, -NR'S(O)₂NHR'', -NHS(O)₂NR'R'', -NR'S(O)₂NR'R''', -NHR', -NR'R'', -N₃, perfluoro(C₁-C₄)alkoxy, and perfluoro(C₁-C₄)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, C₁₋₈ alkyl, C₃₋₆ cycloalkyl, cycloalkylalkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryl-C₁₋₄ alkyl, and aryloxy-C₁₋₄ 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, -NH₂, -NO₂, -CN, -C(O)OH, -C(S)OH, -C(O)NH₂, -C(S)NH₂, -S(O)₂NH₂, -NHC(O)NH₂, -NH C(S)NH₂, -NHS(O)₂NH₂, -C(NH)NH₂, -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)₂R^{a1}, -C(O)NHR^{a1}, -C(S)NHR^{a1}, -C(O)NR^{a1}R^{a2}, -C(S)NR^{a1}R^{a2}, -S(O)₂NHR^{a1}, -S(O)₂NR^{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)₂R^{a1}, -NR^{a1}S(O)₂R^{a2}, -NHC(O)NHR^{a1}, -NHC(S)NHR^{a1}, -NR^{a1}C(O)NH₂, -NR^{a1}C(S)NH₂, -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)₂NHR^{a1}, -NR^{a1}S(O)₂NH₂, -NR^{a1}S(O)₂NHR^{a2}, -NHS(O)₂NR^{a1}R^{a2}, -NR^{a1}S(O)₂NR^{a2}R^{a3}, -NHR^{a1}, -NR^{a1}R^{a2}, -N₃, perfluoro(C₁-C₄)alkoxy, and perfluoro(C₁-C₄)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, C₁₋₈ alkyl, C₃₋₆ cycloalkyl, cycloalkylalkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryl-C₁₋₄ alkyl, or aryloxy-C₁₋₄ 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.

[0049] 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)-(CH₂)_q-U-, wherein T and U are independently -NH-, -O-, -CH₂- 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-(CH₂)_r-B-, wherein A and B are independently -CH₂-, -O-, -NH-, -S-, -S(O)-, -S(O)₂-, -S(O)₂NR' 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 $-(\text{CH}_2)_s\text{-X}-(\text{CH}_2)_t-$, where s and t are independently integers of from 0 to 3, and X is $-\text{O}-$, $-\text{NR}'-$, $-\text{S}-$, $-\text{S}(\text{O})-$, $-\text{S}(\text{O})_2-$, or $-\text{S}(\text{O})_2\text{NR}'-$. The substituent R' in $-\text{NR}'-$ and $-\text{S}(\text{O})_2\text{NR}'-$ is selected from hydrogen or unsubstituted C_{1-6} alkyl.

[0050] “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 $-\text{C}(\text{O})\text{OR}$, wherein R is, for example, methyl, ethyl, *t*-butyl, benzyl, phenylethyl, $\text{CH}_2=\text{CHCH}_2-$, and the like, groups of the formula $-\text{C}(\text{O})\text{R}'$, wherein R' is, for example, methyl, phenyl, trifluoromethyl, and the like, groups of the formula $-\text{SO}_2\text{R}''$, 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).

[0051] “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. In addition, abbreviations as used herein have respective meanings as follows:

$^{\circ}\text{C}$	Degree Celsius
aq	Aqueous
ATP	Adenosine triphosphate
BME	Beta-mercptoethanol
BOC	<i>tert</i> -Butoxycarbonyl

Brij	Polyglycol ether
BSA	Bovine serum albumin
DCM	Dichloromethane
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
DTT	Dithiothreitol
EDTA	Ethylenediaminetetraacetic acid
EtOAc	Ethyl acetate
FBS	Fetal bovine serum
g	Gram
Glu	Glutamic acid
h	Hour
HEPES	4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid
HPLC	High-pressure liquid chromatography
IPTG	Isopropyl-beta-D-thiogalactopyranoside
L	Liter
M	Molar
Me	Methyl
MeOH	methanol
mg	Milligram
mL	Milliliter
mM	Millimolar
mmol	Millimole
mU	Milliunit
MOPS	3-(N-morpholino)propansulfonic acid

MS ESI	Mass spectrometry electrospray ionization
N	Normal
ng	nanogram
nm	nanometers
nM	Nanomolar
NMR	Nuclear magnetic resonance
NP-40	Tergitol-type NP-40
OD ₆₀₀	Absorbance of a sample measured at a wavelength of 600 nm
Ph	Phenyl
PMSF	Phenylmethylsulfonyl fluoride
s	Second
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
Tris	Tris(hydroxymethyl)aminomethane
Tyr	Tyrosine
µL	Microliter

[0052] 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.

[0053] 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.

[0054] "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.

[0055] Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galacturonic 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.

[0056] 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.

[0057] 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.

[0058] 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).

[0059] 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 300 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 300-400, 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).

[0060] 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.

[0061] 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.

[0062] 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.

[0063] 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 μ M or less, 100 nM or less, 10 nM or less, or 1 nM or less.

[0064] 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, 300, 400, 500, 1000, or 10,000-fold greater affinity.

[0065] 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.

[0066] As used herein, the term “lone pair” or “lone pair of electrons” refers to a pair of electrons in the outermost shell of an atom, in particular a nitrogen atom, that are not used in bonding.

[0067] 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.

[0068] "Prodrugs" mean any compound which releases an active parent drug, such as a compound according to Formula (I) or any subformulas described herein, *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of a compound disclosed herein are prepared by modifying functional groups present in the compound 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 disclosed herein in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compounds. Prodrugs include compounds of the present disclosure wherein a hydroxy, amino, carboxyl or sulfhydryl group in a compound of the present disclosure 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 the present disclosure, 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.

[0069] "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.

[0070] "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).

[0071] 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.

[0072] 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.

[0073] 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.

[0074] 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.*

[0075] “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.

[0076] 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 reacquiring a disorder or condition or one or more of its attendant symptoms.

[0077] “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.

[0078] "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.

[0079] 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, D830Y, 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.

[0080] 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 radiolabelled with radioactive isotopes, such as for example tritium (³H), iodine-125 (¹²⁵I), carbon-14 (¹⁴C),

carbon-11 (¹¹C) or fluorine-18 (¹⁸F). 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.

[0081] The term "deuterated" as used herein alone or as part of a group, means substituted deuterium atoms. When a particular position is designated as holding deuterium (stated as "D" or "deuterium"), it is understood that the abundance of deuterium at that position is substantially greater than the natural abundance of deuterium, which is 0.015% (i.e., at least 50.1% incorporation of deuterium).

[0082] 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 compound of the disclosure holds a fully or partially deuterium substituted alkyl, aryl or heteroaryl group. In one embodiment, the deuterium substituted compound of the disclosure holds a fully or partially deuterium substituted alkyl group, e.g., -CD₃, CD₂CD₃, -CD₂CD₂CD₃ (n-propyl-D7), -CD(CD₃)₂ (iso-propyl-D7), -CD₂CD₂CD₂CD₃ (n-butyl-D9), -CD₂-CD(CD₃)₂ (iso-butyl-D9) and the like. In another embodiment, the deuterium substituted compound of the disclosure holds a fully or partially deuterium substituted aryl, such as phenyl, e.g., C₆D₅ or a fully or partially deuterium substituted heteroaryl, e.g., pyrazoly-d₂, thiazoly-d₂, pyridyl-d₃, and the like.

[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 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 ²H (deuterium, D), ³H (tritium), ¹¹C, ¹³C, ¹⁴C, ¹⁵N, ¹⁸F, ³¹P, ³²P, ³⁵S, ³⁶Cl, and ¹²⁵I. 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 (³H). Certain isotopically-labeled compounds of the present disclosure (e.g., those labeled with ³H and ¹⁴C) are useful in compound and/or substrate tissue distribution assays. Tritiated (i.e., ³H) and carbon-14 (i.e., ¹⁴C) and

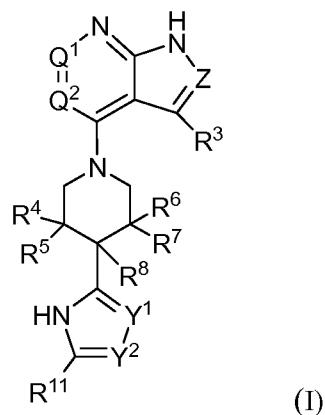
fluorine-18 (^{18}F) isotopes are useful for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (i.e., ^2H) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased *in vivo* half-life or reduced dosage requirements) and hence may be utilized 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

[0086] The present disclosure concerns compounds of Formulas (I), (II), (IIa), (IIa-1) or (IIa-1a) 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.

III. Compounds

[0087] In one aspect, the present disclosure provides compounds of formula (I):



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

[0088] In some embodiments of compounds of formula (I), the compounds have molecular weights less than 650. In some embodiments, the compounds have molecular weights less than 600. In other embodiments, the compounds have molecular weights less than 550. In other embodiments, the compounds have molecular weights less than 500. In yet other embodiments, the compounds have molecular weights less than 450.

[0089] In some embodiments of compounds of formula (I), Z is N or CR¹. In one embodiment, Z is N. in another embodiment, Z is CR¹. Other variables Q¹, Q², R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R¹¹, Y¹, Y², R⁸, R⁹ and R¹⁰ are as defined in any of the embodiments as disclosed herein.

[0090] In some embodiments of compounds of formula (I), or any subgeneric formulas of formula (I), or any embodiments of compounds of formula (I) or subgeneric formulas as described herein, Q¹ is N or CH. In some embodiments of compounds of formula (I), Q¹ is CH. Other variables Q², Z, R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R¹¹, Y¹, Y², R⁸, R⁹ and R¹⁰ are as defined in any of the embodiments as disclosed herein. In some embodiments of compounds of formula (I), Q¹ is CH, Q² is N, Z is CR¹ and Y¹ is N.

[0091] In some embodiments of compounds of formula (I), or any subgeneric formulas of formula (I), or any embodiments of compounds of formula (I) or subgeneric formulas as described herein, Q² is N or CH. In some embodiments of compounds of formula (I), Q² is N. Other variables Q¹, Z, R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R¹¹, Y¹, Y², R⁸, R⁹ and R¹⁰ are as defined in any of the embodiments as disclosed herein.

[0092] In some embodiments of compounds of formula (I), or any subgeneric formulas of formula (I), or any embodiments of compounds of formula (I) or subgeneric formulas as described herein, Y¹ is N or CR⁹. In some embodiments of compounds of formula (I), Y¹ is N. Other variables Q¹, Q², Z, R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R¹¹, Y¹, Y², R⁸, R⁹ and R¹⁰ are as defined in any of the embodiments as disclosed herein.

[0093] In some embodiments of compounds of formula (I), or any subgeneric formulas of formula (I), or any embodiments of compounds of formula (I) or subgeneric formulas as described herein, Y² is N or CR¹⁰. In some embodiments of compounds of formula (I), Y² is CR¹⁰. Other variables Q¹, Q², Z, R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R¹¹, Y¹, Y², R⁸, R⁹ and R¹⁰ are as defined in any of the embodiments as disclosed herein.

[0094] In some embodiments of compounds of formula (I), or any subgeneric formulas of formula (I), or any embodiments of compounds of formula (I) or subgeneric formulas as described herein, R¹ is C₁₋₆alkyl, aryl or heteroaryl, each of which is optionally substituted with from 1-3 R^a substituents independently selected from C₁₋₆alkyl, C₁₋₆alkoxy, C₂₋₆alkenyl, C₂₋₆alkynyl, aryl, aryl-C₁₋₄alkyl, heteroaryl, heteroaryl-C₁₋₄alkyl, C₃₋₆cycloalkyl, C₃₋₆cycloalkyl-C₁₋₄alkyl, C₃₋₆cycloalkenyl, CH₂=CH-, C₃₋₆cycloalkyl-C₂₋₄alkenyl, C₃₋₆cycloalkyl-C₂₋₄alkynyl, heterocycloalkyl, heterocycloalkyl-C₁₋₄alkyl or R^b; or two adjacent R^a substituents on an aromatic ring are taken together with the atoms to which they are attached form a 5- or 6-membered ring having from 0-2 heteroatoms selected from O, N or S; wherein each R^b is independently selected from halogen, CN, -OH, -NH₂, -NO₂, -C(O)OH, -C(S)OH, -C(O)NH₂, -C(S)NH₂, -S(O)₂NH₂, -NHC(O)NH₂, -NHC(S)NH₂, -NHS(O)₂NH₂, -C(NH)NH₂, -OR^c, -SR^c, -OC(O)R^c, -OC(S)R^c, -C(O)R^c, -C(S)R^c, -C(O)OR^c, -C(S)OR^c, -S(O)R^c, -S(O)₂R^c, -C(O)NHR^c, -C(S)NHR^c, -C(O)NR^cR^c, -C(S)NR^cR^c, -S(O)₂NH^c, -S(O)NR^cR^c, -C(NH)NHR^c, -C(NH)NR^cR^c, -NHC(O)R^c, -NHC(S)R^c, -NR^cC(O)R^c, -NR^cC(S)R^c, -NHS(O)₂R^c, -NR^cS(O)₂R^c, -NHC(O)NHR^c, -NHC(S)NHR^c, -NR^cC(O)NH₂, -NR^cC(S)NH₂, -NR^cC(O)NHR^c, -NR^c

C(S)NHR^c, -NHC(O)NR^cR^c, -NHC(S)NR^cR^c, -NR^cC(O)NR^cR^c, -NR^cC(S)NR^cR^c, -NHS(O)₂NHR^c, -NR^cS(O)₂NH₂, -NR^cS(O)₂NHR^c, -NHS(O)₂NR^cR^c, -NR^cS(O)₂NR^cR^c, -NHR^c, R^c or -NR^cR^c, wherein each R^c is independently selected from C₁₋₆alkyl, aryl, aryl-C₁₋₂alkyl, C₃₋₆cycloalkyl, C₃₋₆cycloalkyl-C₁₋₄alkyl, heteroaryl, heteroaryl-C₁₋₄alkyl, heterocycloalkyl or heterocycloalkyl-C₁₋₄alkyl; or two R^c groups when attached to the same nitrogen atom are taken together with the nitrogen atom to which they are attached form a 4-, 5- or 6-membered ring; wherein the aliphatic or aromatic portion of each R^a is further optionally substituted with from 1-3 R^d groups independently selected from halogen, CN, -OH, -NH₂, -NO₂, -C(O)OH, -C(S)OH, -C(O)NH₂, -C(S)NH₂, -S(O)₂NH₂, -NHC(O)NH₂, -NHC(S)NH₂, -NHS(O)₂NH₂, -C(NH)NH₂, -OR^e, -SR^e, -OC(O)R^e, -OC(S)R^e, -P(=O)HR^e, -P(=O)R^eR^e, -PH(=O)OR^e, -P(=O)(OR^c)₂, -OP(=O)(OR^c)₂, -C(O)R^e, -C(S)R^e, -C(O)OR^e, -C(S)OR^e, -S(O)R^e, -S(O)₂R^e, -C(O)NHR^e, -C(S)NHR^e, -C(O)NR^eR^e, -C(S)NR^eR^e, -S(O)₂NHR^e, -S(O)₂NR^eR^e, -C(NH)NHR^e, -C(NH)NR^eR^e, -NHC(O)R^e, -NHC(S)R^e, -NR^eC(O)R^e, -NR^eC(S)R^e, -NHS(O)₂R^e, -NR^eS(O)₂R^e, -NHC(O)NHR^e, -NHC(S)NHR^e, -NR^eC(O)NH₂, -NR^eC(S)NH₂, -NR^eC(O)NHR^e, -NR^eC(S)NHR^e, -NHC(O)NR^eR^e, -NHC(S)NR^eR^e, -NR^eC(O)NR^eR^e, -NR^eC(S)NR^eR^e, -NHS(O)₂NHR^e, -NR^eS(O)₂NH₂, -NR^eS(O)₂NHR^e, -NHS(O)₂NR^eR^e, -NR^eS(O)₂NR^eR^e, -NHR^e, -NR^eR^e or R^e; wherein each R^e is independently C₁₋₆alkyl or aryl; or two R^e groups when attached to the same nitrogen atom are taken together with the nitrogen atom to which they are attached form a 4- to 6-membered ring; wherein each R^c is further optionally substituted with from 1-3 R^f substituents independently selected from halogen, CN, -OH, -NH₂, -NO₂, -C(O)OH, -C(S)OH, -C(O)NH₂, -C(S)NH₂, -S(O)₂NH₂, -NHC(O)NH₂, -NHC(S)NH₂, -NHS(O)₂NH₂, -C(NH)NH₂, -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(O)NR^gR^g, -S(O)NHR^g, -S(O)₂NR^gR^g, -NHC(O)R^g, -NR^gC(O)R^g, -NR^gS(O)₂R^g, -NHC(O)NHR^g, -NR^gC(O)NH₂, -NR^gC(O)NHR^g, -NHC(O)NR^gR^g, -NHC(S)NR^gR^g, -NR^gC(O)NR^gR^g, -NHS(O)₂NHR^g, -NR^gS(O)₂NH₂, -NR^gS(O)₂NHR^g, -NHS(O)₂NR^gR^g, -NR^gS(O)₂NR^gR^g, -NHR^g, -NR^gR^g or R^g, wherein each R^g is independently C₁₋₆alkyl. Other variables Q¹, Q², Z, R², R³, R⁴, R⁵, R⁶, R⁷, R¹¹, Y¹, Y², R⁸, R⁹ and R¹⁰ are as defined in any of the embodiments as disclosed herein.

[0095] In some embodiments of compounds of formula (I), or any subgeneric formulas of formula (I), or any embodiments of compounds of formula (I) or subgeneric formulas as described herein, R¹ is optionally substituted C₁₋₆alkyl. In some instances, R¹ is C₁₋₆alkyl, optionally substituted with from 1-3 independently selected R^a; or 1-3 independently selected R^b; or 1-3 independently selected R^c; 1-3 independently selected R^d; or 1-3 independently selected R^f; or 1-3 independently selected R^g groups. In certain instances, R¹ is CH₃. Other variables Q¹, Q², Z, R², R³, R⁴, R⁵, R⁶, R⁷, R¹¹, Y¹, Y², R⁸, R⁹ and R¹⁰ are as defined in any of the embodiments as disclosed herein.

[0096] In some embodiments of compounds of formula (I), or any subgeneric formulas of formula (I), or any embodiments of compounds of formula (I) or subgeneric formulas as described herein, R¹ is optionally substituted aryl or heteroaryl. In some instances, R¹ is aryl or heteroaryl, each of which is optionally

substituted with from 1-3 independently selected R^a; or 1-3 independently selected R^b; or 1-3 independently selected R^c; 1-3 independently selected R^d; or 1-3 independently selected R^f; or 1-3 independently selected R^g groups; or two adjacent substituents on the aryl or heteroaryl ring are optionally taken together with the atoms to which they attach form an optionally substituted 5- or 6-membered ring having from 0-2 heteroatoms selected from O, N or S as ring members. In certain instances, R¹ is aryl or heteroaryl, each of which is optionally substituted with from 1-3 R¹² substituents independently selected from halogen, CN, C₁-alkyl, C₁-alkoxy, C₃-cycloalkyl, C₃-cycloalkylalkyl, C₁-haloalkyl, C₁-haloalkoxy, heterocycloalkyl, heterocycloalkylalkyl, -C(O)NH₂, -C(O)NHR^g, -C(O)NHR^gR^g, -COOH, -COOR^g, -SO₂NH₂, -SO₂NHR^g, -SO₂NR^gR^g, -NHSO₂R^g, -NHC(O)R^g or -OC(O)R^g. In certain instances, R¹ is aryl or heteroaryl, each of which is optionally substituted with from 1-3 R¹³ substituents independently selected from halogen, CN, C₁-alkyl, C₁-alkoxy, -CF₃, -CHF₂, CH₂F, -OCF₃, -OCHF₂, -OCH₂F, -NHR^g, -N(R^g)₂, 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, C(O)NH₂, -C(O)NHCH₃, -C(O)NH(CH₃)₂, -COOH, -COOCH₃, -SO₂NH₂, -SO₂NHCH₃, -SO₂N(CH₃)₂, -NHSO₂CH₃, -NHC(O)CH₃ or -OC(O)CH₃. Other variables Q¹, Q², Z, R², R³, R⁴, R⁵, R⁶, R⁷, R¹¹, Y¹, Y², R⁸, R⁹ and R¹⁰ are as defined in any of the embodiments as disclosed herein.

[0097] In some embodiments of compounds of formula (I), or any subgeneric formulas of formula (I), or any embodiments of compounds of formula (I) or subgeneric formulas as described herein, R¹ is optionally substituted aryl, wherein two adjacent substituents on the aryl ring are optionally taken together with the atoms to which they attach form an optionally substituted 5- or 6-membered ring having from 0-2 heteroatoms selected from O, N or S as ring members. In one embodiment, the 5- or 6-membered ring is an optionally substituted heterocycloalkyl ring having from 1-2 oxygen atoms as ring members. In some instances, R¹ is aryl, optionally substituted with from 1-3 independently selected R^a; or 1-3 independently selected R^b; or 1-3 independently selected R^c; 1-3 independently selected R^d; or 1-3 independently selected R^f; or 1-3 independently selected R^g groups. In certain instances, R¹ is phenyl, optionally substituted with from 1-3 independently selected R^a; or 1-3 independently selected R^b; or 1-3 independently selected R^c; 1-3 independently selected R^d; or 1-3 independently selected R^f; or 1-3 independently selected R^g groups. In certain instances, R¹ is phenyl, optionally substituted with from 1-3 R¹² substituents independently selected from halogen, CN, C₁-alkyl, C₁-alkoxy, C₃-cycloalkyl, C₃-cycloalkylalkyl, C₁-haloalkyl, C₁-haloalkoxy, heterocycloalkyl, heterocycloalkylalkyl, -C(O)NH₂, -C(O)NHR^g, -C(O)NHR^gR^g, -COOH, -COOR^g, -SO₂NH₂, -SO₂NHR^g, -SO₂NR^gR^g, -NHSO₂R^g, -NHC(O)R^g or -OC(O)R^g. In some instances, R¹ is phenyl, optionally substituted with from 1-3 R¹³ substituents independently selected from halogen, CN, C₁-alkyl, C₁-alkoxy, -CF₃, -CHF₂, CH₂F, -OCF₃, -OCHF₂, -OCH₂F, -NHR^g, -N(R^g)₂, 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, C(O)NH₂, -C(O)NHCH₃, -C(O)NH(CH₃)₂, -COOH, -COOCH₃, -SO₂NH₂, -SO₂NHCH₃, -SO₂N(CH₃)₂, -NHSO₂CH₃, -NHC(O)CH₃ or -OC(O)CH₃; or two adjacent R¹² substituents on the phenyl ring together with the carbon atoms to which they attach form a

5- or 6-membered fused ring having from 0-2 heteroatoms as ring members selected from O, N or S, wherein the 5- or 6-membered fused ring is optionally substituted with from 1-2 independently selected R^f groups; or 1-2 independently selected halogens; or 1-2 fluorine atoms. In some instances, two adjacent R¹² substituents on the phenyl ring together with the carbon atoms to which they attach form a 5- or 6-membered fused heterocycloalkyl ring having from 1-2 oxygen atoms, wherein wherein the 5- or 6-membered fused ring is optionally substituted with from 1-2 independently selected R^f groups; or independently selected 1-2 halogens; or 1-2 fluorine atoms. In some embodiments, R¹ is C₁₋₆alkyl, phenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 4-pyrazolyl or 3-pyrazolyl, each of which is optionally substituted with from 1-3 R^c or 1-3 R^d groups. In some embodiments, R¹ is C₁₋₆alkyl, phenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 4-pyrazolyl or 3-pyrazolyl, each of which is optionally substituted with from 1-3 R¹² substituents independently selected from halogen, CN, C₁₋₆alkyl, C₁₋₆alkoxy, C₃₋₆cycloalkyl, C₃₋₆cycloalkylalkyl, C₁₋₆haloalkyl, C₁₋₆haloalkoxy, heterocycloalkyl, heterocycloalkylalkyl, -NHR^g, -N(R^g)₂, -C(O)NH₂, -C(O)NHR^g, -C(O)NHR^gR^g, -COOH, -COOR^g, -SO₂NH₂, -SO₂NHR^g, -SO₂NR^gR^g, -NSO₂R^g, -NHC(O)R^g or -OC(O)R^g. In some embodiments, R¹² is selected from halogen, CN, C₁₋₆alkyl, C₁₋₆alkoxy, -CF₃, -CHF₂, CH₂F, -OCF₃, -OCHF₂, -OCH₂F, -NHR^g, -N(R^g)₂, 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, C(O)NH₂, -C(O)NHCH₃, -C(O)NH(CH₃)₂, -COOH, -COOCH₃, -SO₂NH₂, -SO₂NHCH₃, -SO₂N(CH₃)₂, -NSO₂CH₃, -NHC(O)CH₃ or -OC(O)CH₃. Other variables Q¹, Q², Z, R², R³, R⁴, R⁵, R⁶, R⁷, R¹¹, Y¹, Y², R⁸, R⁹ and R¹⁰ are as defined in any of the embodiments as disclosed herein.

[0098] In some embodiments of compounds of formula (I), or any subgeneric formulas of formula (I), or any embodiments of compounds of formula (I) or subgeneric formulas as described herein, R¹ is phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-cyanophenyl, 3-cyanophenyl, 4-cyanophenyl, 2-methylcarbamoylphenyl, 3-methylcarbamoylphenyl, 4-methylcarbamoylphenyl, 2-sulfamoylphenyl, 3-sulfamoylphenyl, 4-sulfamoylphenyl, 2-methylaminosulfonylphenyl, 3-methylaminosulfonylphenyl, 4-methylaminosulfonylphenyl, 2-acetamidophenyl, 3-acetamidophenyl, 4-acetamidophenyl, 2-(C₁₋₆alkyl)phenyl, 3-(C₁₋₆alkyl)phenyl, 4-(C₁₋₆alkyl)phenyl, 2-methanesulfonamidophenyl, 3-methanesulfonamidophenyl, 4-methanesulfonamidophenyl, 2-trifluoromethylphenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 2-trifluoromethoxyphenyl, 3-trifluoromethoxyphenyl, 4-trifluoromethoxyphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-ethoxyphenyl, 3-ethoxyphenyl, 4-ethoxyphenyl, 2-carboxyphenyl, 3-carboxyphenyl, 4-carboxyphenyl, 2-methoxycarbonylphenyl, 3-methoxycarbonylphenyl, 4-methoxycarbonylphenyl, 2-difluoromethylphenyl, 3-difluoromethylphenyl, 4-difluoromethylphenyl, 3-methyl-4-methoxyphenyl, 3-methyl-4-ethoxyphenyl, 3-methoxy-4-methylphenyl, 3-methoxy-4-ethylphenyl, 3-ethoxy-4-methylphenyl, 3-ethoxy-4-ethylphenyl, 1,3-benzodioxol-4-yl, 1,3-benzodioxol-5-yl, 2,2-difluoro-1,3-benzodioxol-4-yl, 2,2-difluoro-1,3-benzodioxol-5-yl, 2,3-dihydro-1,4-benzodioxin-5-yl or 2,3-dihydro-1,4-benzodioxin-6-yl, each of which is optionally substituted with from 1-2 independently selected R^f; 1-2 independently selected R¹²; or 1-2 independently

selected R¹³ groups. Other variables Q¹, Q², Z, R², R³, R⁴, R⁵, R⁶, R⁷, R¹¹, Y¹, Y², R⁸, R⁹ and R¹⁰ are as defined in any of the embodiments as disclosed herein.

[0099] In some embodiments of compounds of formula (I), or any subgeneric formulas of formula (I), or any embodiments of compounds of formula (I) or subgeneric formulas as described herein, R¹ is optionally substituted heteroaryl; or two adjacent substituents on the heteroaryl ring are taken together with the atoms to which they attach form an optionally substituted 5- or 6-membered ring having from 0-2 heteroatoms selected from O, N or S as ring members. In one embodiment, the 5- or 6-membered ring is an optionally substituted heterocycloalkyl ring having from 1-2 oxygen atoms as ring members. In some instances, R¹ is heteroaryl, optionally substituted with from 1-3 independently selected R^a; or 1-3 independently selected R^b; or 1-3 independently selected R^c; 1-3 independently selected R^d; or 1-3 independently selected R^f; 1-3 independently selected R^g; 1-3 independently selected R¹²; or 1-3 independently selected R¹³ groups. Other variables Q¹, Q², Z, R², R³, R⁴, R⁵, R⁶, R⁷, R¹¹, Y¹, Y², R⁸, R⁹ and R¹⁰ are as defined in any of the embodiments as disclosed herein.

[0100] In some embodiments of compounds of formula (I), or any subgeneric formulas of formula (I), or any embodiments of compounds of formula (I) or subgeneric formulas as described herein, R¹ is 2-pyridyl, 3-pyridyl, 4-pyridyl, 4-pyrazolyl or 3-pyrazolyl, each of which is optionally substituted with from 1-3 independently selected R^a; or 1-3 independently selected R^b; or 1-3 independently selected R^c; 1-3 independently selected R^d; or 1-3 independently selected R^f; or 1-3 independently selected R^g groups; or 1-3 independently selected R¹²; or 1-3 independently selected R¹³ groups; or two adjacent substituents on the heteroaryl ring are taken together with the atoms to which they attach form an optionally substituted 5- or 6-membered ring having from 0-2 heteroatoms selected from O, N or S as ring members. Other variables Q¹, Q², Z, R², R³, R⁴, R⁵, R⁶, R⁷, R¹¹, Y¹, Y², R⁸, R⁹ and R¹⁰ are as defined in any of the embodiments as disclosed herein.

[0101] In some embodiments of compounds of formula (I), or any subgeneric formulas of formula (I), or any embodiments of compounds of formula (I) or subgeneric formulas as described herein, R¹ is pyridyl, (e.g., 2-pyridyl, 3-pyridyl or 4-pyridyl), optionally substituted with from 1-3 independently selected R¹²; or 1-3 independently selected R¹³ groups; or two adjacent substituents on the pyridyl ring are taken together with the atoms to which they attach form an optionally substituted 5- or 6-membered ring having from 0-2 heteroatoms selected from O, N or S as ring members. Other variables Q¹, Q², Z, R², R³, R⁴, R⁵, R⁶, R⁷, R¹¹, Y¹, Y², R⁸, R⁹ and R¹⁰ are as defined in any of the embodiments as disclosed herein.

[0102] In some embodiments of compounds of formula (I), or any subgeneric formulas of formula (I), or any embodiments of compounds of formula (I) or subgeneric formulas as described herein, R¹ is pyrazolyl (e.g., 4-pyrazolyl or 3-pyrazolyl), optionally substituted with from 1-3 independently selected R¹²; or 1-3 independently selected R¹³ groups; or two two adjacent substituents on the pyrazolyl ring are taken together

with the atoms to which they attach form an optionally substituted 5- or 6-membered ring having from 0-2 heteroatoms selected from O, N or S as ring members. Other variables Q¹, Q², Z, R², R³, R⁴, R⁵, R⁶, R⁷, R¹¹, Y¹, Y², R⁸, R⁹ and R¹⁰ are as defined in any of the embodiments as disclosed herein.

[0103] In some embodiments of compounds of formula (I), or any subgeneric formulas of formula (I), or any embodiments of compounds of formula (I) or subgeneric formulas as described herein, R¹ is 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-methoxy-4-pyridyl, 2-methoxy-3-pyridyl, 2-methoxy-5-pyridyl, 2-methoxy-6-pyridyl, 2-methyl-4-pyridyl, 2-methyl-3-pyridyl, 2-methyl-5-pyridyl, 2-methyl-6-pyridyl, 6-methyl-4-pyridyl, 6-methyl-3-pyridyl, 2-(4-morphlino)-4-pyridyl, 3-(4-morphlino)-4-pyridyl, 2-(4-morphlino)-3-pyridyl, 2-cyano-4-pyridyl, 2-cyano-3-pyridyl, 2-cyano-5-pyridyl, 2-cyano-6-pyridyl, 2-(1-piperidinyl)-4-pyridyl, 2-(1-piperidinyl)-3-pyridyl, 2-(1-piperidinyl)-5-pyridyl, 2-(1-piperidinyl)-6-pyridyl, 2-isopropoxy-4-pyridyl, 2-(1-pyrrolidinyl)-4-pyridyl, 2-(1-pyrrolidinyl)-3-pyridyl, 2-(1-pyrrolidinyl)-5-pyridyl, 2-(1-pyrrolidinyl)-6-pyridyl, 2-trifluoromethoxy-4-pyridyl, 2-trifluoromethoxy-3-pyridyl, 2-trifluoromethoxy-5-pyridyl, 2-trifluoromethoxy-6-pyridyl, 2-fluoro-4-pyridyl, 2-fluoro-3-pyridyl, 2-fluoro-5-pyridyl, 2-fluoro-6-pyridyl, 2-chloro-4-pyridyl, 2-chloro-3-pyridyl, 2-chloro-5-pyridyl, 2-chloro-6-pyridyl, 2-trifluoromethyl-4-pyridyl, 2-trifluoromethyl-3-pyridyl, 2-trifluoromethyl-5-pyridyl, 2-trifluoromethyl-6-pyridyl, 2-methylcarbamoyl-4-pyridyl, 2-methylcarbamoyl-3-pyridyl, 2-methylcarbamoyl-5-pyridyl, 2-methylcarbamoyl-6-pyridyl, 2-methanesulfonamido-4-pyridyl, 2-methanesulfonamido-3-pyridyl, 2-methanesulfonamido-5-pyridyl, 2-methanesulfonamido-6-pyridyl, 1H-4-pyrazolyl, 1H-3-pyrazolyl, 1-methyl-3-pyrazolyl, 1-methyl-4-pyrazolyl, 1-methyl-5-pyrazolyl, 1-difluoromethyl-3-pyrazolyl, 1-difluoromethyl-4-pyrazolyl, 1-difluoromethyl-5-pyrazolyl, or 1,2-dimethyl-4-pyrazolyl, each of which is optionally substituted with from 1-2 independently selected R¹²; or 1-2 independently selected R¹³ groups. Other variables Q¹, Q², Z, R², R³, R⁴, R⁵, R⁶, R⁷, R¹¹, Y¹, Y², R⁸, R⁹ and R¹⁰ are as defined in any of the embodiments as disclosed herein.

[0104] In some embodiments of compounds of formula (I), or any subgeneric formulas of formula (I), or any embodiments of compounds of formula (I) or subgeneric formulas as described herein, the hydrogen atoms in R¹ 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 R¹ 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.

[0105] In some embodiments of compounds of formula (I), or any subgeneric formulas of formula (I), or any embodiments of compounds of formula (I) or subgeneric formulas as described herein, R² is H, halogen, CH₃, CH₃O, or CN, wherein CH₃ or CH₃O is optionally substituted with from 1 to 3 halogens. In another embodiment, R² is H. In some instances, R² is H, halogen, CH₃, CH₃O, or CN. Other variables Q¹, Q², Z,

R^1 , R^3 , R^4 , R^5 , R^6 , R^7 , R^{11} , Y^1 , Y^2 , R^8 , R^9 and R^{10} are as defined in any of the embodiments as disclosed herein.

[0106] In some embodiments of compounds of formula (I), or any subgeneric formulas of formula (I), or any embodiments of compounds of formula (I) or subgeneric formulas as described herein, R^3 is H, F, CH_3 , CH_3O , CHF_2 , CH_2F , CF_3 , CHF_2O , CH_2FO or CF_3O . In one embodiment, R^3 is H. In one embodiment, R^3 is D. In some embodiments, R^3 is F, CH_3 , CH_3O , CHF_2 , CH_2F , CF_3 , CHF_2O , CH_2FO or CF_3O . In some embodiments, the hydrogen atoms in R^3 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 R^3 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. Other variables Q^1 , Q^2 , Z , R^1 , R^2 , R^4 , R^5 , R^6 , R^7 , R^{11} , Y^1 , Y^2 , R^8 , R^9 and R^{10} are as defined in any of the embodiments as disclosed herein.

[0107] In some embodiments of compounds of formula (I), or any subgeneric formulas of formula (I), or any embodiments of compounds of formula (I) or subgeneric formulas as described herein, R^4 , R^5 , R^6 and R^7 are each independently H, C_{1-4} alkyl or C_{1-4} haloalkyl. In another embodiment, R^4 , R^5 , R^6 and R^7 are H. Other variables Q^1 , Q^2 , Z , R^1 , R^2 , R^3 , R^{11} , Y^1 , Y^2 , R^8 , R^9 and R^{10} are as defined in any of the embodiments as disclosed herein.

[0108] In some embodiments of compounds of formula (I), or any subgeneric formulas of formula (I), or any embodiments of compounds of formula (I) or subgeneric formulas as described herein, R^1 is optionally substituted aryl or optionally substituted heteroaryl as described herein and R^8 is H, C_{1-4} alkyl or C_{1-4} haloalkyl. In some instances, R^8 is H, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, CF_3 , CHF_2 or CH_2F and R^1 is optionally substituted aryl or optionally substituted heteroaryl as described herein. In another embodiment, R^8 is H or C_{1-4} alkyl. In another embodiment, R^8 is H, methyl, or ethyl. In another embodiment, R^8 is H. In another embodiment, R^8 is D. In yet another embodiment, R^8 is CH_3 . In another embodiment, R^8 is CD_3 . In another embodiment, R^8 is CD_2CD_3 . In some embodiments, the hydrogen atoms in R^8 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 R^8 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. Other variables Q^1 , Q^2 , Z , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^{11} , Y^1 , Y^2 , R^9 and R^{10} are as defined in any of the embodiments as disclosed herein.

[0109] In some embodiments of compounds of formula (I), or any subgeneric formulas of formula (I), or any embodiments of compounds of formula (I) or subgeneric formulas as described herein, R^1 is optionally substituted C_{1-6} alkyl as described herein and R^8 is C_{1-4} alkyl or C_{1-4} haloalkyl. In some embodiments, R^8 is H,

C_{1-4} alkyl or C_{1-4} haloalkyl. In some instances, R^1 is methyl or ethyl and R^8 is C_{1-4} alkyl or C_{1-4} haloalkyl. In some embodiments, R^8 is C_{1-4} alkyl. In another embodiment, R^8 is methyl. In another embodiment, R^8 is ethyl. Other variables Q^1 , Q^2 , Z , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^{11} , Y^1 , Y^2 , R^9 and R^{10} are as defined in any of the embodiments as disclosed herein.

[0110] In some embodiments of compounds of formula (I), or any subgeneric formulas of formula (I), or any embodiments of compounds of formula (I) or subgeneric formulas as described herein, when Y^1 is CR^9 , and R^9 is H, C_{1-4} alkyl or C_{1-4} haloalkyl. In one embodiment, R^9 is H. In some instances, R^9 is C_{1-4} alkyl or C_{1-4} haloalkyl. In other instances, R^9 is C_{1-4} alkyl. Other variables Q^1 , Q^2 , Z , R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^{11} , Y^2 , R^8 and R^{10} are as defined in any of the embodiments as disclosed herein.

[0111] In some embodiments of compounds of formula (I), or any subgeneric formulas of formula (I), or any embodiments of compounds of formula (I) or subgeneric formulas as described herein, when Y^2 is CR^{10} , and R^{10} and R^{11} are each independently C_{1-6} alkyl, aryl- C_{1-4} alkyl, heteroaryl- C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl- C_{1-4} alkyl, C_{1-6} haloalkyl, aryl or heteroaryl, each of which is optionally substituted with from 1-3 R^c or 1-3 R^d substituents; or two adjacent R^c substituents or R^d substituents on an aromatic ring are taken together with the atoms to which they are attached form a 5- or 6-membered ring having from 0-2 heteroatoms selected from O, N or S. Other variables Q^1 , Q^2 , Z , R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , Y^1 , and R^9 are as defined in any of the embodiments as disclosed herein.

[0112] In some embodiments of compounds of formula (I), or any subgeneric formulas of formula (I), or any embodiments of compounds of formula (I) or subgeneric formulas as described herein, when Y^2 is CR^{10} , one of R^{10} or R^{11} is optionally substituted C_{1-4} alkyl, optionally substituted C_{3-6} cycloalkyl or C_{1-4} haloalkyl and the other R^{10} or R^{11} is optionally substituted aryl or optionally substituted heteroaryl. In some instances, one of R^{10} or R^{11} is C_{1-6} alkyl, aryl- C_{1-4} alkyl, heteroaryl- C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl- C_{1-4} alkyl or C_{1-6} haloalkyl and the other R^{10} or R^{11} is aryl or heteroaryl, each of which is optionally substituted with from 1-3 independently selected R^c ; or 1-3 independently selected R^d ; or two adjacent R^c substituents or R^d substituents on an aromatic ring are taken together with the atoms to which they are attached form a 5- or 6-membered ring having from 0-2 heteroatoms selected from O, N or S. In some instances, one of R^{10} or R^{11} is C_{1-6} alkyl, aryl- C_{1-4} alkyl, heteroaryl- C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl- C_{1-4} alkyl or C_{1-6} haloalkyl and the other R^{10} or R^{11} is aryl or heteroaryl, each of which is optionally substituted with from 1-3 independently selected R^f ; 1-3 independently selected R^g ; 1-3 independently selected R^{12} ; or 1-3 independently selected R^{13} substituents. In some embodiments, when Y^2 is CR^{10} , one of R^{10} or R^{11} is C_{1-4} alkyl or C_{1-4} haloalkyl and the other R^{10} or R^{11} is optionally substituted aryl or optionally substituted heteroaryl. Other variables Q^1 , Q^2 , Z , R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , Y^1 , and R^9 are as defined in any of the embodiments as disclosed herein.

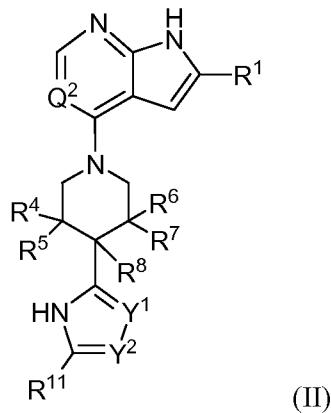
[0113] In some embodiments of compounds of formula (I), or any subgeneric formulas of formula (I), or any embodiments of compounds of formula (I) or subgeneric formulas as described herein, when Y^2 is CR^{10} ,

one of R¹⁰ or R¹¹ is C₁₋₄alkyl and the other R¹⁰ or R¹¹ is aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted with from 1-3 independently selected R^c; or 1-3 independently selected R^d; or 1-3 independently selected R^f; 1-3 independently selected R^g; 1-3 independently selected R¹²; or 1-3 independently selected R¹³ substituents; or two adjacent substituents on an aromatic ring are taken together with the atoms to which they are attached form a 5- or 6-membered ring having from 0-2 heteroatoms selected from O, N or S, wherein the 5- or 6-membered ring is optionally substituted with from 1-2 halogens. In some embodiments, one of R¹⁰ or R¹¹ is methyl and the other R¹⁰ or R¹¹ is optionally substituted aryl or optionally substituted heteroaryl, for example, the aryl or heteroaryl is optionally substituted with from 1-3 independently selected R^c; or 1-3 independently selected R^d; or 1-3 independently selected R^f; 1-3 independently selected R^g; 1-3 independently selected R¹²; or 1-3 independently selected R¹³ substituents; or two adjacent substituents on an aromatic ring are taken together with the atoms to which they are attached form a 5- or 6-membered ring having from 0-2 heteroatoms selected from O, N or S, wherein the 5- or 6-membered ring is optionally substituted with from 1-2 halogens. In one instance, R¹⁰ is methyl and R¹¹ is optionally substituted aryl or optionally substituted heteroaryl. In another instance, R¹¹ is methyl and R¹⁰ is optionally substituted aryl or optionally substituted heteroaryl. Other variables Q¹, Q², Z, R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, Y¹, and R⁹ are as defined in any of the embodiments as disclosed herein.

[0114] In some embodiments of compounds of formula (I), or any subgeneric formulas of formula (I), or any embodiments of compounds of formula (I) or subgeneric formulas as described herein, when Y² is CR¹⁰, one of R¹⁰ or R¹¹ is -CH₃, -CH₂CH₃, -CF₃, or cyclopropyl, and the other R¹⁰ or R¹¹ is phenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-thiophenyl, 2,3-dihydro-1,4-benzodioxin-6-yl, 1,3-benzodioxol-5-yl, or 2,2-difluoro-1,3-benzodioxol-5-yl, wherein at each occurrence, the other R¹⁰ or R¹¹ is optionally substituted with from 1-3 independently selected R¹² or 1-3 independently selected R¹³ groups. In some embodiments, one of R¹⁰ or R¹¹ is -CH₃ and the other R¹⁰ or R¹¹ is phenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-thiophenyl, 2,3-dihydro-1,4-benzodioxin-6-yl, 1,3-benzodioxol-5-yl, or 2,2-difluoro-1,3-benzodioxol-5-yl, wherein at each occurrence, the other R¹⁰ or R¹¹ is optionally substituted with from 1-3 independently selected R¹² or 1-3 independently selected R¹³ groups. In some instances, one of R¹⁰ or R¹¹ is methyl and the other R¹⁰ or R¹¹ is phenyl optionally substituted with from 1-3 independently selected R^d; or 1-3 independently selected R^f; or 1-3 independently selected R¹²; or 1-3 independently selected R¹³ groups. For example, if R¹⁰ is methyl, then R¹¹ is optionally substituted aryl or optionally substituted heteroaryl. In other instances, one of R¹⁰ or R¹¹ is methyl and the other R¹⁰ or R¹¹ is heteroaryl, optionally substituted with from 1-3 independently selected R^d; or 1-3 independently selected R^f; or 1-3 independently selected R¹²; or 1-3 independently selected R¹³ groups. Other variables Q¹, Q², Z, R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, Y¹, and R⁹ are as defined in any of the embodiments as disclosed herein.

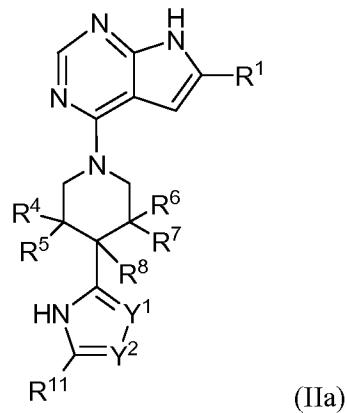
Subformulae of Formulas (I)

[0115] In one group of embodiments of the disclosure, compounds of formula (I) has subformula (II):



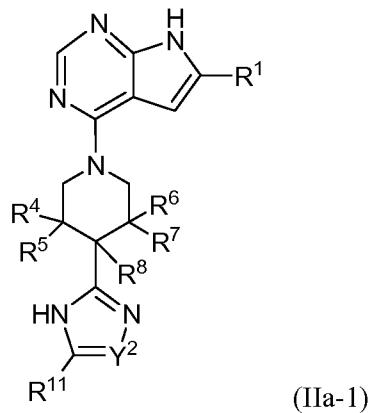
The variables R¹, Q², R⁴, R⁵, R⁶, R⁷, R⁸, Y¹, Y², R⁹, R¹⁰ and R¹¹ are as defined in any of the embodiments of formula (I) as disclosed herein. In some embodiments, R¹ is optionally substituted aryl or optionally substituted heteroaryl. In some embodiments, Q² is N. In other embodiments, R⁴, R⁵, R⁶ and R⁷ are H. In other embodiments, R⁸ is H or C₁₋₄alkyl. In one embodiment, R⁸ is C₁₋₄alkyl, e.g., methyl or ethyl. In some embodiments, Y¹ is N. In some embodiments, Y² is CR¹⁰. In some embodiments, R¹⁰ and R¹¹ are each independently C₁₋₆alkyl, aryl-C₁₋₄alkyl, heteroaryl-C₁₋₄alkyl, C₃₋₆cycloalkyl, C₃₋₆cycloalkyl-C₁₋₄alkyl, C₁₋₆haloalkyl, aryl or heteroaryl, each of which is optionally substituted with from 1-3 independently selected R^c or 1-3 independently selected R^d substituents; or 1-3 independently selected R^f; or 1-3 independently selected R^g; or 1-3 independently selected R¹²; or 1-3 independently selected R¹³ groups; or two adjacent substituents on an aromatic ring are taken together with the atoms to which they are attached form an optionally substituted 5- or 6-membered ring having from 0-2 heteroatoms selected from O, N or S. In some embodiments, one of R¹⁰ or R¹¹ is C₁₋₆alkyl, aryl-C₁₋₄alkyl, heteroaryl-C₁₋₄alkyl, C₃₋₆cycloalkyl, C₃₋₆cycloalkyl-C₁₋₄alkyl or C₁₋₆haloalkyl and the other R¹⁰ or R¹¹ is aryl or heteroaryl, each of which is optionally substituted with from 1-3 independently selected R^c; or 1-3 independently selected R^d; or 1-3 independently selected R^f; or 1-3 independently selected R^g; or 1-3 independently selected R¹²; or 1-3 independently selected R¹³ substituents; or two adjacent substituents on an aromatic ring are taken together with the atoms to which they are attached form an optionally substituted 5- or 6-membered ring having from 0-2 heteroatoms selected from O, N or S. In some embodiments, one of R¹⁰ or R¹¹ is methyl and the other R¹⁰ or R¹¹ is phenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-thiophenyl, 2,3-dihydro-1,4-benzodioxin-6-yl, 1,3-benzodioxol-5-yl, 2,2-difluoro-1,3-benzodioxol-5-yl, wherein at each occurrence, the other R¹⁰ or R¹¹ is optionally substituted with from 1-3 R¹².

[0116] In a second group of embodiments of the disclosure, compounds of formulas (I) or (II) have subformula (IIa):



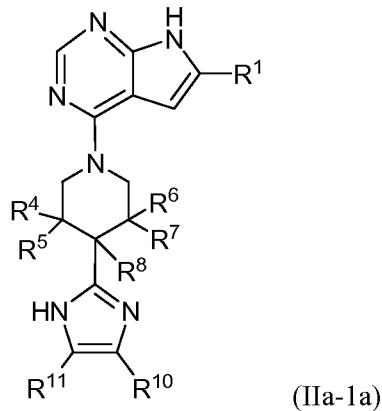
The variables R¹, R⁴, R⁵, R⁶, R⁷, R⁸, Y¹, Y², R⁹, R¹⁰ and R¹¹ are as defined in any of the embodiments of formulas (I) or (II) as disclosed herein.

[0117] In a third group of embodiments of the disclosure, compounds of formulas (I), (II) or (IIa) have subformula (IIa-1):



The variables R¹, R⁴, R⁵, R⁶, R⁷, R⁸, Y¹, Y², R¹⁰ and R¹¹ are as defined in any of the embodiments of formulas (I), (II) or (IIa) as disclosed herein.

[0118] In a fourth group of embodiments of the disclosure, compounds of formulas (I), (II), (IIa) or (IIa-1) have subformula (IIa-1a):



The variables R¹, R⁴, R⁵, R⁶, R⁷, R⁸, R¹⁰ and R¹¹ are as defined in any of the embodiments of formulas (I), (II), (IIa) or (IIa-1) as disclosed herein. In some embodiments, R⁴, R⁵, R⁶, R⁷ and R⁸ are H. In other embodiments, R⁸ is H. In other embodiments, R⁸ is H and R¹ is optionally substituted aryl or optionally substituted heteroaryl. In other embodiments, R⁸ is C₁₋₄alkyl and R¹ is optionally substituted alkyl, optionally substituted aryl or optionally substituted heteroaryl. In other embodiments, R⁸ is C₁₋₄alkyl and R¹ is optionally substituted alkyl. In other embodiments, R⁸ is C₁₋₄alkyl and R¹ is optionally substituted aryl or optionally substituted heteroaryl. In some embodiments, R¹⁰ is C₁₋₄alkyl. In other embodiments, R¹⁰ is C₁₋₄alkyl and R¹¹ is optionally substituted aryl or optionally substituted heteroaryl. The optionally substituted alkyl, optionally substituted aryl or optionally substituted heteroaryl when substituted can be substituted with from 1-3 independently selected R^c; or 1-3 independently selected R^d; or 1-3 independently selected R^f; or 1-3 independently selected R^g; or 1-3 independently selected R¹²; or 1-3 independently selected R¹³ substituents; or two adjacent substituents on an aromatic ring are taken together with the atoms to which they are attached form an optionally substituted 5- or 6-membered ring having from 0-2 heteroatoms selected from O, N or S.

[0119] In some embodiments, the disclosure provides any of the compounds set forth in Table 1 or Table 2, 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-3001 to P-3003, P-3006 to P-3011, P-3014 to P-3119, P-3122 to P-3124, P-3132 to P-3207 and P-3209 to P-3256 as described herein or pharmaceutically acceptable salts, hydrates, solvates, tautomers or isomers thereof. In certain embodiments, the disclosure provides any of the compounds P-3004 to P-3005, P-3120, P-3121 and P-3125 to P-3131 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), (IIa), (IIa-1), (IIa-1a), or any of the subformulas as described herein, or any of the compounds described in the examples, or any of the compounds described herein, or pharmaceutically acceptable salts, hydrates, solvates, tautomers or isomers thereof.

[0120] In some embodiments, the disclosure provides a compound selected from:

4-[4-(5-methyl-4-phenyl-1H-imidazol-2-yl)-1-piperidyl]-6-(4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine	P-3001
6-(4-fluorophenyl)-4-[4-(4-methyl-5-phenyl-1H-imidazol-2-yl)-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	P-3002
6-(2-methoxy-4-pyridyl)-4-[4-(4-methyl-5-phenyl-1H-imidazol-2-yl)-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	P-3003
6-(4-fluorophenyl)-4-[4-[5-(4-fluorophenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	P-3006
4-[4-[5-(4-fluorophenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-(2-methoxy-4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine	P-3007
4-[4-(4-cyclopropyl-5-phenyl-1H-imidazol-2-yl)-1-piperidyl]-6-(2-methoxy-4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine	P-3008
4-[4-(4-cyclopropyl-5-phenyl-1H-imidazol-2-yl)-1-piperidyl]-6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidine	P-3009
4-[4-[4-(4-cyclopropyl-5-phenyl-1H-imidazol-2-yl)-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	P-3010
6-(4-fluorophenyl)-4-[4-[4-methyl-5-[3-(trifluoromethoxy)phenyl]-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	P-3011
6-(2-methoxy-4-pyridyl)-4-[4-[4-methyl-5-[3-(trifluoromethoxy)phenyl]-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	P-3014
4-[4-[4-[5-(4-methoxyphenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	P-3015
4-[4-[4-[5-(3-fluorophenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	P-3016
4-[4-[5-(4-methoxyphenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-(2-methoxy-4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine	P-3017
4-[4-[4-[5-(3-fluoro-4-methoxy-phenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	P-3018
4-[4-[5-(3-fluorophenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-(2-methoxy-4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine	P-3019
4-[4-[4-[5-(4-fluorophenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	P-3020
4-[4-[4-[5-(3-methoxyphenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	P-3021
4-[4-[5-(3-methoxyphenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-(2-methoxy-4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine	P-3022
4-[4-[5-(4-methoxy-3-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-(2-methoxy-4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine	P-3023
4-[4-[5-(3-ethoxyphenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidine	P-3024
4-[4-[4-[5-(3-ethoxyphenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	P-3025
4-[4-[5-(4-ethoxyphenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidine	P-3026

4-[4-[4-[5-(4-ethoxyphenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	P-3027
6-(4-fluorophenyl)-4-[4-[5-(4-methoxyphenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	P-3028
6-(4-fluorophenyl)-4-[4-[5-(4-methoxy-3-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	P-3029
4-[4-[4-[5-(4-methoxy-3-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	P-3030
4-[4-[5-(4-ethoxyphenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-(2-methoxy-4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine	P-3031
6-(4-fluorophenyl)-4-[4-methyl-4-(4-methyl-5-phenyl-1H-imidazol-2-yl)-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	P-3032
6-(2-methoxy-4-pyridyl)-4-[4-methyl-4-(4-methyl-5-phenyl-1H-imidazol-2-yl)-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	P-3033
4-[4-[5-(3-ethoxyphenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-(2-methoxy-4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine	P-3034
4-[4-[5-(4-chlorophenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidine	P-3035
4-[4-[5-(3,4-dimethoxyphenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidine	P-3036
4-[4-[5-(4-chlorophenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-(2-methoxy-4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine	P-3037
4-[4-[4-[5-(4-chlorophenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	P-3038
4-[4-[4-[5-(3,4-dimethoxyphenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	P-3039
6-(4-fluorophenyl)-4-[4-[5-(4-methoxyphenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	P-3040
4-[4-[5-(4-methoxyphenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-6-(2-methoxy-4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine	P-3041
4-[4-[5-(3,4-dimethoxyphenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-(2-methoxy-4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine	P-3042
4-[4-[4-[5-(4-methoxyphenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	P-3043
4-[4-[4-(4-methyl-5-phenyl-1H-imidazol-2-yl)-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzamide	P-3044
6-(2-methoxypyrimidin-5-yl)-4-[4-(4-methyl-5-phenyl-1H-imidazol-2-yl)-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	P-3045
4-[4-(4-methyl-5-phenyl-1H-imidazol-2-yl)-1-piperidyl]-6-(1-methylpyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidine	P-3046
4-[4-[4-(4-methyl-5-phenyl-1H-imidazol-2-yl)-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	P-3047
4-[4-(4-methyl-5-phenyl-1H-imidazol-2-yl)-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzenesulfonamide	P-3048
N-methyl-3-[4-[4-(4-methyl-5-phenyl-1H-imidazol-2-yl)-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzamide	P-3049

6-[1-(difluoromethyl)pyrazol-4-yl]-4-[4-(4-methyl-5-phenyl-1H-imidazol-2-yl)-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	P-3050
3-[4-[4-(4-methyl-5-phenyl-1H-imidazol-2-yl)-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzenesulfonamide	P-3051
6-(4-fluorophenyl)-4-[4-[5-(4-methoxy-3-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	P-3052
4-[4-[4-[5-(4-methoxy-3-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	P-3053
4-[4-[5-(4-methoxy-3-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-6-(2-methoxy-4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine	P-3054
4-[4-ethyl-4-[5-(4-methoxyphenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidine	P-3055
4-[4-ethyl-4-[5-(4-methoxy-3-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidine	P-3056
6-(4-fluorophenyl)-4-[4-[5-(4-fluorophenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	P-3057
4-[4-[5-(4-chlorophenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidine	P-3058
4-[4-[5-(4-ethylphenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-(2-methoxy-4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine	P-3059
4-[4-[5-(4-ethylphenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidine	P-3060
4-[4-[4-[5-(4-ethylphenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	P-3061
6-(4-fluorophenyl)-4-[4-[4-methyl-5-(p-tolyl)-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	P-3062
4-[4-[5-(4-methoxyphenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-6-methyl-7H-pyrrolo[2,3-d]pyrimidine	P-3063
4-[4-[5-(4-fluorophenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-6-methyl-7H-pyrrolo[2,3-d]pyrimidine	P-3064
4-[4-[5-(4-ethoxy-3-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidine	P-3065
4-[4-[4-[5-(4-ethoxy-3-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	P-3066
4-[4-[5-(4-ethoxy-3-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-(2-methoxy-4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine	P-3067
4-[4-[5-(1,3-benzodioxol-5-yl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidine	P-3068
4-[4-[4-[5-(1,3-benzodioxol-5-yl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	P-3069
4-[4-[5-(1,3-benzodioxol-5-yl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-(2-methoxy-4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine	P-3070
N-[3-[4-[4-(4-methyl-5-phenyl-1H-imidazol-2-yl)-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]phenyl]acetamide	P-3071
6-(6-methoxy-3-pyridyl)-4-[4-(4-methyl-5-phenyl-1H-imidazol-2-yl)-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	P-3072

6-(1,3-dimethylpyrazol-4-yl)-4-[4-(4-methyl-5-phenyl-1H-imidazol-2-yl)-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	P-3073
4-[4-(4-methyl-5-phenyl-1H-imidazol-2-yl)-1-piperidyl]-6-(6-methyl-3-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine	P-3074
6-(2-ethoxy-4-pyridyl)-4-[4-(4-methyl-5-phenyl-1H-imidazol-2-yl)-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	P-3075
4-[4-[4-(4-methyl-5-phenyl-1H-imidazol-2-yl)-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]-2-pyridyl]morpholine	P-3076
4-[4-(4-methyl-5-phenyl-1H-imidazol-2-yl)-1-piperidyl]-6-[2-(4-methyl-1-piperidyl)-4-pyridyl]-7H-pyrrolo[2,3-d]pyrimidine	P-3077
6-(2-isopropoxy-4-pyridyl)-4-[4-(4-methyl-5-phenyl-1H-imidazol-2-yl)-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	P-3078
4-[4-(4-methyl-5-phenyl-1H-imidazol-2-yl)-1-piperidyl]-6-(2-pyrrolidin-1-yl-4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine	P-3079
4-[4-(4-methyl-5-phenyl-1H-imidazol-2-yl)-1-piperidyl]-6-[3-(trifluoromethoxy)phenyl]-7H-pyrrolo[2,3-d]pyrimidine	P-3080
6-(3-fluorophenyl)-4-[4-(4-methyl-5-phenyl-1H-imidazol-2-yl)-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	P-3081
6-(3-chlorophenyl)-4-[4-(4-methyl-5-phenyl-1H-imidazol-2-yl)-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	P-3082
N-[3-[4-(4-methyl-5-phenyl-1H-imidazol-2-yl)-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]phenyl]methanesulfonamide	P-3083
4-[4-[5-(2,3-dihydro-1,4-benzodioxin-6-yl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidine	P-3084
6-(4-fluorophenyl)-4-[4-[4-methyl-5-[4-(trifluoromethoxy)phenyl]-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	P-3085
4-[4-[4-methyl-5-[4-(trifluoromethoxy)phenyl]-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	P-3086
6-(2-methoxy-4-pyridyl)-4-[4-[4-methyl-5-[4-(trifluoromethoxy)phenyl]-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	P-3087
6-(2-methoxy-4-pyridyl)-4-[4-[4-methyl-5-(p-tolyl)-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	P-3088
4-[4-[4-methyl-5-(p-tolyl)-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	P-3089
4-[4-[4-methyl-5-(5-methyl-2-thienyl)-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	P-3090
4-[4-[5-(4-isopropoxyphenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-(2-methoxy-4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine	P-3091
6-(4-fluorophenyl)-4-[4-[5-(4-isopropoxyphenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	P-3092
4-[4-[4-(4-isopropoxyphenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	P-3093
4-[4-[5-(3-ethoxy-4-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidine	P-3094
4-[4-[5-(3-ethoxy-4-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	P-3095

4-[4-[5-(3-ethoxy-4-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-(2-methoxy-4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine	P-3096
4-[4-(4-methyl-5-phenyl-1H-imidazol-2-yl)-1-piperidyl]-6-[2-(trifluoromethyl)-4-pyridyl]-7H-pyrrolo[2,3-d]pyrimidine	P-3097
4-[4-(4-methyl-5-phenyl-1H-imidazol-2-yl)-1-piperidyl]-6-[3-(trifluoromethyl)phenyl]-7H-pyrrolo[2,3-d]pyrimidine	P-3098
4-[4-[5-(4-ethoxy-3-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-6-methyl-7H-pyrrolo[2,3-d]pyrimidine	P-3099
4-[4-[5-(3-ethoxy-4-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-6-methyl-7H-pyrrolo[2,3-d]pyrimidine	P-3100
4-[4-[5-(4-ethylphenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-6-methyl-7H-pyrrolo[2,3-d]pyrimidine	P-3101
4-[4-[5-(4-methoxy-3-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-6-methyl-7H-pyrrolo[2,3-d]pyrimidine	P-3102
6-(4-fluorophenyl)-4-[4-[5-(3-methoxy-4-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	P-3103
4-[4-[5-(3-methoxy-4-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-(2-methoxy-4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine	P-3104
4-[4-[5-(3-methoxy-4-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-6-methyl-7H-pyrrolo[2,3-d]pyrimidine	P-3105
4-[4-[4-[5-(3-methoxy-4-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	P-3106
6-[1-(difluoromethyl)pyrazol-4-yl]-4-[4-[5-(4-fluorophenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	P-3107
6-[1-(difluoromethyl)pyrazol-4-yl]-4-[4-[5-(4-methoxyphenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	P-3108
4-[4-[5-(2,2-difluoro-1,3-benzodioxol-5-yl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidine	P-3109
4-[4-[4-[5-(2,2-difluoro-1,3-benzodioxol-5-yl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	P-3110
4-[4-[5-(2,2-difluoro-1,3-benzodioxol-5-yl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-(2-methoxy-4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine	P-3111
4-[4-[4-[5-(6-methoxy-3-pyridyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	P-3112
4-[4-[4-[5-(difluoromethoxy)phenyl]-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	P-3113
6-[1-(difluoromethyl)pyrazol-4-yl]-4-[4-[5-(3-methoxyphenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	P-3114
4-[4-[4-[4-(difluoromethoxy)phenyl]-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-[1-(difluoromethyl)pyrazol-4-yl]-7H-pyrrolo[2,3-d]pyrimidine	P-3115
6-[1-(difluoromethyl)pyrazol-4-yl]-4-[4-[4-methyl-5-[4-(trifluoromethoxy)phenyl]-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	P-3116
6-(2-methoxy-4-pyridyl)-4-[4-[4-methyl-5-(5-methyl-2-thienyl)-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	P-3117
6-(4-fluorophenyl)-4-[4-[4-methyl-5-(5-methyl-2-thienyl)-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	P-3118

4-[4-[5-(5-chloro-2-thienyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidine	P-3119
6-(1,3-dimethylpyrazol-4-yl)-4-[4-[4-methyl-5-[4-(trifluoromethoxy)phenyl]-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	P-3122
4-[4-[5-(3-methoxyphenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl]-1-piperidyl]-6-(2-methoxy-4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine	P-3123
4-[4-[4-[5-(3-methoxyphenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	P-3124
4-[4-[4-[5-(2,3-dihydro-1,4-benzodioxin-6-yl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	P-3132
6-[1-(difluoromethyl)pyrazol-4-yl]-4-[4-[5-(2,3-dihydro-1,4-benzodioxin-6-yl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	P-3133
6-(2-methoxy-4-pyridyl)-4-[4-[5-(p-tolyl)-4-(trifluoromethyl)-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	P-3134
6-(4-fluorophenyl)-4-[4-[5-(p-tolyl)-4-(trifluoromethyl)-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	P-3135
6-(4-fluorophenyl)-4-[4-[4-methyl-5-[4-(trifluoromethyl)phenyl]-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	P-3136
4-[4-[4-methyl-5-[4-(trifluoromethyl)phenyl]-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	P-3137
4-[4-[5-(1,3-benzodioxol-5-yl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-[1-(difluoromethyl)pyrazol-4-yl]-7H-pyrrolo[2,3-d]pyrimidine	P-3138
6-[1-(difluoromethyl)pyrazol-4-yl]-4-[4-[5-(4-ethoxy-3-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	P-3139
4-[4-ethyl-4-[5-(4-methoxyphenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-methyl-7H-pyrrolo[2,3-d]pyrimidine	P-3140
4-[4-ethyl-4-[5-(4-methoxy-3-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-methyl-7H-pyrrolo[2,3-d]pyrimidine	P-3141
4-[4-[5-(4-ethoxy-3-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-4-ethyl-1-piperidyl]-6-methyl-7H-pyrrolo[2,3-d]pyrimidine	P-3142
4-[4-[5-(1,3-benzodioxol-5-yl)-4-methyl-1H-imidazol-2-yl]-4-ethyl-1-piperidyl]-6-methyl-7H-pyrrolo[2,3-d]pyrimidine	P-3143
4-[4-[5-(2,3-dihydro-1,4-benzodioxin-6-yl)-4-methyl-1H-imidazol-2-yl]-4-ethyl-1-piperidyl]-6-methyl-7H-pyrrolo[2,3-d]pyrimidine	P-3144
4-[4-[5-(4-ethoxyphenyl)-4-methyl-1H-imidazol-2-yl]-4-ethyl-1-piperidyl]-6-methyl-7H-pyrrolo[2,3-d]pyrimidine	P-3145
4-[4-[5-(4-methoxyphenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl]-1-piperidyl]-6-(2-methoxy-4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine	P-3146
6-(4-fluorophenyl)-4-[4-[5-(4-methoxyphenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	P-3147
4-[4-[4-[5-(4-methoxyphenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	P-3148
6-(2-methoxy-4-pyridyl)-4-[4-[4-methyl-5-[4-(trifluoromethyl)phenyl]-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	P-3149
4-[4-[5-(1,3-benzodioxol-5-yl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-6-methyl-7H-pyrrolo[2,3-d]pyrimidine	P-3150

4-[4-[5-(2,3-dihydro-1,4-benzodioxin-6-yl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-6-methyl-7H-pyrrolo[2,3-d]pyrimidine	P-3151
4-[4-[5-(2,2-difluoro-1,3-benzodioxol-5-yl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-6-methyl-7H-pyrrolo[2,3-d]pyrimidine	P-3152
6-[1-(difluoromethyl)pyrazol-4-yl]-4-[4-[5-(4-methoxyphenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	P-3153
6-[1-(difluoromethyl)pyrazol-4-yl]-4-[4-[5-(4-methoxy-3-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	P-3154
4-[4-[5-(1,3-benzodioxol-5-yl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-6-[1-(difluoromethyl)pyrazol-4-yl]-7H-pyrrolo[2,3-d]pyrimidine	P-3155
4-[4-[5-(4-methoxyphenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-6-(6-methoxy-3-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine	P-3156
4-[4-[5-(4-methoxy-3-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-6-(6-methoxy-3-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine	P-3157
4-[4-[5-(1,3-benzodioxol-5-yl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-6-(6-methoxy-3-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine	P-3158
4-[4-[4-[5-(1,3-benzodioxol-5-yl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	P-3159
4-[4-[4-[5-(4-ethoxy-3-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	P-3160
4-[4-[4-[5-(4-ethoxyphenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	P-3161
4-[4-[4-[5-(4-difluoromethyl)phenyl]-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	P-3162
4-[4-[4-[5-(3-fluoro-4-methoxy-phenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	P-3163
4-[4-[4-[5-(4-difluoromethyl)phenyl]-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	P-3164
6-methyl-4-[4-methyl-4-[4-methyl-5-[4-(trifluoromethyl)phenyl]-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	P-3165
4-[4-[5-(3-methoxyphenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-6-methyl-7H-pyrrolo[2,3-d]pyrimidine	P-3166
4-[4-[4-[5-(3-methoxyphenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	P-3167
6-[1-(difluoromethyl)pyrazol-4-yl]-4-[4-[5-(3-methoxyphenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	P-3168
4-[4-[5-(3-methoxyphenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-6-(6-methoxy-3-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine	P-3169
6-[1-(difluoromethyl)pyrazol-4-yl]-4-[4-[5-(4-ethoxyphenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	P-3170
4-[4-[5-(4-ethoxyphenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-6-(6-methoxy-3-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine	P-3171
4-[4-[4-[5-(6-methoxy-3-pyridyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	P-3172
4-[4-[4-[5-(5-fluoro-6-methoxy-3-pyridyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	P-3173

4-[4-[5-(4-chlorophenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-6-methyl-7H-pyrrolo[2,3-d]pyrimidine	P-3174
4-[4-[5-(4-chlorophenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-6-[1-(difluoromethyl)pyrazol-4-yl]-7H-pyrrolo[2,3-d]pyrimidine	P-3175
4-[4-[5-(4-chlorophenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-6-(6-methoxy-3-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine	P-3176
4-[4-[4-methyl-4-[4-methyl-5-[4-(trifluoromethyl)phenyl]-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	P-3177
6-(6-methoxy-3-pyridyl)-4-[4-methyl-4-[4-methyl-5-[4-(trifluoromethyl)phenyl]-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	P-3178
6-[1-(difluoromethyl)pyrazol-4-yl]-4-[4-methyl-4-[4-methyl-5-[4-(trifluoromethyl)phenyl]-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	P-3179
4-[4-[4-[5-(4-chlorophenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	P-3180
4-[4-[4-[5-(5-fluoro-6-methoxy-3-pyridyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	P-3181
6-[1-(difluoromethyl)pyrazol-4-yl]-4-[4-[5-(6-methoxy-3-pyridyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	P-3182
4-[4-[5-(3-fluoro-4-methoxy-phenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-6-methyl-7H-pyrrolo[2,3-d]pyrimidine	P-3183
4-[4-[5-[4-(difluoromethyl)phenyl]-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-6-methyl-7H-pyrrolo[2,3-d]pyrimidine	P-3184
4-[4-[4-(5-fluoro-6-methoxy-3-pyridyl)-5-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-6-methyl-7H-pyrrolo[2,3-d]pyrimidine	P-3185
4-[4-[4-(6-methoxy-3-pyridyl)-5-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-6-methyl-7H-pyrrolo[2,3-d]pyrimidine	P-3186
6-[1-(difluoromethyl)pyrazol-4-yl]-4-[4-[5-(3-fluoro-4-methoxy-phenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	P-3187
4-[4-[5-(3-fluoro-4-methoxy-phenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-6-(6-methoxy-3-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine	P-3188
4-[4-[5-[4-(difluoromethyl)phenyl]-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-6-[1-(difluoromethyl)pyrazol-4-yl]-7H-pyrrolo[2,3-d]pyrimidine	P-3189
4-[4-[5-[4-(difluoromethyl)phenyl]-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-6-(6-methoxy-3-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine	P-3190
4-[4-[5-[3-(difluoromethoxy)phenyl]-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-6-methyl-7H-pyrrolo[2,3-d]pyrimidine	P-3191
4-[4-[5-[3-(difluoromethoxy)phenyl]-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-6-[1-(difluoromethyl)pyrazol-4-yl]-7H-pyrrolo[2,3-d]pyrimidine	P-3192
4-[4-[5-[3-(difluoromethoxy)phenyl]-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-6-(6-methoxy-3-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine	P-3193
4-[4-[4-[5-[3-(difluoromethoxy)phenyl]-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	P-3194
4-[4-[4-[5-[4-(difluoromethoxy)phenyl]-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	P-3195
4-[4-[5-[4-(difluoromethoxy)phenyl]-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-6-methyl-7H-pyrrolo[2,3-d]pyrimidine	P-3196

6-[1-(difluoromethyl)pyrazol-4-yl]-4-[4-(5-ethyl-4-methyl-1H-imidazol-2-yl)-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	P-3197
4-[4-[4-(5-ethyl-4-methyl-1H-imidazol-2-yl)-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	P-3198
4-[4-[4-(5-(3-fluoro-4-methoxy-phenyl)-4-methyl-1H-imidazol-2-yl)-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzoic acid	P-3199
4-[4-[5-(4-chlorophenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-3-methyl-1H-pyrazolo[3,4-d]pyrimidine	P-3200
4-[4-[5-[3-(difluoromethoxy)phenyl]-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-3-methyl-1H-pyrazolo[3,4-d]pyrimidine	P-3201
4-[4-[5-(3-fluoro-4-methoxy-phenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-3-methyl-1H-pyrazolo[3,4-d]pyrimidine	P-3202
4-[4-[5-(2,2-difluoro-1,3-benzodioxol-5-yl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-3-methyl-1H-pyrazolo[3,4-d]pyrimidine	P-3203
4-[4-[5-[3-(difluoromethoxy)phenyl]-4H-1,2,4-triazol-3-yl]-1-piperidyl]-6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidine	P-3204
4-[4-[5-(4-fluorophenyl)-4H-1,2,4-triazol-3-yl]-1-piperidyl]-6-(2-methoxy-4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine	P-3205
6-(4-fluorophenyl)-4-[4-[5-(4-fluorophenyl)-4H-1,2,4-triazol-3-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	P-3206
4-[4-[5-[3-(difluoromethoxy)phenyl]-4H-1,2,4-triazol-3-yl]-1-piperidyl]-6-(2-methoxy-4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine	P-3207
4-[4-[5-(4-ethoxy-3-fluoro-phenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-6-(6-methoxy-3-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine	P-3209
6-[1-(difluoromethyl)pyrazol-4-yl]-4-[4-[5-(4-ethoxy-3-fluoro-phenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	P-3210
5-[4-[4-(5-(3-fluoro-4-methoxy-phenyl)-4-methyl-1H-imidazol-2-yl)-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]pyridine-2-carbonitrile	P-3211
4-[4-[4-[5-(3-fluoro-4-methoxy-phenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzamide	P-3212
N-[4-[4-[4-[5-(3-fluoro-4-methoxy-phenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]phenyl]methanesulfonamide	P-3213
2-[4-[4-[5-(3-fluoro-4-methoxy-phenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]phenoxy]acetic acid	P-3214
4-[5-[4-[4-[5-(3-fluoro-4-methoxy-phenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]-2-pyridyl]morpholine	P-3215
4-[4-[4-[5-(4-methoxy-3-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzamide	P-3216
2-[4-[4-[5-(4-methoxy-3-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]phenoxy]acetic acid	P-3217
5-[4-[4-[5-(4-methoxy-3-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]-N-methyl-pyridine-2-carboxamide	P-3218
4-[5-[4-[4-[5-(4-methoxy-3-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]-2-pyridyl]morpholine	P-3219
5-[4-[4-[5-(3-fluoro-4-methoxy-phenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]-N-methyl-pyridine-2-carboxamide	P-3220

2-[4-[4-[5-(3-methoxyphenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]phenoxy]acetic acid	P-3221
5-[4-[4-[5-(3-methoxyphenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]-N-methyl-pyridine-2-carboxamide	P-3222
4-[5-[4-[5-(3-methoxyphenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]-2-pyridyl]morpholine	P-3223
2-[4-[4-[5-(4-ethoxyphenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]phenoxy]acetic acid	P-3224
4-[4-[4-[5-(3-methoxyphenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzamide	P-3225
5-[4-[4-[5-(4-ethoxyphenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]-N-methyl-pyridine-2-carboxamide	P-3226
4-[5-[4-[4-[5-(4-ethoxyphenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]-2-pyridyl]morpholine	P-3227
N-[4-[4-[4-[5-(4-methoxy-3-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]phenyl]methanesulfonamide	P-3228
4-[4-[4-[5-(4-ethoxyphenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzamide	P-3229
N-[4-[4-[4-[5-(4-ethoxyphenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]phenyl]methanesulfonamide	P-3230
4-[4-[4-[5-[3-(difluoromethoxy)phenyl]-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzamide	P-3231
N-[4-[4-[4-[5-[3-(difluoromethoxy)phenyl]-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]phenyl]methanesulfonamide	P-3232
2-[4-[4-[4-[5-[3-(difluoromethoxy)phenyl]-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]phenoxy]acetic acid	P-3233
N-[4-[4-[4-[5-(3-methoxyphenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]phenyl]methanesulfonamide	P-3234
5-[4-[4-[5-[4-(difluoromethyl)phenyl]-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]-N-methyl-pyridine-2-carboxamide	P-3235
5-[4-[4-[5-[3-(difluoromethoxy)phenyl]-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]-N-methyl-pyridine-2-carboxamide	P-3236
4-[5-[4-[4-[5-[4-(difluoromethyl)phenyl]-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]-2-pyridyl]morpholine	P-3237
4-[5-[4-[4-[5-[3-(difluoromethoxy)phenyl]-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]-2-pyridyl]morpholine	P-3238
4-[4-[4-[5-[4-(difluoromethyl)phenyl]-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzamide	P-3239
2-[4-[4-[4-[5-[4-(difluoromethyl)phenyl]-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]phenoxy]acetic acid	P-3240
2-[4-[4-[4-[5-[4-(difluoromethyl)phenyl]-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]phenoxy]acetic acid	P-3241
4-[4-[5-[4-(difluoromethoxy)phenyl]-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-6-[1-(difluoromethyl)pyrazol-4-yl]-7H-pyrrolo[2,3-d]pyrimidine	P-3242
4-[4-[4-[5-(4-ethoxy-3-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzamide	P-3243

2-[4-[4-[5-(4-ethoxy-3-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]phenoxy]acetic acid	P-3244
6-[1-(difluoromethyl)pyrazol-4-yl]-4-[4-[5-(4-ethoxy-3-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	P-3245
5-[4-[4-[5-[4-(difluoromethoxy)phenyl]-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]-N-methyl-pyridine-2-carboxamide	P-3246
5-[4-[4-[5-(4-ethoxy-3-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]-N-methyl-pyridine-2-carboxamide	P-3247
4-[5-[4-[4-[5-(4-(difluoromethoxy)phenyl]-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]-2-pyridyl]morpholine	P-3248
4-[5-[4-[4-[5-(4-ethoxy-3-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]-2-pyridyl]morpholine	P-3249
5-[4-[4-[5-(4-methoxy-3-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]pyridine-2-carbonitrile	P-3250
5-[4-[4-[5-(4-ethoxyphenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]pyridine-2-carbonitrile	P-3251
N-[4-[4-[4-[5-[4-(difluoromethyl)phenyl]-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]phenyl]methanesulfonamide	P-3252
4-[4-[4-[5-[4-(difluoromethoxy)phenyl]-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzamide	P-3253
N-[4-[4-[4-[5-[4-(difluoromethoxy)phenyl]-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]phenyl]methanesulfonamide	P-3254
5-[4-[4-[5-[3-(difluoromethoxy)phenyl]-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]pyridine-2-carbonitrile	P-3255
5-[4-[4-[5-(3-methoxyphenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]pyridine-2-carbonitrile	P-3256

or pharmaceutically acceptable salts, hydrates, solvates, tautomers or isomers thereof.

[0121] In some embodiments, the disclosure provides a compound selected from:

6-methyl-4-[4-(4-methyl-5-phenyl-1H-imidazol-2-yl)-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	P-3004
4-[4-[5-(4-fluorophenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-methyl-7H-pyrrolo[2,3-d]pyrimidine	P-3005
4-[4-[5-(1,3-benzodioxol-5-yl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-methyl-7H-pyrrolo[2,3-d]pyrimidine	P-3120
4-[4-[5-(2,3-dihydro-1,4-benzodioxin-6-yl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-methyl-7H-pyrrolo[2,3-d]pyrimidine	P-3121
4-[4-[5-(4-ethoxy-3-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-methyl-7H-pyrrolo[2,3-d]pyrimidine	P-3125
4-[4-[5-(3-ethoxy-4-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-methyl-7H-pyrrolo[2,3-d]pyrimidine	P-3126
4-[4-[5-(2,2-difluoro-1,3-benzodioxol-5-yl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-methyl-7H-pyrrolo[2,3-d]pyrimidine	P-3127
4-[4-[5-(4-methoxy-3-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-methyl-7H-pyrrolo[2,3-d]pyrimidine	P-3128

4-[4-[5-(3-methoxy-4-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-methyl-7H-pyrrolo[2,3-d]pyrimidine	P-3129
4-[4-[5-(4-methoxyphenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-methyl-7H-pyrrolo[2,3-d]pyrimidine	P-3130
4-[4-[5-(3-methoxyphenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-methyl-7H-pyrrolo[2,3-d]pyrimidine	P-3131

or pharmaceutically acceptable salts, hydrates, solvates, tautomers or isomers thereof.

[0122] In some embodiments, the disclosure provides a compound of any of formulas (I), (II), (IIa), (IIa-1) or (IIa-1a), or pharmaceutically acceptable salts, hydrates, solvates, tautomers or isomers thereof.

[0123] In some embodiments, the disclosure provides any of compounds selected from P-3001 to P-3003, P-3006 to P-3011, P-3014 to P-3119, P-3122 to P-3124, P-3132 to P-3207 and P-3209 to P-3256, e.g., compounds P-3001, P-3002, P-3003, P-3006, P-3007, P-3008, P-3009, P-3010, P-3011, P-3014, P-3015, P-3016, P-3017, P-3018, P-3019, P-3020, P-3021, P-3022, P-3023, P-3024, P-3025, P-3026, P-3027, P-3028, P-3029, P-3030, P-3031, P-3032, P-3033, P-3034, P-3035, P-3036, P-3037, P-3038, P-3039, P-3040, P-3041, P-3042, P-3043, P-3044, P-3045, P-3046, P-3047, P-3048, P-3049, P-3050, P-3051, P-3052, P-3053, P-3054, P-3055, P-3056, P-3057, P-3058, P-3059, P-3060, P-3061, P-3062, P-3063, P-3064, P-3065, P-3066, P-3067, P-3068, P-3069, P-3070, P-3071, P-3072, P-3073, P-3074, P-3075, P-3076, P-3077, P-3078, P-3079, P-3080, P-3081, P-3082, P-3083, P-3084, P-3085, P-3086, P-3087, P-3088, P-3089, P-3090, P-3091, P-3092, P-3093, P-3094, P-3095, P-3096, P-3097, P-3098, P-3099, P-3100, P-3101, P-3102, P-3104, P-3105, P-3106, P-3107, P-3108, P-3109, P-3110, P-3111, P-3112, P-3113, P-3114, P-3115, P-3116, P-3117, P-3118, P-3119, P-3122, P-3123, P-3124, P-3132, P-3133, P-3134, P-3135, P-3136, P-3137, P-3138, P-3139, P-3140, P-3141, P-3142, P-3143, P-3144, P-3145, P-3146, P-3147, P-3148, P-3149, P-3150, P-3151, P-3152, P-3153, P-3154, P-3155, P-3156, P-3157, P-3158, P-3159, P-3160, P-3161, P-3162, P-3163, P-3164, P-3165, P-3166, P-3167, P-3168, P-3169, P-3170, P-3171, P-3172, P-3173, P-3174, P-3175, P-3176, P-3177, P-3178, P-3179, P-3180, P-3181, P-3182, P-3183, P-3184, P-3185, P-3186, P-3187, P-3188, P-3189, P-3190, P-3191, P-3192, P-3193, P-3194, P-3195, P-3196, P-3197, P-3198, P-3199, P-3200, P-3201, P-3202, P-3203, P-3204, P-3205, P-3206, P-3207, P-3209, P-3210, P-3211, P-3212, P-3213, P-3214, P-3215, P-3216, P-3217, P-3218, P-3219, P-3220, P-3221, P-3222, P-3223, P-3224, P-3225, P-3226, P-3227, P-3228, P-3229, P-3230, P-3231, P-3232, P-3233, P-3234, P-3235, P-3236, P-3237, P-3238, P-3239, P-3240, P-3241, P-3242, P-3243, P-3244, P-3245, P-3246, P-3247, P-3248, P-3249, P-3250, P-3251, P-3252, P-3253, P-3254, P-3255 or P-3256, or pharmaceutically acceptable salts, hydrates, solvates, tautomers or isomers thereof.

[0124] In some embodiments, the disclosure provides any of compounds selected from P-3004 to P-3005, P-3120, P-3121 or P-3125 to P-3131, e.g., compounds P-3004, P-3005, P-3120, P-3121, P-3125, P-3126, P-3127, P-3128, P-3129, P-3130 or P-3131, or pharmaceutically acceptable salts, hydrates, solvates, tautomers or isomers thereof.

Organic Synthetic Techniques

[0125] 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

[0126] 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. The following is provided in addition to the definitions described above.

(a) *Prodrugs and Metabolites*

[0127] 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.

[0128] 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 metabolism, 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.

[0129] 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:

[0130] 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.

[0131] 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.

[0132] 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.

[0133] 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, 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*.

[0134] 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.

[0135] 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.*, 40:3011-3016; Shan et al., 1997, *J Pharm Sci* 86(7):756-757; Bagshawe, 1995, *Drug Dev. Res.*, 34:230-230; Wermuth, *supra*.

(b) *Tautomers, Stereoisomers, and Regioisomers*

[0136] 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.

[0137] 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.

[0138] 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*

[0139] 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.

[0140] 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.

[0141] 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.

[0142] 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*

[0143] 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.

[0144] 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.

[0145] 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

[0146] In another aspect, the present disclosure provides pharmaceutical compositions comprising/including a pharmaceutically acceptable carrier, excipient and/or diluent 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 some embodiments, the disclosure provides pharmaceutical composition

comprising/including a compound has any of formulas (I), (II), (IIa), (IIa-1) or (IIa-1a) and a pharmaceutically acceptable carrier, excipient and/or diluents.

[0147] 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*, 31st edition, Lippincott, Williams and Wilkins, Philadelphia, PA, 3005 (hereby incorporated by reference herein).

[0148] 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, glycetyl monostearate, glycetyl dibehenate, glycetyl 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, polydextrose, chitosan, gelatin, HPMC (hydroxypropyl methyl celluloses), HPC (hydroxypropyl cellulose), hydroxyethyl cellulose, and the like.

[0149] 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. Unit dosage formulations may be 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.

[0150] 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.

[0151] In some embodiments, oral administration may be used. Pharmaceutical preparations for oral use can be formulated into conventional oral dosage forms such as discreet 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.

[0152] 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.

[0153] 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.

[0154] 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 C₁₂). 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.

[0155] 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 propionate, beclomethasone dipropionate, triamcinolone acetonide, budesonide, and mometasone furoate; beta agonists such as albuterol, salmeterol, and formoterol; anticholinergic agents such as ipratropium bromide or tiotropium; vasodilators such as treprostinal and iloprost; enzymes such as DNAase; therapeutic proteins; immunoglobulin antibodies; an oligonucleotide, such as single or double stranded DNA or RNA, siRNA; antibiotics such as tobramycin; muscarinic receptor antagonists; leukotriene antagonists; cytokine antagonists; protease inhibitors; cromolyn sodium; nedocril sodium; and sodium cromoglycate.

[0156] 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 IC₅₀ 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 30 mg/kg of the subject being treated. Multiple doses may be used.

[0157] 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.

[0158] 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

[0159] The compounds of formulas (I), (II), (IIa), (IIa-1) or (IIa-1a), 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. Pat. Publ. No.

20040002534, 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.

[0160] 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 (AML), 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 seminoma.

Exemplary malignant diseases associated with c-kit

[0161] 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.

[0162] 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.

[0163] Leukemias: SCF binding to the c-kit protects hematopoietic stem and progenitor cells from apoptosis (Lee, et al., 1997, *J. Immunol.* 159:3311-3319), 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* 82:617-631; 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* 82:617-631). 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.

[0164] 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, p310^{BCR-ABL}, has been reported to mediate inhibition of apoptosis (Bedi, et al., *Blood* 1995, 86:1148-1158). Since p310^{BCR-ABL} and c-kit both inhibit apoptosis and p62^{dok} has been suggested as a substrate (Carpino, et al., *Cell* 1997, 88:197-304), clonal expansion mediated by these kinases may occur through a common signaling pathway. However, c-kit has also been reported to interact directly with p310^{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.

[0165] 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 autoocrine 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 autoocrine 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).

[0166] SCF/c-kit autoocrine 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 (Hiota, et al., 1998, Science 279:577-580). Hence, inhibition of c-kit kinase will be an efficacious means for the treatment of these cancers.

[0167] 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. 3002, 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.

[0168] 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. 152:3151-3154). 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.

[0169] 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.

[0170] 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*: 3022-3082). 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).

[0171] 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

[0172] 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).

[0173] 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.

[0174] 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.

[0175] Mastocytosis is limited to the skin in the majority of patients, but can involve other organs in 15-30% 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).

[0176] 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).

[0177] 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.* 94:9017-9031), 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.

[0178] 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* 144:331-328; Yee, et al., 1994, *J. Exp. Med.* 179:1777-1787; Mekori, et al., 1994, *J. Immunol* 153:3194-2303; 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.

[0179] 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., 3002, also showed that for mutations in the catalytic region, inhibitors ST1571 (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.

[0180] 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.

[0181] **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 278:1815-1822). 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.

[0182] 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).

[0183] SCF also directly influences the adhesion of both mast cells (Dastych, et al., 1994, J. Immunol. 152:313-319; 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. 99:1731-1728). 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.

[0184] 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.

[0185] 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* 191:813-831. Thus, c-kit also provides a useful target for the prevention, delay, and/or treatment of multiple sclerosis.

Kinase Activity Assays

[0186] 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 of 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.

[0187] In certain embodiments, compounds of formulas (I), (II), (IIa), (IIa-1) or (IIa-1a), 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), (IIa), (IIa-1) or (IIa-1a) or any of the subformulas or a compound as described herein has an IC₅₀ of less than 10,000 nM, 1,000 nM, less than 500 nM, less than 100 nM, less than 50 nM, less than 30 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 IC₅₀ of less than 10,000 nM, 1,000 nM, less than 500 nM, less than 100 nM, less than 50 nM, less than 30 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, D830Y, 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, D830Y, N822K, N822H, Y823D, Y823C and T670I) activity includes an assay (e.g., biochemical or cell-bases assays) such as described in Example 7 or an assay well known in the art similar to those described in Example 7.

[0188] In some embodiments, compounds of formulas (I), (II), (IIa), (IIa-1) or (IIa-1a), or 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 IC₅₀ of less than 10,000 nM, 1,000 nM, less than 500 nM, less than 100 nM, less than 50 nM, less than 30 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 IC₅₀ 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

[0189] 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), (IIa-1) or (IIa-1a), or any of the subgeneric formulas as described herein, or a compound set forth in Table 1 or Table 2, or a compound of P-3001 to P-3003, P-3006 to P-3011, P-3014 to P-3119, P-3122 to P-3124, P-3132 to P-3207 and P-3209 to P-3256, P-3004 to P-3005, P-3120, P-3121 and P-3125 to P-3131, 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, D830Y, 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), (IIa), (IIa-1) or (IIa-1a), 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), (IIa), (IIa-1) or (IIa-1a), 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

[0190] 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), (IIa-1) or (IIa-1a), or a compound disclosed in the Examples, a compound set forth in Table 1 or Table 2, or a compound of P-3001 to P-3003, P-3006 to P-3011, P-3014 to P-3119, P-3122 to P-3124, P-3132 to P-3207, P-3209 to P-3256, P-3004 to P-3005, P-3120, P-3121 and P-3125 to P-3131, 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 or a compound as disclosed 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, D830Y, 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.

[0191] 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), (IIa), (IIa-1) or (IIa-1a) 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.

[0192] 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), (IIa), (IIa-1) or (IIa-1a) 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.

[0193] 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 palmitoyl 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 another 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.

[0194] 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 erythematosus, 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.

[0195] 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, D830Y, 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.

[0196] 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.

[0197] 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.

[0198] 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, D830Y, 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.

[0199] In some embodiments, a compound of any of formulas (I), (II), (IIa), (IIa-1) or (IIa-1a) 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 30 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 30 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.

[0200] 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), (IIa), (IIa-1) or (IIa-1a) 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.

[0201] In certain embodiments, the disclosure provides use of a compound of any of formulas (I), (II), (IIa), (IIa-1) or (IIa-1a) 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), (IIa-1), or (IIa-1a) 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

[0202] 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.

[0203] 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 formulas (I), (II), (IIa), (IIa-1) or (IIa-1a) 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), (IIa), (IIa-1) or (IIa-1a), 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.

[0204] In some embodiments, the disclosure provides a composition, e.g., a pharmaceutical composition comprising a compound of any of formulas (I), (II), (IIa), (IIa-1) or (IIa-1a), or a compound disclosed in the Examples, a compound set forth in Table 1 or Table 2, or a compound of P-3001 to P-3003, P-3006 to P-3011, P-3014 to P-3119, P-3122 to P-3124, P-3132 to P-3207, P-3209 to P-3256, P-3004 to P-3005, P-3120, P-3121 and P-3125 to P-3131 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, elsamitucin, 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 limiting 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, PLX3397, 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, masoprolol, 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), (IIa), (IIa-1) or (IIa-1a) 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 03188, CI-1040 (PD184352), GSK1130312 (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, BIBF1130 (Vargatef), BIBW2992 (Afatinib), BMS794833, BMS-599626, Brivanib (BMS-540315), Brivanib alaninate(BMS-582664), Cediranib (AZD3171), 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-430 (Desmethyl

Erlotinib, CP-473430), OSI-930, Pazopanib HCl, PD-153035 HCl, PD173074, Pelitinib (EKB-569), PF299804, Ponatinib (AP24534), PP131, 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-573016, 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), (IIa), (IIa-1) or (IIa-1a), or any of the subformulas as described herein, or a compound described herein, or pharmaceutically acceptable salts, solvates, tautomer or isomers thereof, may be administered simultaneously, sequentially or separately in combination with one or more agents as described above.

[0205] 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.

[0206] 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.

[0207] 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, D830Y, 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, D830Y, 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, D830Y, 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.

[0208] 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.

[0209] In another aspect, the disclosure provides kits or containers that include a compound of any of formulas (I), (II), (IIa), (IIa-1) or (IIa-1a) or any of the subformulas as described herein, or a pharmaceutically acceptable salt thereof, 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

[0210] The following examples are offered to illustrate, but not to limit the claimed disclosure.

[0211] 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

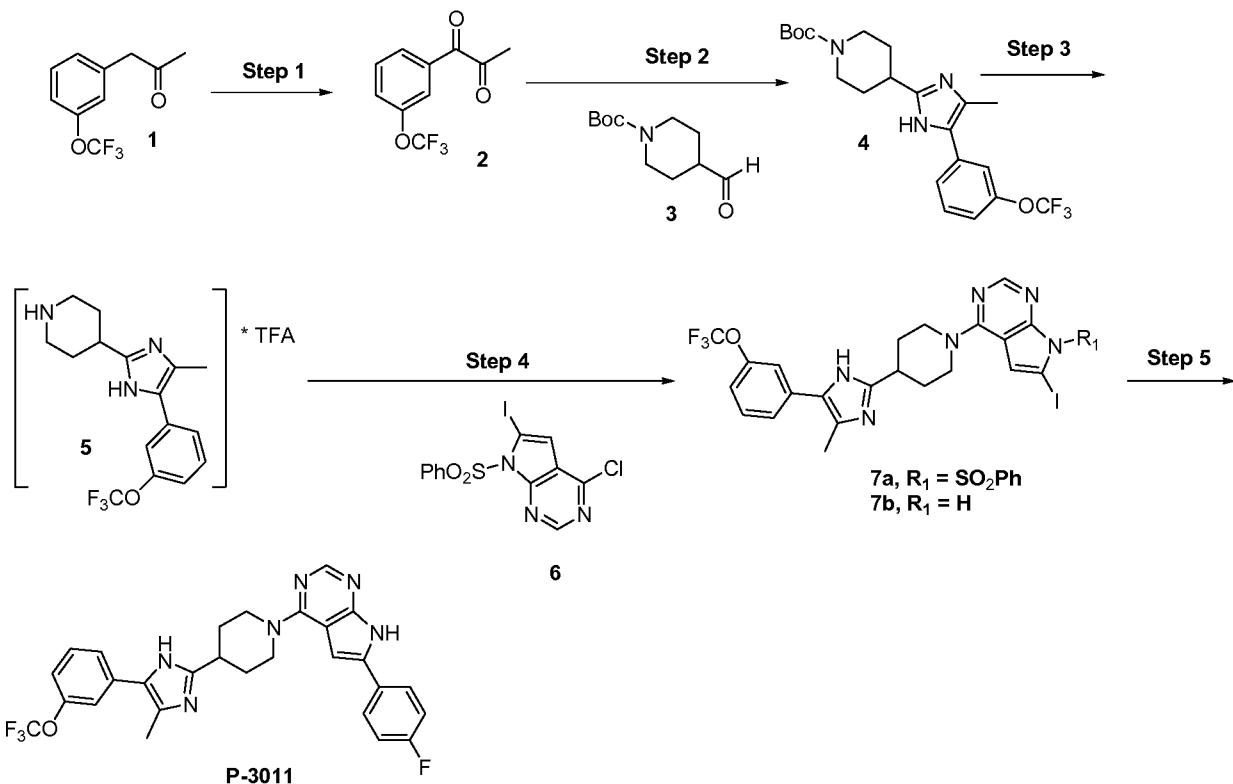
methods may be employed to synthesize the target compounds of this disclosure, and that the approaches described within the body of this document are not exhaustive, but do provide broadly applicable and practical routes to compounds of interest. Starting materials can be In some examples, the mass spectrometry 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.

[0212] Certain molecules disclosed herein 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. Further, it should be noted that the term “deuterated analog” refers to compounds where at least one hydrogen atom has been replaced by a deuterium atom.

[0213] Starting materials are commercially available or can be synthesized as described below. 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 herein.

Example 1: Preparation of 6-(4-fluorophenyl)-4-[4-methyl-5-[3-(trifluoromethoxy)phenyl]-1H-imidazol-2-yl]-1-piperidyl[2,3-d]pyrimidine (P-3011)

Scheme 1.



[0214] Step 1 – Synthesis of 1-[3-(trifluoromethoxy)phenyl]propan-1,2-dione (2): To a flask, 1-[3-(trifluoromethoxy)phenyl]propan-2-one **1** (1.07g, 5 mmol), selenium dioxide (1.088 g, 10 mmol), and 1,4-dioxane (30 mL) were combined and heated at 88 °C overnight. The reaction was filtered through a bed of sodium sulfate to remove selenium solids. The crude material was absorbed onto silica and purified via flash chromatography with a gradient of ethyl acetate (EtOAc) in hexane (30-30%). The yellow-orange desired product **2** (0.619g, 51.7%) was collected and used in the next step.

[0215] Step 2 – Synthesis of tert-butyl 4-[4-methyl-5-[3-(trifluoromethoxy)phenyl]-1H-imidazol-2-yl]piperidine-1-carboxylate (4): Compound 1-[3-(trifluoromethoxy)phenyl]propane-1,2-dione (**2**) (0.619g, 3 mmol) was dissolved in 1-butanol (15.07 mL) in a flask. Tert-butyl 4-formylpiperidine-1-carboxylate **3** (1.08g, 5 mmol) and ammonium acetate (2.929g, 30 mmol) were heated overnight at 55 °C. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate to produce a yellow oily/gummy residue **4** (1.06 g, 93.4%). MS ESI: MS ESI $[\text{M}+\text{H}+]^+ = 426.3$.

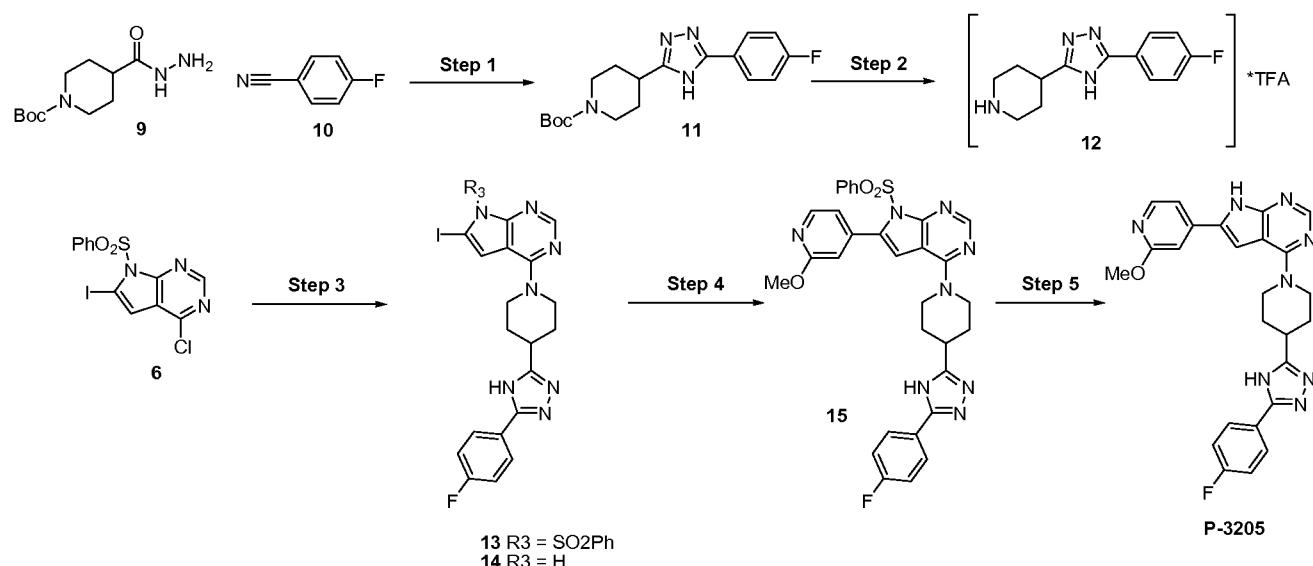
[0216] Step 3 – Synthesis of compound (5): Compound **4** was taken through deprotection with trifluoroacetic acid (TFA) in dichloromethane (DCM) at 0 °C. Extra TFA was used. The reaction mixture was stirred for 4 hours and volatiles were removed under reduced pressure. The isolated product as a dark red gummy residue was dried under vacuum overnight without further purification. MS ESI [M+H+] = 326.2.

[0217] Step 4 – Synthesis of 6-iodo-4-[4-[4-methyl-5-[3-(trifluoromethoxy)phenyl]-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine (7a) and 7-(benzenesulfonyl)-6-iodo-4-[4-[4-methyl-5-[3-(trifluoromethoxy)phenyl]-1H-imidazol-2-yl]-1-piperidyl]pyrrolo[2,3-d]pyrimidine (7b): In a microwave vial, 4-[4-methyl-5-[3-(trifluoromethoxy)phenyl]-1H-imidazol-2-yl]piperidine; 2,2,2-trifluoroacetic acid (**5**) (1.30 g), 7-(benzenesulfonyl)-4-chloro-6-iodo-pyrrolo[2,3-d]pyrimidine (**6**) (0.98 g, 2 mmol), potassium carbonate (1.94 g, 14 mmol) and acetonitrile (9.8 mL) were combined and heated at 100 °C for 40 minutes. The reaction mixture was filtered through a bed of sodium sulfate and evaporated under reduced pressure. The crude was absorbed onto silica and purified via flash chromatography, eluting off silica cartridge with 0-30% methanol (MeOH) in dichloromethane to afford the product 7-(benzenesulfonyl)-6-iodo-4-[4-[4-methyl-5-[3-(trifluoromethoxy)phenyl]-1H-imidazol-2-yl]-1-piperidyl]pyrrolo[2,3-d]pyrimidine **7a** (0.961 g, 46.5%) and 6-iodo-4-[4-[4-methyl-5-[3-(trifluoromethoxy)phenyl]-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine **7b** (0.31 g, 15%). The data from the ¹H NMR spectra was consistent with the structures of the compounds.

[0218] Step 5 - Synthesis of 6-(4-fluorophenyl)-4-[4-[4-methyl-5-[3-(trifluoromethoxy)phenyl]-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine (P-3011): In a microwave reaction vessel, compound 6-iodo-4-[4-[4-methyl-5-[3-(trifluoromethoxy)phenyl]-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine **7b** (0.1102 g, 0.179 mmol), (4-fluorophenyl)boronic acid (0.33 g, 0.233 mmol), potassium carbonate (0.538 mL 1M, aq), acetonitrile (0.75 mL), and 1,1'-bis(diphenylphosphino)ferrocene-palladium (II) dichloride dichloromethane complex (0.015 g, 0.018 mmol) were combined and heated at 100 °C for 40 minutes. The reaction was diluted with EtOAc and filtered through a bed of sodium sulfate. The reaction was then concentrated at reduced pressure. The crude was absorbed onto silica and purified via flash chromatography with 0-30% MeOH in DCM. The fractions were concentrated down a lightly yellow colored solid. The product was then diluted with acetonitrile and subjected to reverse phase purification to afford the product **P-3011** as a white powder. (9 mg, 8.9%). MS ESI [M+H+] = 537.5. The data from the ¹H NMR spectrum was consistent with the structure of the compound.

Example 2: Preparation of 4-[4-[5-(4-fluorophenyl)-4H-1,2,4-triazol-3-yl]-1-piperidyl]-6-(2-methoxy-4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine (P-3205)

Scheme 2.



[0219] Step 1 – Synthesis of tert-butyl 4-[5-(4-fluorophenyl)-4H-1,2,4-triazol-3-yl]piperidine-1-carboxylate (11):

In a microwave vial, tert-butyl 4-(hydrazinecarbonyl) piperidine-1-carboxylate **9** (0.3 g, 3 mmol), 4-fluorobenzonitrile **10** (0.448 g, 4 mmol), 1-butanol (3.385 mL), and K_2CO_3 (0.085 g, 0.6 mmol) were combined and heated at 150 °C for 3 hours. The reaction mixture was allowed to cool, and diluted with water. The reaction mixture was extracted with ethyl acetate three times. The combined organic layers were washed with brine, dried over sodium sulfate and evaporated under reduced pressure. The crude residue was purified via flash chromatography on silica gel with 0-30% MeOH in dichloromethane (DCM) as an eluent. The product **11** (0.223 g, 49.6%) was isolated as a light yellow oil. MS ESI $[\text{M}+\text{H}^+]$ = 347.2.

[0220] Step 2 – Synthesis of 4-[5-(4-fluorophenyl)-4H-1,2,4-triazol-3-yl]piperidine-2,2,2-trifluoroacetic acid (12):

In a flask, tert-butyl 4-[5-(4-fluorophenyl)-4H-1,2,4-triazol-3-yl]piperidine-1-carboxylate **11** (0.524, 2 mmol) was dissolved in DCM (5.82 mL) at 0 °C. Trifluoroacetic acid (1.17 mL) was added and the reaction was stirred at room temperature (~ 22 °C) for about 2 hours. The reaction was concentrated down under reduced pressure. More DCM solvent was added to the flask, and the solvent was removed again under reduced pressure. The addition of solvent and evaporation process was repeated to ensure removal of TFA. The residue **12** (0.377g, 96%) was dried under vacuum overnight and used in the next step without further purification.

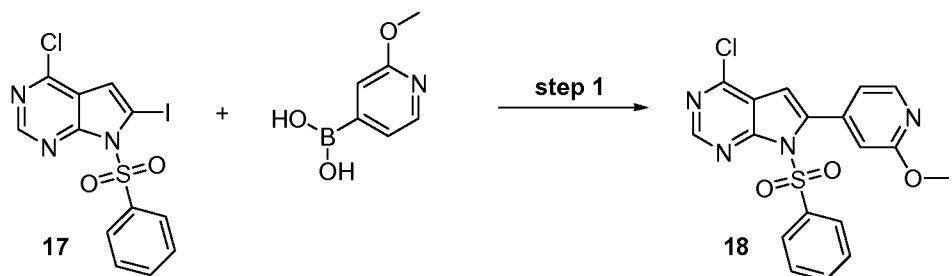
[0221] Step 3 – Synthesis of 7-(benzenesulfonyl)-4-[4-[5-(4-fluorophenyl)-4H-1,2,4-triazol-3-yl]-1-piperidyl]-6-iodo-pyrrolo[2,3-d]pyrimidine (13) and 4-[4-[5-(4-fluorophenyl)-4H-1,2,4-triazol-3-yl]-1-piperidyl]-6-iodo-7H-pyrrolo[2,3-d]pyrimidine (14): In a microwave vessel, 7-(benzenesulfonyl)-4-chloro-6-iodo-pyrrolo[2,3-d]pyrimidine **6** (0.5 g, 1 mmol), 4-[5-(4-fluorophenyl)-4H-1,2,4-triazol-3-yl]piperidine-2,2,2-trifluoroacetic acid **12** (0.644 g, 1.5 mmol), potassium carbonate (0.823 g, 6 mmol), and acetonitrile (3.734 mL) were combined and heated at 100 °C for 40 minutes. The reaction was diluted with EtOAc and filtered through a layer of sodium sulfate. The crude product was concentrated and purified via flash chromatography on silica with 0-30% MeOH in DCM to afford both compound **13** (0.35 g, 46.7%) and compound **14** (0.08 g, 13.7%).

[0222] Step 4 – Synthesis of 7-(benzenesulfonyl)-4-[4-[5-(4-fluorophenyl)-4H-1,2,4-triazol-3-yl]-1-piperidyl]-6-(2-methoxy-4-pyridyl)pyrrolo[2,3-d]pyrimidine (15): In a microwave reaction vessel, 7-(benzenesulfonyl)-4-[4-[5-(4-fluorophenyl)-4H-1,2,4-triazol-3-yl]-1-piperidyl]-6-iodo-pyrrolo[2,3-d]pyrimidine **13** (0.167 g, 0.265 mmol), (2-methoxy-4-pyridyl)boronic acid (0.061 g, 0.4 mmol), potassium carbonate (1.06 mL, 1M, aq), acetonitrile (1.1 mL), and 1,1'-bis(diphenylphosphino)ferrocene-palladium (II) dichloride dichloromethane complex (0.022 g, 0.027 mmol) were combined and heated at 100 °C for 40 minutes. The reaction was diluted with EtOAc and filtered through a bed of sodium sulfate. The reaction mixture was then concentrated at reduced pressure. The crude was purified via flash chromatography on silica with 0-30% MeOH in DCM as an eluent. The fractions were combined and concentrated down to a tan oil residue (**15**), which was used in the next step without further purification.

[0223] Step 5 – Synthesis of 4-[4-[5-(4-fluorophenyl)-4H-1,2,4-triazol-3-yl]-1-piperidyl]-6-(2-methoxy-4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine (16): Compound **15** was mixed with MeOH (2.7 mL) and subjected to potassium hydroxide (2.16 mL, 1M, aq) at 55 °C. The reaction mixture was stirred for about 3 hours. After confirmation that the starting material was reacted, the reaction mixture was concentrated and acidified to pH 4-5 with an aqueous HCl (10%) solution. The crude was purified via flash chromatography on silica with 0-30% MeOH in DCM as an eluent. The collected fractions were diluted with acetonitrile and subjected to reverse phase purification to afford the desired product **P-3205** (30 mg, 15.2%), as a light yellow powder after freeze-drying. MS ESI $[M+H+] = 471.0$. The data from the 1H NMR spectrum was consistent with the structure of the compound.

Example 3. Preparation of 6-(2-methoxy-4-pyridyl)-4-[5-(p-tolyl)-4-(trifluoromethyl)-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine (P-3134)

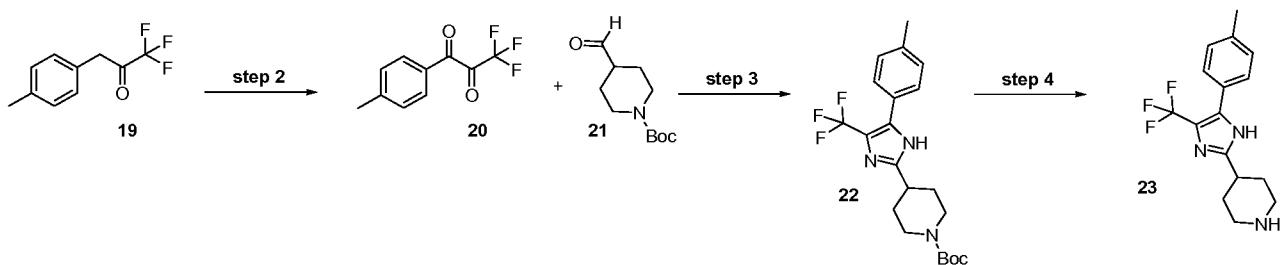
Scheme 3.



[0224] Step 1: Synthesis of 7-(benzenesulfonyl)-4-chloro-6-(2-methoxy-4-pyridyl)pyrrolo[2,3-d]pyrimidine (18):

To a solution of **17** (1 g, 2.38 mmol) and **2** (0.53 g, 3.57 mmol) in acetonitrile (12.45 mL, 238.31 mmol) and 1M potassium carbonate (7.15 mL) in water was added [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (II) (0.09 g, 0.12 mmol) and the mixture was stirred at 100 °C for 40 minutes in an oil bath. Upon completion the mixture was poured over brine and extracted with ethyl acetate (3 X 150 mL). The organic layers were combined, dried over sodium sulfate, filtered, and then evaporated to dryness. The resulting crude solid was mounted on silica gel and purified, eluting with 20-80% ethyl acetate in hexanes to give 0.712 g of compound (**18**) in ~95% purity.

Scheme 4



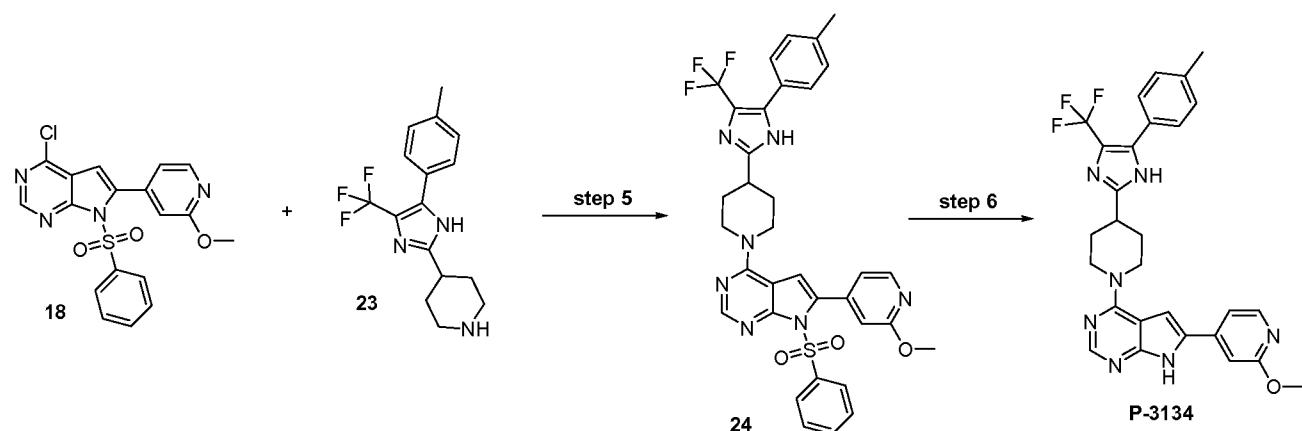
[0225] Step 2: Synthesis of 3,3,3-trifluoro-1-(p-tolyl)propane-1,2-dione (20): To a solution of **19** in 1,4-dioxane (6.84 mL, 80.21 mmol) was added selenium dioxide (0.06 mL, 2.29 mmol) and the mixture was stirred at 80 °C for 12 hours. Upon completion the solution was filtered through celite then concentrated under reduced pressure to give 0.295 g of **20**, as a viscous amber oil in ~91% purity. The material was carried on to the next step.

[0226] Step 3: Synthesis of tert-butyl 4-[5-(p-tolyl)-4-(trifluoromethyl)-1H-imidazol-2-yl]piperidine-1-carboxylate (22): To a solution of **20** (0.2 g, 0.96 mmol) and **21** (0.23 mL, 0.8 mmol) in 2-propanol (6.1 mL, 79.69 mmol) was added ammonium acetate (0.26 mL, 3.98 mmol) and the mixture was stirred at 65 °C for 12

hours. Upon completion, the solution was diluted in water and extracted with ethyl acetate (2 X 150 mL). The organic layers were combined, washed with brine, dried over sodium sulfate, filtered, and then evaporated to dryness. The resulting crude solid was mounted on silica gel and purified, eluting with 20-80% ethyl acetate in hexanes to give 0.234 g of **22**, as a viscous amber oil in >95% purity. This material was carried on to the next step without further purification.

[0227] Step 4: Synthesis of 4-[5-(p-tolyl)-4-(trifluoromethyl)-1H-imidazol-2-yl]piperidine (23): To a solution of compound (**22**) (96%, 0.23 g, 0.53 mmol) in dichloromethane (2.21 mL, 34.47 mmol) was added trifluoroacetic acid (0.74 mL, 9.56 mmol) and the solution was stirred at room temperature for 2 hours. Upon completion, the mixture was evaporated to dryness then washed with di-ethyl ether to give 0.182 g of (**23**) in about 90% purity.

Scheme 5.



[0228] Step 5: Synthesis of 7-(benzenesulfonyl)-6-(2-methoxy-4-pyridyl)-4-[4-[5-(p-tolyl)-4-(trifluoromethyl)-1H-imidazol-2-yl]-1-piperidyl]pyrrolo[2,3-d]pyrimidine (24): To a solution of **18** (0.1 g, 0.32 mmol) and **23** (0.15 g, 0.48 mmol) in acetonitrile (4.0 mL, 64.64 mmol) was added CsCO_3 (300 mg, 0.96 mmol). This mixture was heated to 100 °C for 40 minutes in a microwave reactor. Upon completion, the solution was diluted in brine and extracted with ethyl acetate (2 X 150 mL). The organic layers were combined, dried over Na_2SO_4 , filtered, and evaporated to dryness. The resulting brown solid was mounted on to silica gel and purified using 0-10% MeOH in DCM over 30 minutes (Agilent FPS, 24g column), resulting in 0.084 grams of **24** in ~93% purity. This material was used in the next step without further purification.

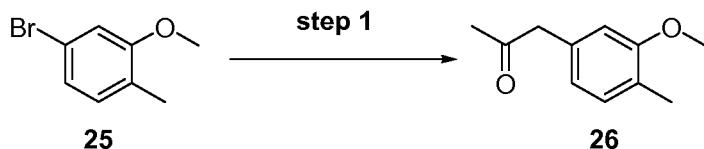
[0229] Step 6: Synthesis of 6-(2-methoxy-4-pyridyl)-4-[4-[5-(p-tolyl)-4-(trifluoromethyl)-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine (P-3134): To a solution of compound **24** (0.084 g, 0.21 mmol) in methanol (10 mL) was added 1M KOH in water (2 mL) and the solution was allowed to stir at room temperature for 2 hours. Upon completion, the solution was poured over brine and extracted with ethyl

acetate (2 X 150 mL). The organic layers were combined, washed with brine, dried over sodium sulfate, filtered, and evaporated to dryness. The resulting crude material was dissolved in acetonitrile (5 mL), and purified by reverse phase prep-HPLC to give 0.021 g of (**P-3134**). MS ESI [M-H]⁺ = 532.3. The data from the ¹H NMR spectrum was consistent with the structure of the compound.

[0230] Examples 4-6 and Schemes 6-8 outline the synthesis of some of the precursor compounds used in the preparation of the compounds of the present disclosure.

Example 4. Synthesis of 1-(3-methoxy-4-methyl-phenyl)-propan-2-one (25)

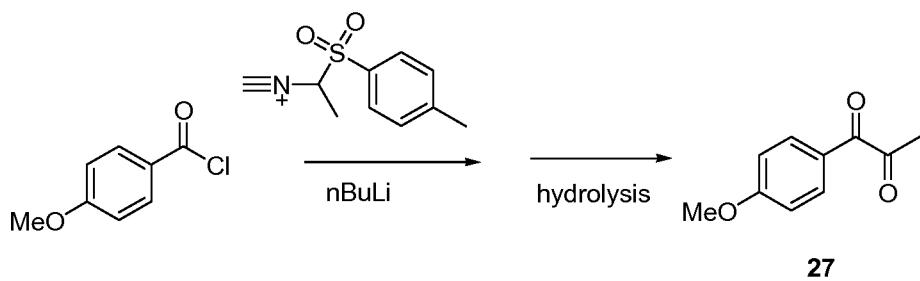
Scheme 6.



[0231] The mixture of 4-bromo-2-methoxy-1-methyl-benzene (2010.6 mg, 10 mmol) (**25**), acetone (11.03 ml, 150 mmol), palladium(ii) acetate (0.04 mL, 0.5 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (578.62 mg, 1 mmol) and cesium carbonate (1.6 ml, 20 mmol) in 1,4-dioxane (40 ml) was purged with nitrogen gas and heated at 100 °C for five hours. The mixture was filtered through a short bed of Celite and concentrated down. The residue was purified by flash chromatography eluting with 10% ethyl acetate in hexane to afford 1,480 mg (83%) of 1-(3-methoxy-4-methyl-phenyl)propan-2-one (**26**) as a yellow oil. The data from the ¹H NMR spectrum was consistent with the structure of the compound.

Example 5. Synthesis of 1-(4-methoxyphenyl)propane-1,2-dione (27)

Scheme 7.

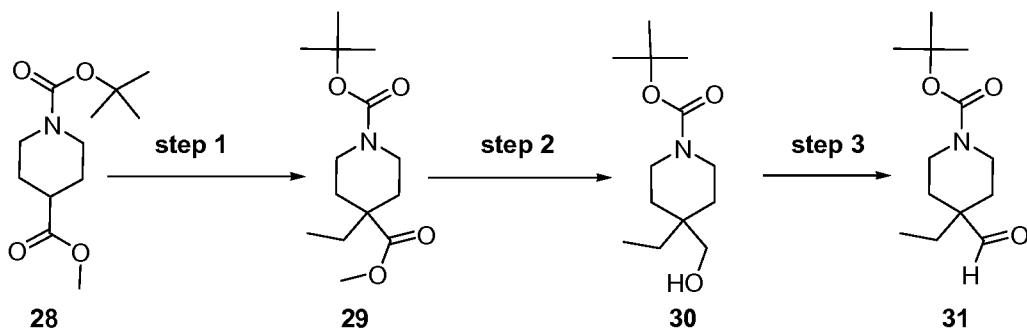


[0232] In a dry vial, 1-methyl-tosylmethyl isocyanide (0.136 g, 0.645 mmol) was mixed with tetrahydrofuran (THF) (3.8 mL) at -75 °C. n-butyllithium (0.44 mL, 1.2 M in hexanes) was added in one portion and stirred for 5 min before 4-methoxybenzoyl chloride (0.1 g, 0.586 mmol) was added in one portion to the reaction.

The reaction stirred overnight at ambient conditions. The reaction was diluted with 1N HCl and water. The reaction was then extracted with EtOAc 3x. The combined organic layers were then washed with brine, dried over sodium sulfate and concentrated. Purification with EtOAc in hexane afforded the product (**27**) as a yellow oil. (0.189 g, 36.2%). The data from the ¹H NMR spectrum was consistent with the structure of the compound.

Example 6. Preparation of 1-boc-4-Ethyl-4-formyl-piperidine (30)

Scheme 8.



[0233] Step 1: Synthesis of ethyl 1-boc-4-methyl-4-piperidine carboxylate (29): To the mixture of N-boc-piperidine-4-carboxylic acid methyl ester (4865.99 mg, 20 mmol) (**28**) in tetrahydrofuran (40 mL) at -78 °C under nitrogen gas was added slowly the solution of 2M lithium diisopropylamide in THF (20 mL). After stirring at -78 °C for one hour, iodoethane (3.2 ml, 40 mmol) was added then stirred for additional one hour. The mixture was brought to room temperature over 30 minutes and quenched with saturated ammonium chloride. The mixture was extracted with ethyl acetate which was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated down. The residue was purified by flash chromatography eluting with 10% ethyl acetate in hexane to provide 4,500 mg (82.9%) of ethyl 1-boc-4-methyl-4-piperidine carboxylate (**29**) as colorless oil.

[0234] Step 2: Synthesis of 1-boc-4-ethyl-4-(hydroxymethyl)-piperidine (30): To an ice cold solution of ethyl 1-boc-4-methyl-4-piperidine carboxylate (4500 mg, 16.58 mmol) (**29**) in anhydrous tetrahydrofuran (80 mL) under nitrogen gas was added slowly 1M lithium aluminum hydride (19.9 mL), then stirred at 0 °C for two hours. The reaction was quenched sequentially with 0.597 mL water, 1.33 mL 10%NaOH & 0.896 mL water. The mixture was dried over anhydrous magnesium sulfate, filtered & concentrated down to provide 3,500 mg (86.7%) of 1-boc-4-ethyl-4-(hydroxymethyl)-piperidine (**30**) as a colorless oil, which was used for next step without purification.

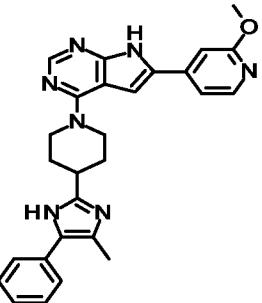
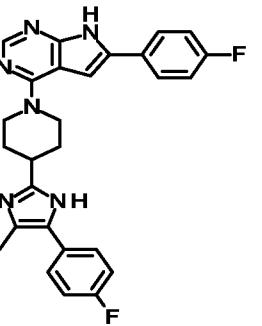
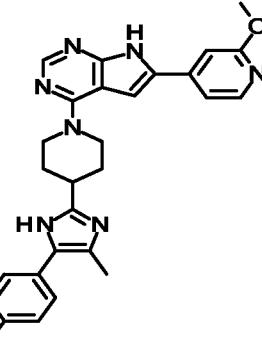
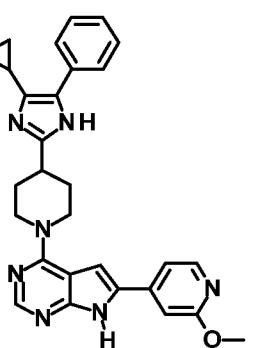
[0235] Step 3: Synthesis of 1-boc-4-ethyl-4-formyl-piperidine (31): To the solution of oxalyl chloride (1.34 mL, 15.82 mmol) in dichloromethane (40 mL) chilled to -78 °C was added slowly the solution of

dimethyl sulfoxide (2.25 ml, 31.64 mmol) in dichloromethane (7 mL) under nitrogen gas. After stirring for 5 minutes, the mixture of 1-boc-4-ethyl-4-(hydroxymethyl)-piperidine (3500 mg, 14.38 mmol) (**30**) in dichloromethane (15 mL) was added drop wise in to the reaction mixture which was then stirred at -78 °C for 20 minutes. Triethylamine (4.21 mL, 30.2 mmol) was added to the reaction mixture. The resulting mixture was stirred for additional 5 minutes then gradually brought to room temperature for over 1 hour period. The mixture was quenched slowly with water and extracted with dichloromethane which was washed with brine, dried over MgSO₄; filtered and concentrated down. The resulting residue was purified by flash chromatography eluting with 10-20% ethyl acetate in hexane to provide 2,700 mg (62.2%) of 1-boc-4-ethyl-4-formyl-piperidine (**31**) as colorless oil. The data from the ¹H NMR spectrum was consistent with the structure of the compound.

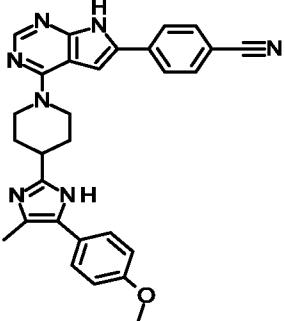
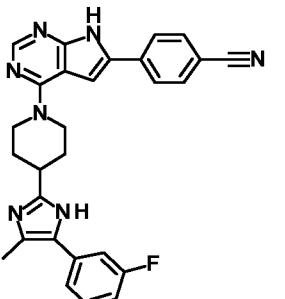
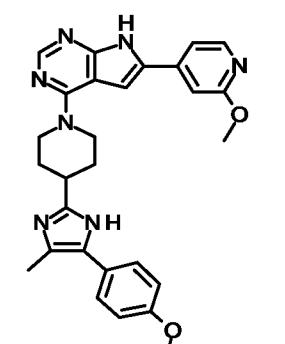
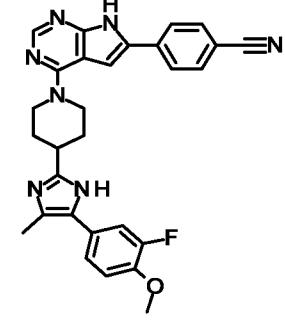
[0236] Compounds listed in Tables 1 and 2 below, e.g., compounds P-3001 to P-3003, P-3006 to P-3011, P-3014 to P-3119, P-3122 to P-3124, P-3132 to P-3207 and P-3209 to P-3256 in Table 1 and P-3004 to P-3005, P-3130, P-3131 and P-3125 to P-3131 in Table 2, were prepared according to the synthetic protocols set forth in Examples 1 to 6 and Schemes 1 to 8. The ¹H NMR and mass spectroscopy data were consistent with the structures of the compounds.

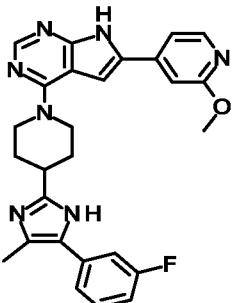
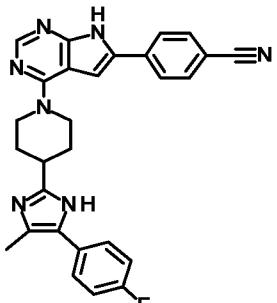
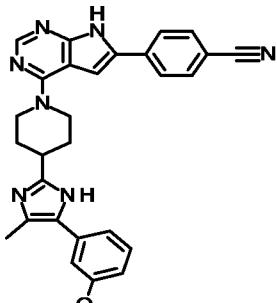
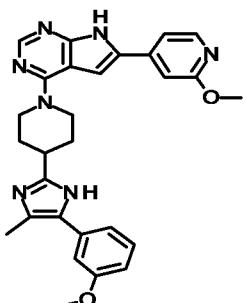
Table 1

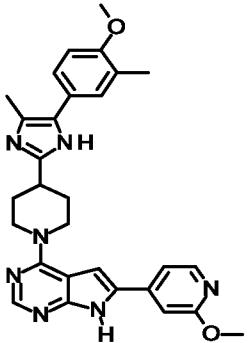
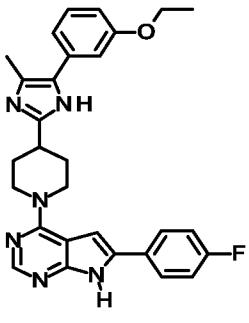
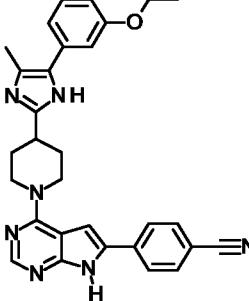
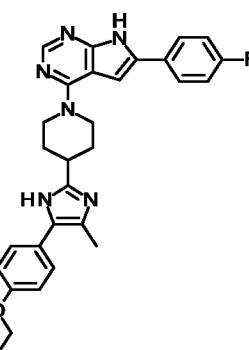
No.	Compound	Name	MS(ESI) [M+H ⁺] ⁺ or [M-H ⁻] ⁻ observed
P-3001		4-[4-(5-methyl-4-phenyl-1H-imidazol-2-yl)-1-piperidyl]-6-(4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine	435.4
P-3002		6-(4-fluorophenyl)-4-[4-(4-methyl-5-phenyl-1H-imidazol-2-yl)-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	452.95

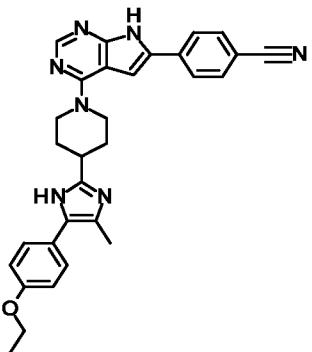
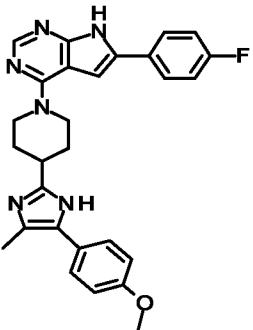
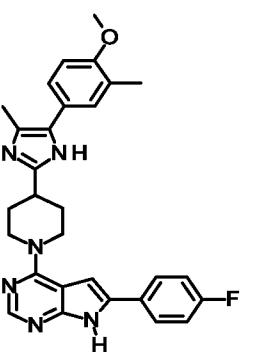
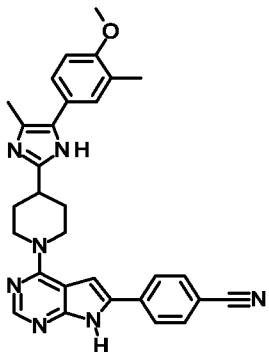
P-3003	 <p>6-(2-methoxy-4-pyridyl)-4-[4-(4-methyl-5-phenyl-1H-imidazol-2-yl)-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine</p>	466.0
P-3006	 <p>6-(4-fluorophenyl)-4-[4-[5-(4-fluorophenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine</p>	471.5
P-3007	 <p>4-[4-[5-(4-fluorophenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-(2-methoxy-4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine</p>	484.1
P-3008	 <p>4-[4-(4-cyclopropyl-5-phenyl-1H-imidazol-2-yl)-1-piperidyl]-6-(2-methoxy-4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine</p>	492.8

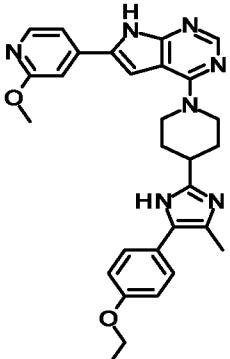
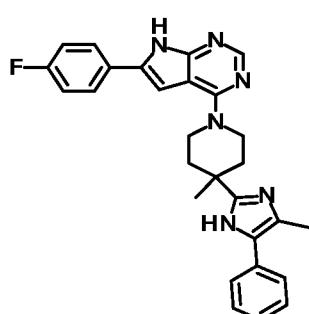
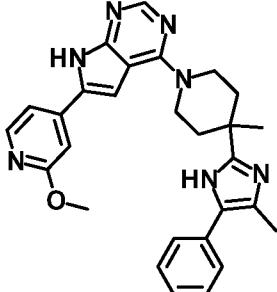
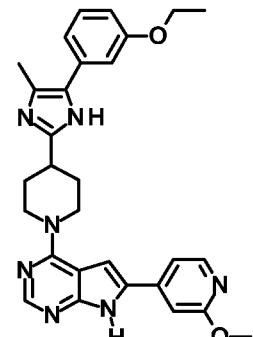
P-3009		4-[4-(4-cyclopropyl-5-phenyl-1H-imidazol-2-yl)-1-piperidyl]-6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidine	479.1
P-3010		4-[4-[4-(4-cyclopropyl-5-phenyl-1H-imidazol-2-yl)-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	486.7
P-3011		6-(4-fluorophenyl)-4-[4-[4-methyl-5-[3-(trifluoromethoxy)phenyl]-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	537.5
P-3014		6-(2-methoxy-4-pyridyl)-4-[4-[4-methyl-5-[3-(trifluoromethoxy)phenyl]-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	548.4

P-3015		4-[4-[4-[5-(4-methoxyphenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	490.6
P-3016		4-[4-[4-[5-(3-fluorophenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	478.1
P-3017		4-[4-[5-(4-methoxyphenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-(2-methoxy-4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine	496.1
P-3018		4-[4-[4-[5-(3-fluoro-4-methoxy-phenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	508.7

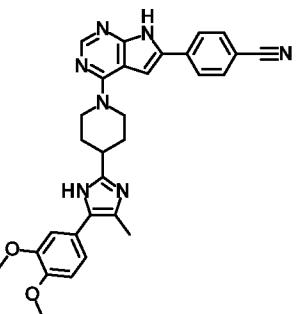
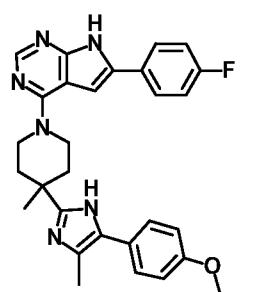
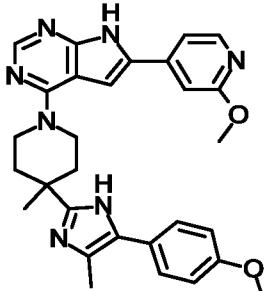
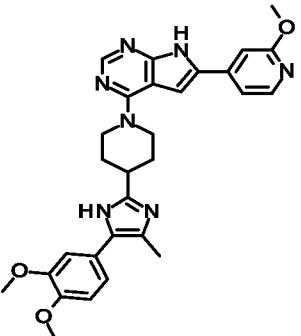
P-3019		4-[4-[5-(3-fluorophenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-(2-methoxy-4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine	484.5
P-3020		4-[4-[4-(4-fluorophenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	478.3
P-3021		4-[4-[4-[5-(3-methoxyphenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	490.7
P-3022		4-[4-[5-(3-methoxyphenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-(2-methoxy-4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine	496.6

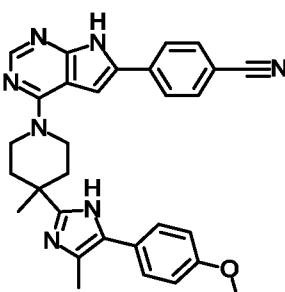
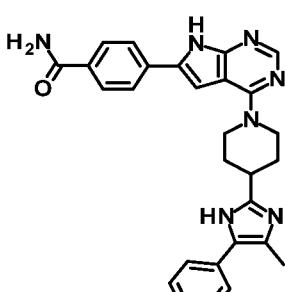
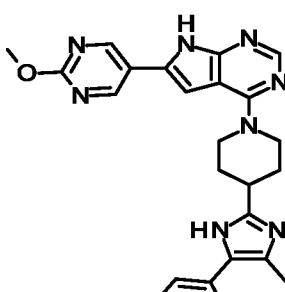
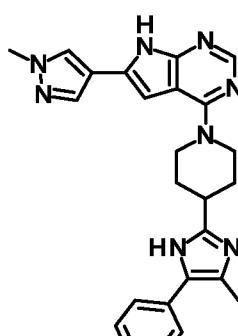
P-3023		4-[4-[5-(4-methoxy-3-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-(2-methoxy-4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine	508.3
P-3024		4-[4-[5-(3-ethoxyphenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidine	495.2*
P-3025		4-[4-[4-[5-(3-ethoxyphenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	502.3*
P-3026		4-[4-[5-(4-ethoxyphenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidine	497.4

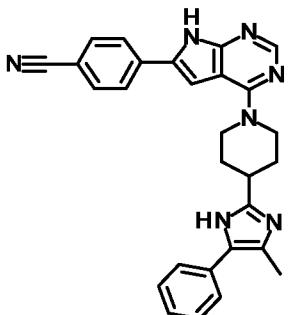
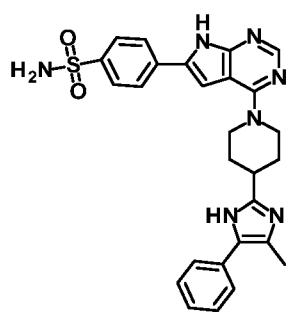
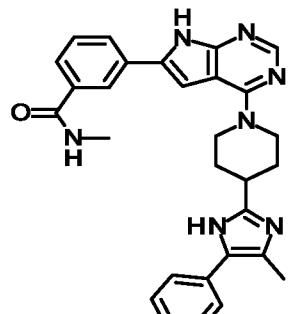
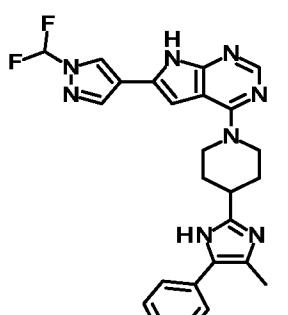
P-3027		4-[4-[4-[5-(4-ethoxyphenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	504.3
P-3028		6-(4-fluorophenyl)-4-[4-[5-(4-methoxyphenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	483.4
P-3029		6-(4-fluorophenyl)-4-[4-[5-(4-methoxy-3-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	495.3*
P-3030		4-[4-[4-[5-(4-methoxy-3-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	502.3*

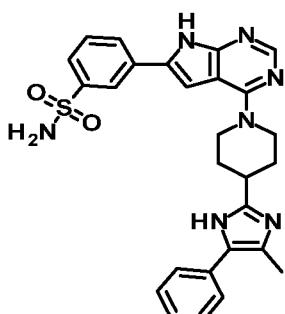
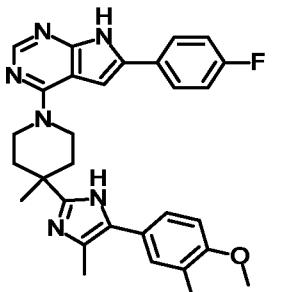
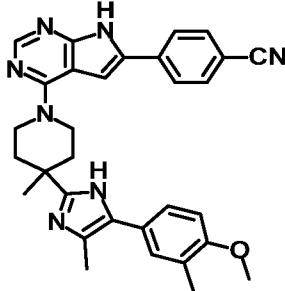
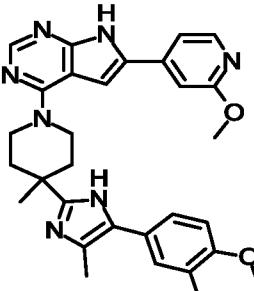
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P-3032		6-(4-fluorophenyl)-4-[4-methyl-4-(4-methyl-5-phenyl-1H-imidazol-2-yl)-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	467.3
P-3033		6-(2-methoxy-4-pyridyl)-4-[4-methyl-4-(4-methyl-5-phenyl-1H-imidazol-2-yl)-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	480.4
P-3034		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*

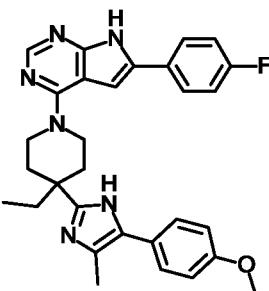
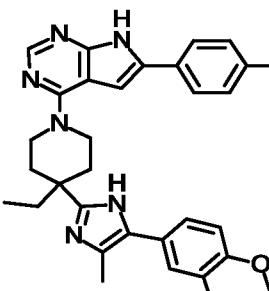
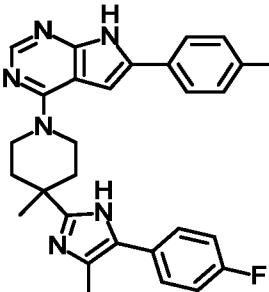
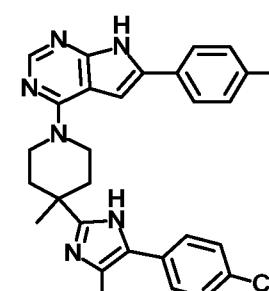
P-3035		4-[4-[5-(4-chlorophenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidine	487.3
P-3036		4-[4-[5-(3,4-dimethoxyphenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidine	513.4
P-3037		4-[4-[5-(4-chlorophenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-(2-methoxy-4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine	500.3
P-3038		4-[4-[5-(4-chlorophenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	494.3

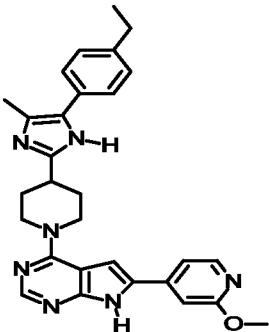
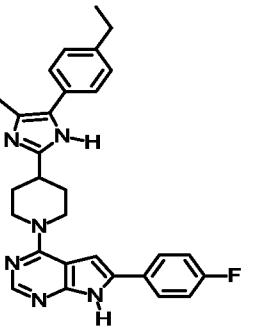
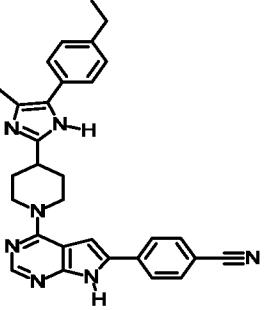
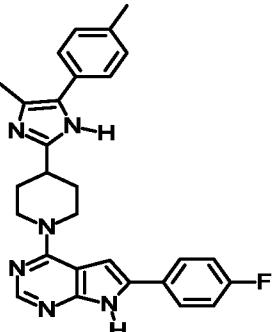
P-3039		4-[4-[5-(3,4-dimethoxyphenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-ylbenzonitrile	530.4
P-3040		6-(4-fluorophenyl)-4-[4-[5-(4-methoxyphenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	497.4
P-3041		4-[4-[5-(4-methoxyphenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-6-(2-methoxy-4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine	510.4
P-3042		4-[4-[5-(3,4-dimethoxyphenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-(2-methoxy-4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine	526.4

P-3043		4-[4-[5-(4-methoxyphenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	504.4
P-3044		4-[4-[4-(4-methyl-5-phenyl-1H-imidazol-2-yl)-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzamide	478.3
P-3045		6-(2-methoxypyrimidin-5-yl)-4-[4-(4-methyl-5-phenyl-1H-imidazol-2-yl)-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	467.2
P-3046		4-[4-(4-methyl-5-phenyl-1H-imidazol-2-yl)-1-piperidyl]-6-(1-methylpyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidine	439.6

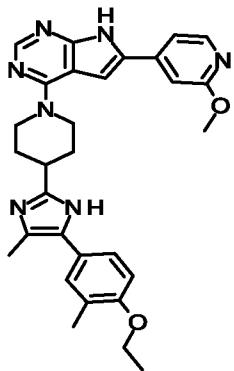
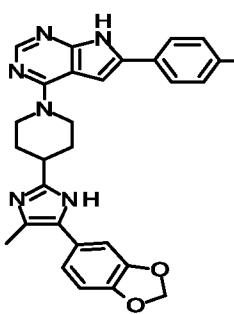
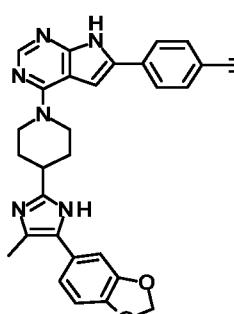
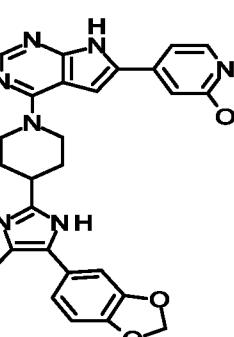
P-3047		4-[4-[4-(4-methyl-5-phenyl-1H-imidazol-2-yl)-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	460.3
P-3048		4-[4-[4-(4-methyl-5-phenyl-1H-imidazol-2-yl)-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzenesulfonamide	514.3
P-3049		N-methyl-3-[4-[4-(4-methyl-5-phenyl-1H-imidazol-2-yl)-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzamide	492.4
P-3050		6-[1-(difluoromethyl)pyrazol-4-yl]-4-[4-(4-methyl-5-phenyl-1H-imidazol-2-yl)-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	475

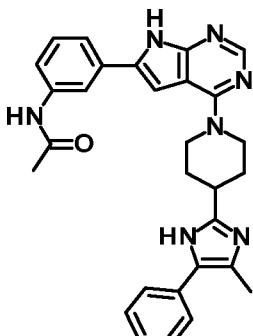
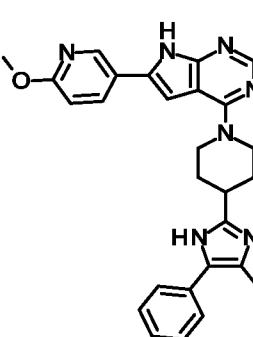
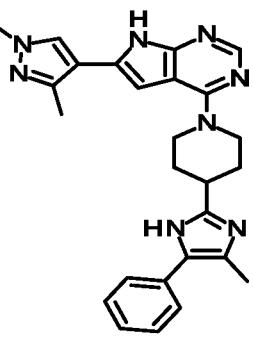
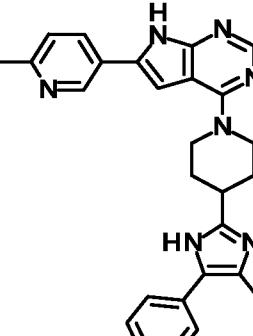
P-3051		3-[4-[4-(4-methyl-5-phenyl-1H-imidazol-2-yl)-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzenesulfonamide	514.3
P-3052		6-(4-fluorophenyl)-4-[4-[5-(4-methoxy-3-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	511.3
P-3053		4-[4-[4-[5-(4-methoxy-3-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	518.4
P-3054		4-[4-[5-(4-methoxy-3-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-6-(2-methoxy-4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine	524.4

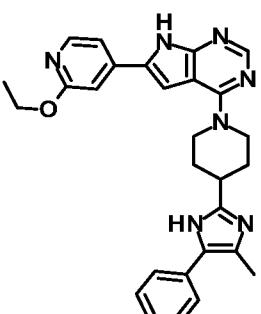
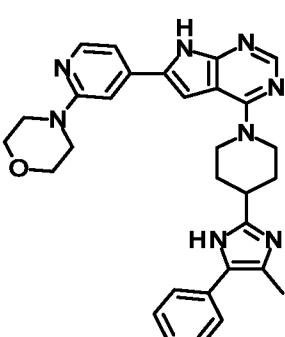
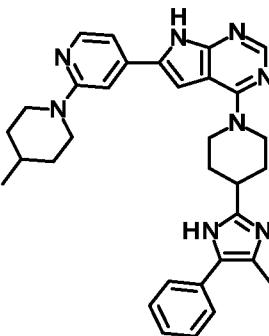
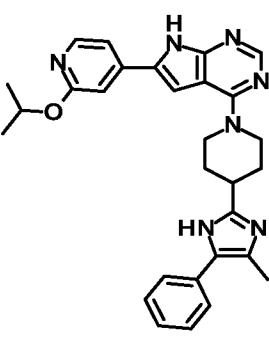
P-3055		4-[4-ethyl-4-[5-(4-methoxyphenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidine	511.4
P-3056		4-[4-ethyl-4-[5-(4-methoxy-3-methylphenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidine	525.4
P-3057		6-(4-fluorophenyl)-4-[4-[5-(4-fluorophenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	485.4
P-3058		4-[4-[5-(4-chlorophenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidine	501.4

P-3059		4-[4-[5-(4-ethylphenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-(2-methoxy-4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine	494.5
P-3060		4-[4-[5-(4-ethylphenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidine	479.3*
P-3061		4-[4-[4-[5-(4-ethylphenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	486.3*
P-3062		6-(4-fluorophenyl)-4-[4-[4-methyl-5-(p-tolyl)-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	465.3*

P-3063		4-[4-[5-(4-methoxyphenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-6-methyl-7H-pyrrolo[2,3-d]pyrimidine	417.3
P-3064		4-[4-[5-(4-fluorophenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-6-methyl-7H-pyrrolo[2,3-d]pyrimidine	405.3
P-3065		4-[4-[5-(4-ethoxy-3-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidine	511.4
P-3066		4-[4-[4-[5-(4-ethoxy-3-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	518.4

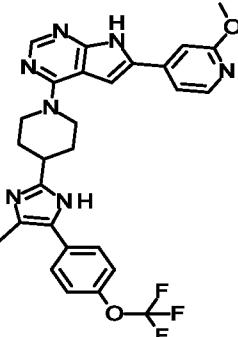
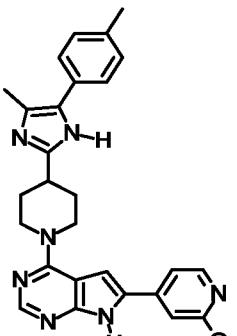
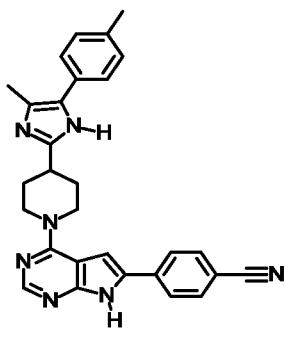
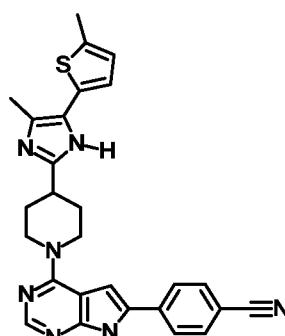
P-3067	 <p>4-[4-[5-(4-ethoxy-3-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-(2-methoxy-4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine</p>	524.5
P-3068	 <p>4-[4-[5-(1,3-benzodioxol-5-yl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidine</p>	497.3
P-3069	 <p>4-[4-[5-(1,3-benzodioxol-5-yl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile</p>	504.4
P-3070	 <p>4-[4-[5-(1,3-benzodioxol-5-yl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-(2-methoxy-4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine</p>	510.4

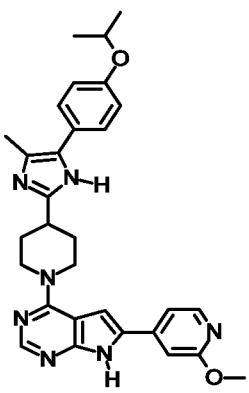
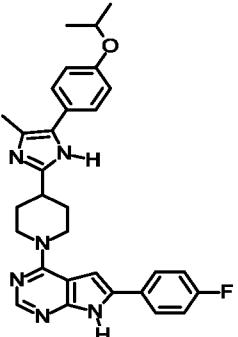
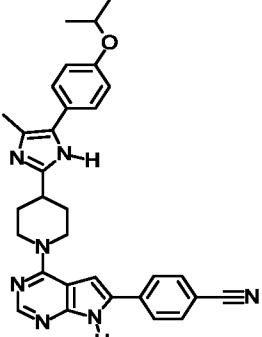
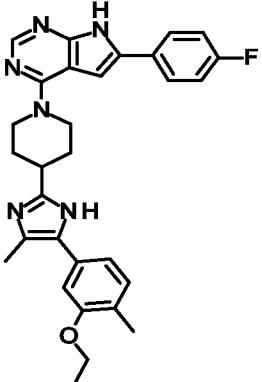
P-3071		N-[3-[4-[4-(4-methyl-5-phenyl-1H-imidazol-2-yl)-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]phenyl]acetamide	492.4
P-3072		6-(6-methoxy-3-pyridyl)-4-[4-(4-methyl-5-phenyl-1H-imidazol-2-yl)-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	466.3
P-3073		6-(1,3-dimethylpyrazol-4-yl)-4-[4-(4-methyl-5-phenyl-1H-imidazol-2-yl)-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	453.1
P-3074		4-[4-(4-methyl-5-phenyl-1H-imidazol-2-yl)-1-piperidyl]-6-(6-methyl-3-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine	450.1

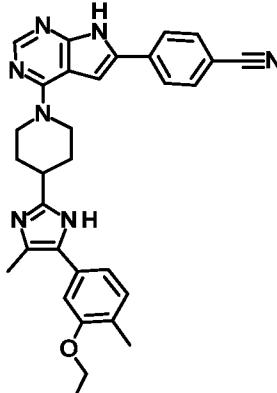
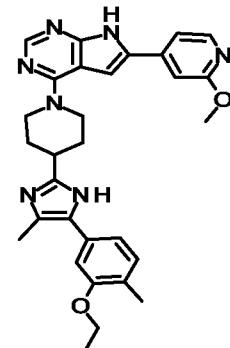
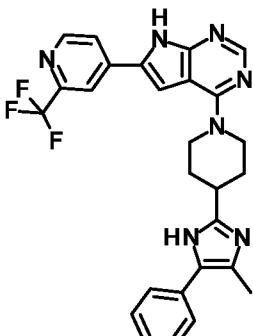
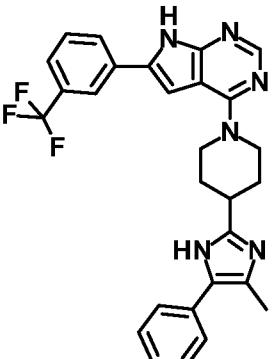
P-3075	 <p>6-(2-ethoxy-4-pyridyl)-4-[4-(4-methyl-5-phenyl-1H-imidazol-2-yl)-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine</p>	480.1
P-3076	 <p>4-[4-[4-(4-methyl-5-phenyl-1H-imidazol-2-yl)-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]-2-pyridylmorpholine</p>	531.2
P-3077	 <p>4-[4-(4-methyl-5-phenyl-1H-imidazol-2-yl)-1-piperidyl]-6-[2-(4-methyl-1-piperidyl)-4-pyridyl]-7H-pyrrolo[2,3-d]pyrimidine</p>	533.2
P-3078	 <p>6-(2-isopropoxy-4-pyridyl)-4-[4-(4-methyl-5-phenyl-1H-imidazol-2-yl)-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine</p>	494.5

P-3079		4-[4-(4-methyl-5-phenyl-1H-imidazol-2-yl)-1-piperidyl]-6-(2-pyrrolidin-1-yl-4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine	505.3
P-3080		4-[4-(4-methyl-5-phenyl-1H-imidazol-2-yl)-1-piperidyl]-6-[3-(trifluoromethoxy)phenyl]-7H-pyrrolo[2,3-d]pyrimidine	519.4
P-3081		6-(3-fluorophenyl)-4-[4-(4-methyl-5-phenyl-1H-imidazol-2-yl)-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	453.1
P-3082		6-(3-chlorophenyl)-4-[4-(4-methyl-5-phenyl-1H-imidazol-2-yl)-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	469.3

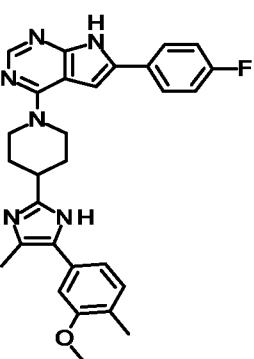
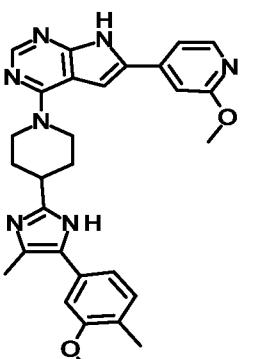
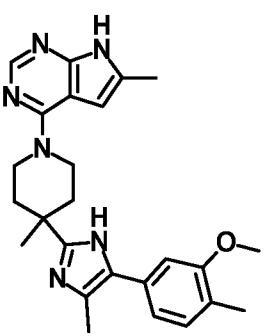
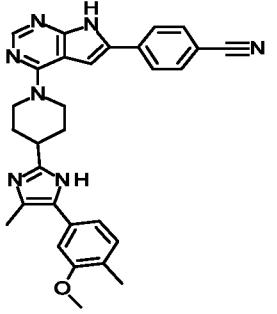
P-3083		N-[3-[4-(4-methyl-5-phenyl-1H-imidazol-2-yl)-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]phenyl]methanesulfonamide	528.1
P-3084		4-[4-[5-(2,3-dihydro-1,4-benzodioxin-6-yl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidine	511.4
P-3085		6-(4-fluorophenyl)-4-[4-[4-methyl-5-[4-(trifluoromethoxy)phenyl]-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	537.4
P-3086		4-[4-[4-methyl-5-[4-(trifluoromethoxy)phenyl]-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	544.3

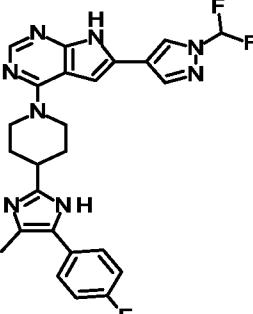
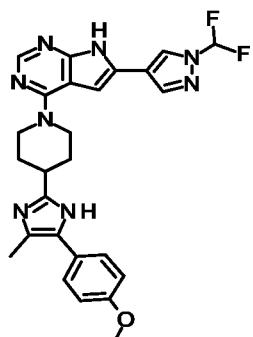
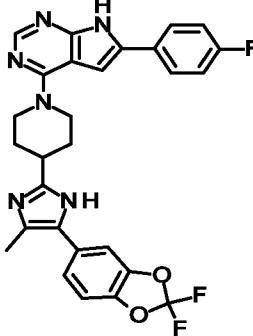
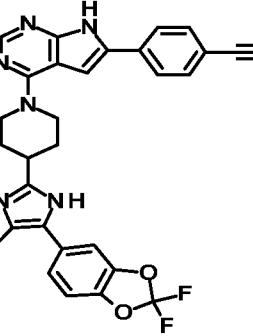
P-3087		6-(2-methoxy-4-pyridyl)-4-[4-[4-methyl-5-[4-(trifluoromethoxy)phenyl]-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	550.4
P-3088		6-(2-methoxy-4-pyridyl)-4-[4-[4-methyl-5-(p-tolyl)-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	478.3*
P-3089		4-[4-[4-[4-methyl-5-(p-tolyl)-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	472.3*
P-3090		4-[4-[4-[4-methyl-5-(5-methyl-2-thienyl)-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	478.2*

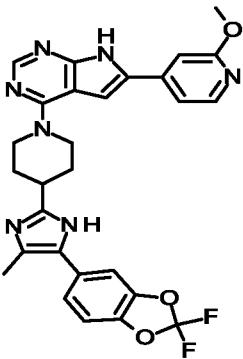
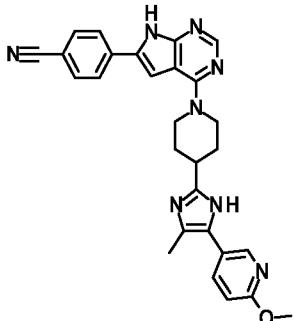
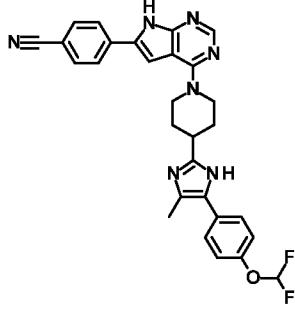
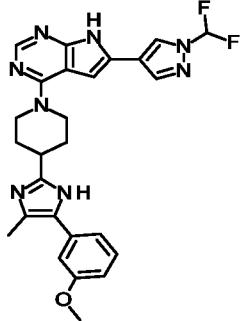
P-3091		4-[4-[5-(4-isopropoxyphenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-(2-methoxy-4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine	522.3*
P-3092		6-(4-fluorophenyl)-4-[4-[5-(4-isopropoxyphenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	509.3*
P-3093		4-[4-[5-(4-isopropoxyphenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	516.3*
P-3094		4-[4-[5-(3-ethoxy-4-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidine	511.4

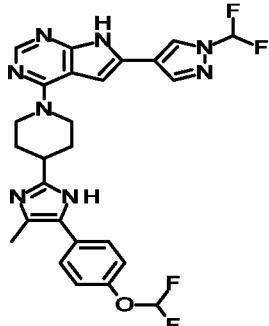
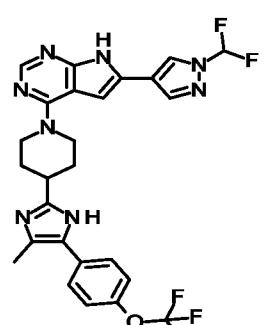
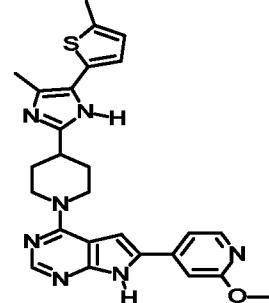
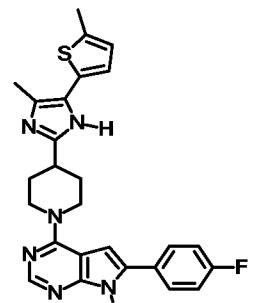
P-3095	 <p>4-[4-[4-[5-(3-ethoxy-4-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile</p>	518.4
P-3096	 <p>4-[4-[5-(3-ethoxy-4-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-(2-methoxy-4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine</p>	524.4
P-3097	 <p>4-[4-(4-methyl-5-phenyl-1H-imidazol-2-yl)-1-piperidyl]-6-[2-(trifluoromethyl)-4-pyridyl]-7H-pyrrolo[2,3-d]pyrimidine</p>	504.4
P-3098	 <p>4-[4-(4-methyl-5-phenyl-1H-imidazol-2-yl)-1-piperidyl]-6-[3-(trifluoromethyl)phenyl]-7H-pyrrolo[2,3-d]pyrimidine</p>	503.2

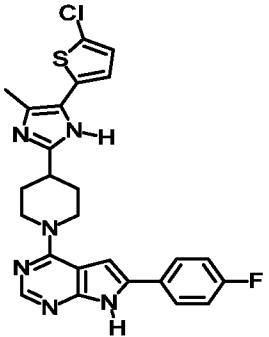
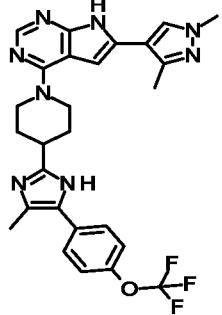
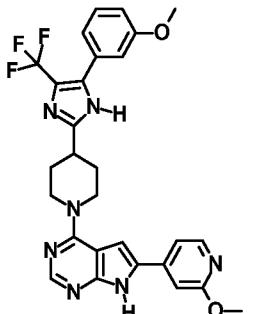
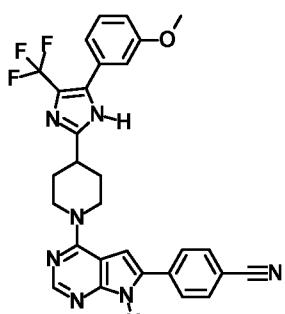
P-3099		4-[4-[5-(4-ethoxy-3-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-6-methyl-7H-pyrrolo[2,3-d]pyrimidine	445.3
P-3100		4-[4-[5-(3-ethoxy-4-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-6-methyl-7H-pyrrolo[2,3-d]pyrimidine	445.3
P-3101		4-[4-[5-(4-ethylphenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-6-methyl-7H-pyrrolo[2,3-d]pyrimidine	415.4
P-3102		4-[4-[5-(4-methoxy-3-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-6-methyl-7H-pyrrolo[2,3-d]pyrimidine	431.4

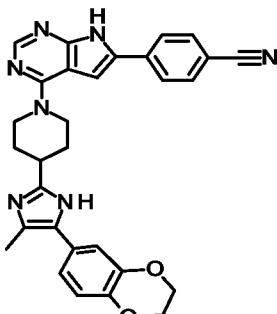
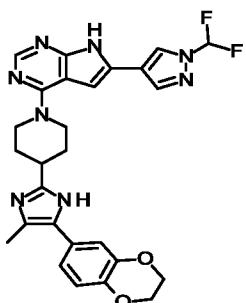
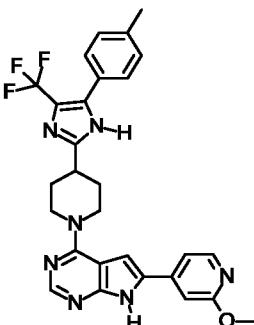
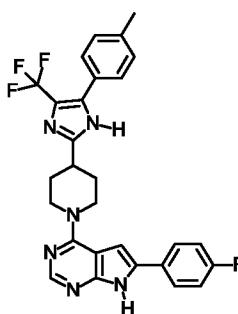
P-3103		6-(4-fluorophenyl)-4-[4-[5-(3-methoxy-4-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	497.2
P-3104		4-[4-[5-(3-methoxy-4-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-(2-methoxy-4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine	510.3
P-3105		4-[4-[5-(3-methoxy-4-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-methyl-7H-pyrrolo[2,3-d]pyrimidine	431.2
P-3106		4-[4-[4-[5-(3-methoxy-4-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	504.4

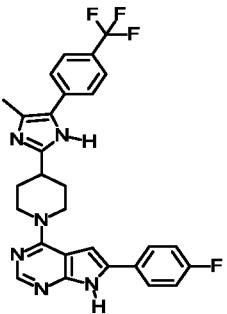
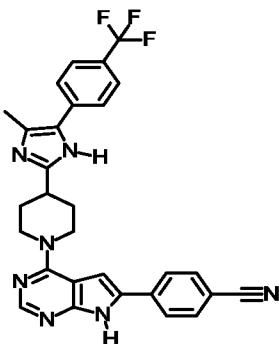
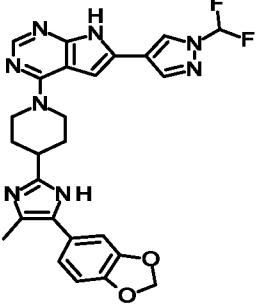
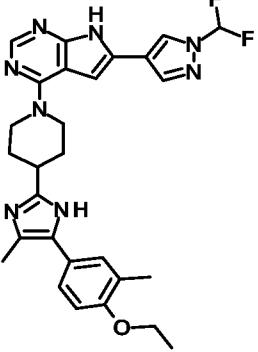
P-3107		6-[1-(difluoromethyl)pyrazol-4-yl]-4-[4-[5-(4-fluorophenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	493.3
P-3108		6-[1-(difluoromethyl)pyrazol-4-yl]-4-[4-[5-(4-methoxyphenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	505.4
P-3109		4-[4-[5-(2,2-difluoro-1,3-benzodioxol-5-yl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidine	533.4
P-3110		4-[4-[5-(2,2-difluoro-1,3-benzodioxol-5-yl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	540.3

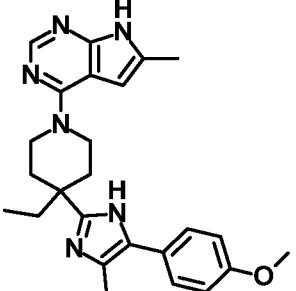
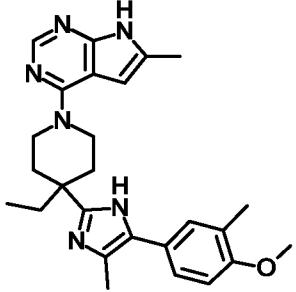
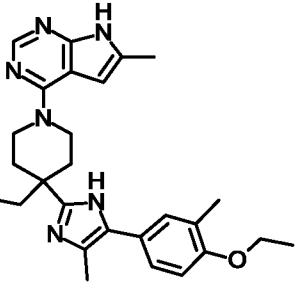
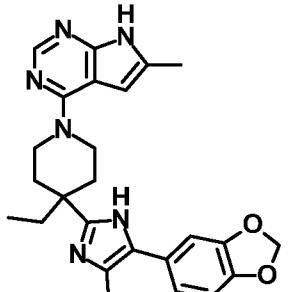
P-3111		4-[4-[5-(2,2-difluoro-1,3-benzodioxol-5-yl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-(2-methoxy-4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine	546.4
P-3112		4-[4-[4-[5-(6-methoxy-3-pyridyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	491.4
P-3113		4-[4-[4-[5-[4-(difluoromethoxy)phenyl]-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	526.0
P-3114		6-[1-(difluoromethyl)pyrazol-4-yl]-4-[4-[5-(3-methoxyphenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	505.4

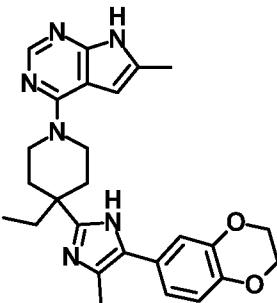
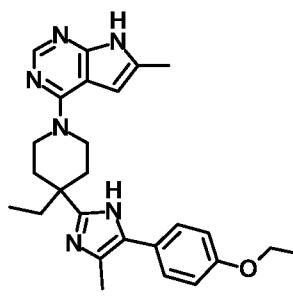
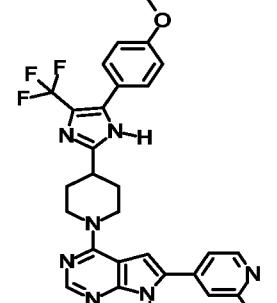
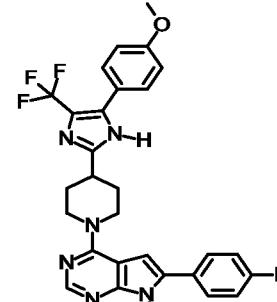
P-3115		4-[4-[5-[4-(difluoromethoxy)phenyl]-1H-imidazol-2-yl]-1-piperidyl]-6-[1-(difluoromethyl)pyrazol-4-yl]-7H-pyrrolo[2,3-d]pyrimidine	541.4
P-3116		6-[1-(difluoromethyl)pyrazol-4-yl]-4-[4-[4-methyl-5-[4-(trifluoromethoxy)phenyl]-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	559.4
P-3117		6-(2-methoxy-4-pyridyl)-4-[4-[4-methyl-5-(5-methyl-2-thienyl)-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	484.3*
P-3118		6-(4-fluorophenyl)-4-[4-[4-methyl-5-(5-methyl-2-thienyl)-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	471.3*

P-3119		4-[4-[5-(5-chloro-2-thienyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidine	491.2*
P-3122		6-(1,3-dimethylpyrazol-4-yl)-4-[4-[4-methyl-5-[4-(trifluoromethoxy)phenyl]-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	537.4
P-3123		4-[4-[5-(3-methoxyphenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl]-1-piperidyl]-6-(2-methoxy-4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine	548.3*
P-3124		4-[4-[5-(3-methoxyphenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	542.3*

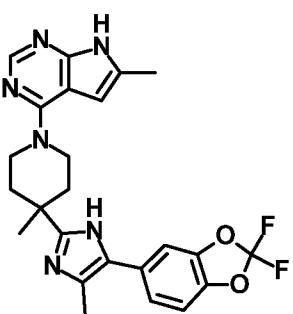
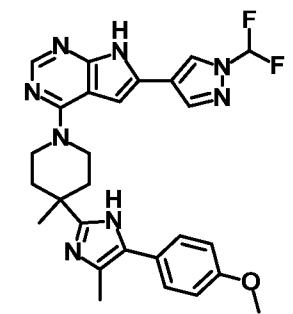
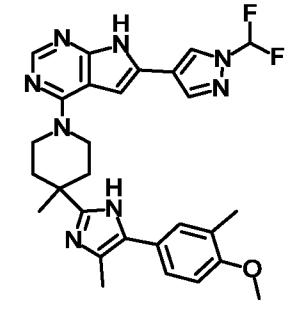
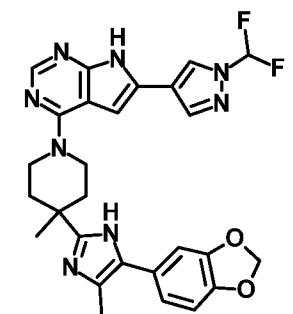
P-3132		4-[4-[4-[5-(2,3-dihydro-1,4-benzodioxin-6-yl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	518.35
P-3133		6-[1-(difluoromethyl)pyrazol-4-yl]-4-[4-[5-(2,3-dihydro-1,4-benzodioxin-6-yl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	533.35
P-3134		6-(2-methoxy-4-pyridyl)-4-[4-[5-(p-tolyl)-4-(trifluoromethyl)-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	532.3*
P-3135		6-(4-fluorophenyl)-4-[4-[5-(p-tolyl)-4-(trifluoromethyl)-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	519.3*

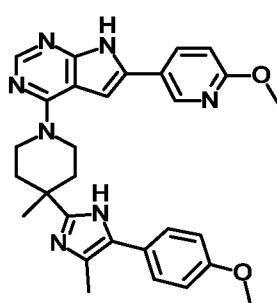
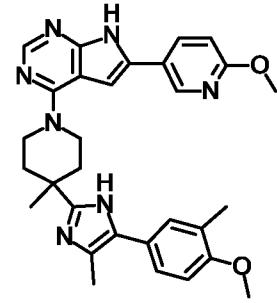
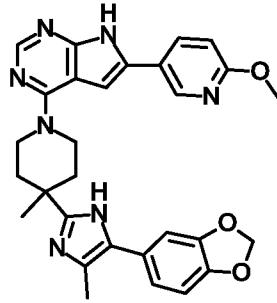
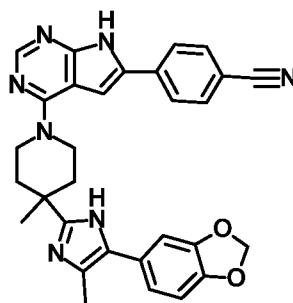
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P-3137		4-[4-[4-[4-methyl-5-[4-(trifluoromethyl)phenyl]-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	526.3*
P-3138		4-[4-[5-(1,3-benzodioxol-5-yl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-[1-(difluoromethyl)pyrazol-4-yl]-7H-pyrrolo[2,3-d]pyrimidine	519.3
P-3139		6-[1-(difluoromethyl)pyrazol-4-yl]-4-[4-[5-(4-ethoxy-3-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	533.4

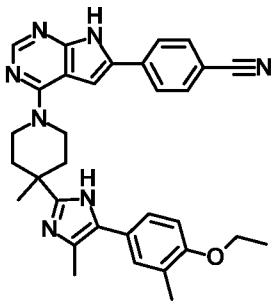
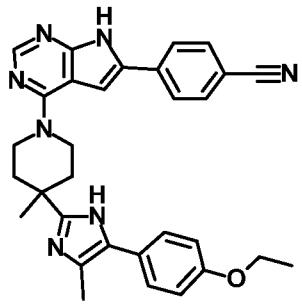
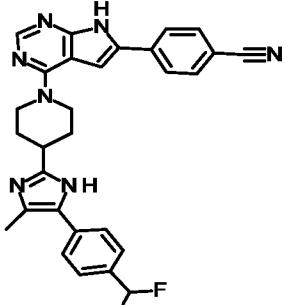
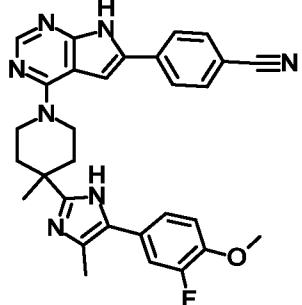
P-3140		4-[4-ethyl-4-[5-(4-methoxyphenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-methyl-7H-pyrrolo[2,3-d]pyrimidine	431.3
P-3141		4-[4-ethyl-4-[5-(4-methoxy-3-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-methyl-7H-pyrrolo[2,3-d]pyrimidine	445.4
P-3142		4-[4-[5-(4-ethoxy-3-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-4-ethyl-1-piperidyl]-6-methyl-7H-pyrrolo[2,3-d]pyrimidine	459.4
P-3143		4-[4-[5-(1,3-benzodioxol-5-yl)-4-methyl-1H-imidazol-2-yl]-4-ethyl-1-piperidyl]-6-methyl-7H-pyrrolo[2,3-d]pyrimidine	445.3

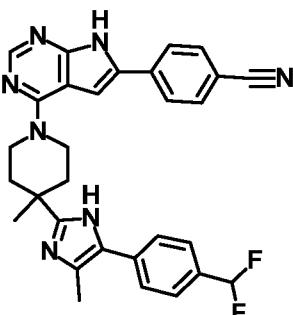
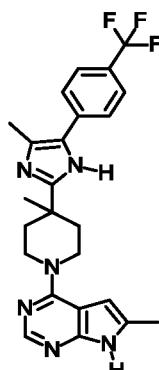
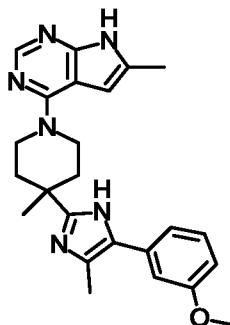
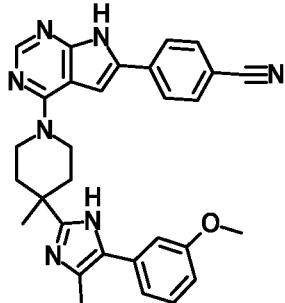
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P-3145		4-[4-[5-(4-ethoxyphenyl)-4-methyl-1H-imidazol-2-yl]-4-ethyl-1-piperidyl]-6-methyl-7H-pyrrolo[2,3-d]pyrimidine	445.4
P-3146		4-[4-[5-(4-methoxyphenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl]-1-piperidyl]-6-(2-methoxy-4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine	548.3*
P-3147		6-(4-fluorophenyl)-4-[4-[5-(4-methoxyphenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	535.3*

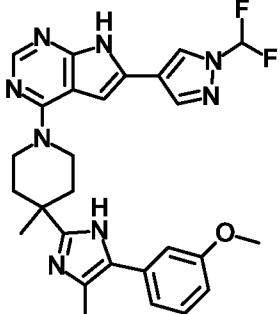
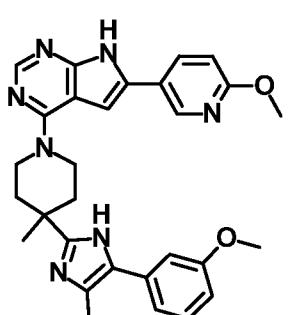
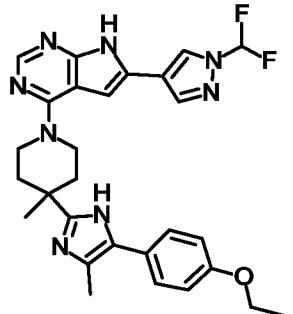
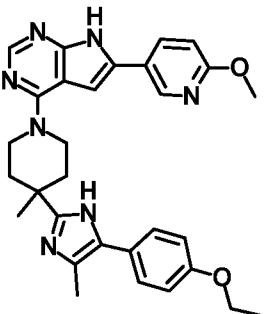
P-3148		4-[4-[4-[5-(4-methoxyphenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	542.3*
P-3149		6-(2-methoxy-4-pyridyl)-4-[4-[4-methyl-5-[4-(trifluoromethyl)phenyl]-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	532.3*
P-3150		4-[4-[5-(1,3-benzodioxol-5-yl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-6-methyl-7H-pyrrolo[2,3-d]pyrimidine	431.3
P-3151		4-[4-[5-(2,3-dihydro-1,4-benzodioxin-6-yl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-6-methyl-7H-pyrrolo[2,3-d]pyrimidine	445.3

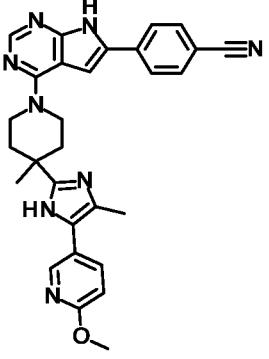
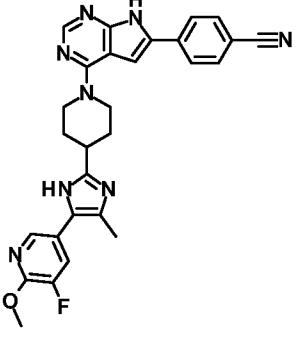
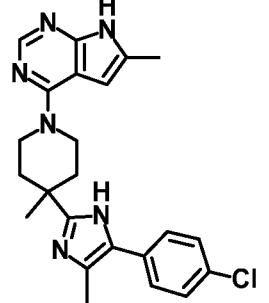
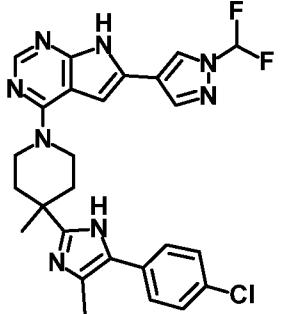
P-3152		4-[4-[5-(2,2-difluoro-1,3-benzodioxol-5-yl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-6-methyl-7H-pyrrolo[2,3-d]pyrimidine	467.3
P-3153		6-[1-(difluoromethyl)pyrazol-4-yl]-4-[4-[5-(4-methoxyphenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	519.4
P-3154		6-[1-(difluoromethyl)pyrazol-4-yl]-4-[4-[5-(4-methoxy-3-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	533.4
P-3155		4-[4-[5-(1,3-benzodioxol-5-yl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-6-[1-(difluoromethyl)pyrazol-4-yl]-7H-pyrrolo[2,3-d]pyrimidine	533.4

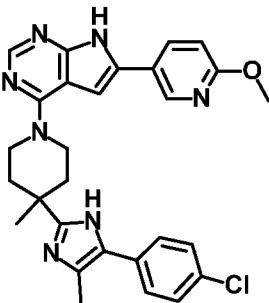
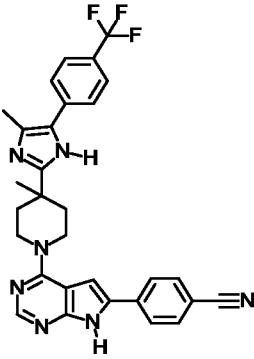
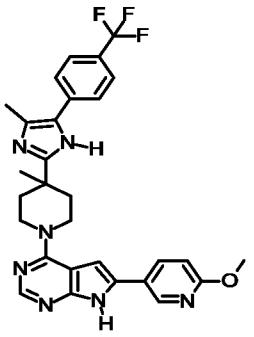
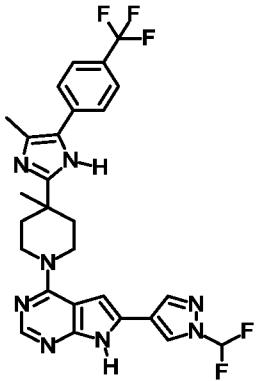
P-3156	 <p>4-[4-[5-(4-methoxyphenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-6-(6-methoxy-3-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine</p>	510.4
P-3157	 <p>4-[4-[5-(4-methoxy-3-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-6-(6-methoxy-3-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine</p>	524.4
P-3158	 <p>4-[4-[5-(1,3-benzodioxol-5-yl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-6-(6-methoxy-3-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine</p>	524.4
P-3159	 <p>4-[4-[5-(1,3-benzodioxol-5-yl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile</p>	518.3

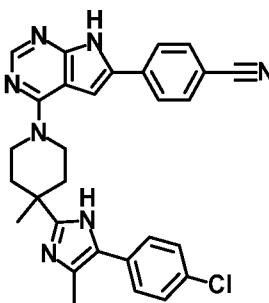
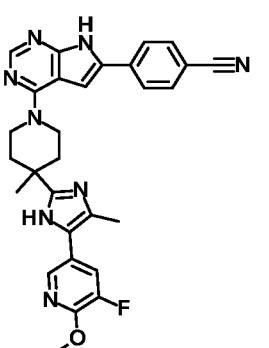
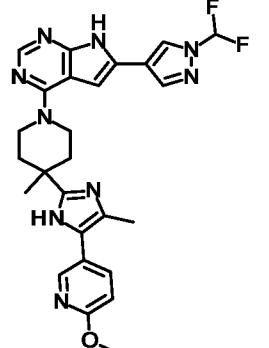
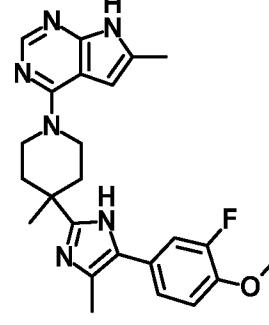
P-3160		4-[4-[4-[5-(4-ethoxy-3-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	532.5
P-3161		4-[4-[4-[5-(4-ethoxyphenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	518.4
P-3162		4-[4-[4-[5-[4-(difluoromethyl)phenyl]-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	510.4
P-3163		4-[4-[4-[5-(3-fluoro-4-methoxy-phenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	522.4

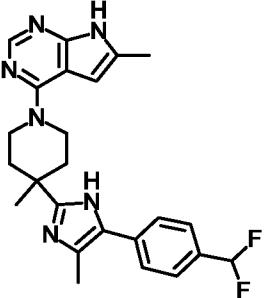
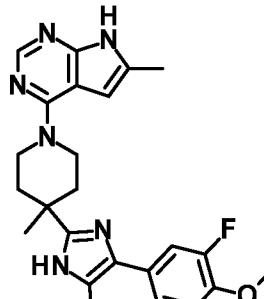
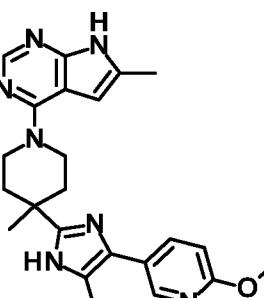
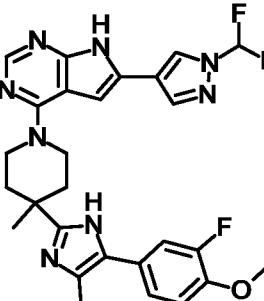
P-3164		4-[4-[5-[4-(difluoromethyl)phenyl]-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	524.4
P-3165		6-methyl-4-[4-methyl-4-[4-methyl-5-[4-(trifluoromethyl)phenyl]-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	453.1*
P-3166		4-[4-[5-(3-methoxyphenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-6-methyl-7H-pyrrolo[2,3-d]pyrimidine	417.4
P-3167		4-[4-[5-(3-methoxyphenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	504.4

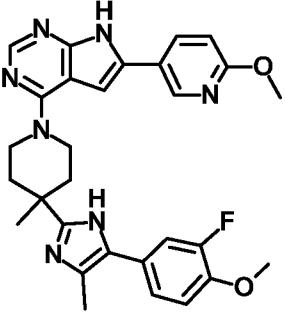
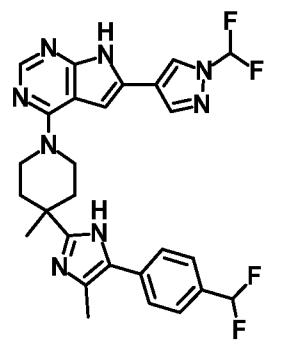
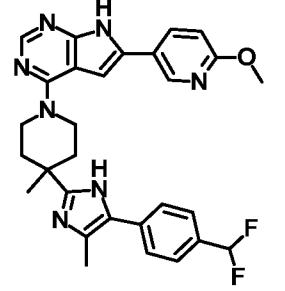
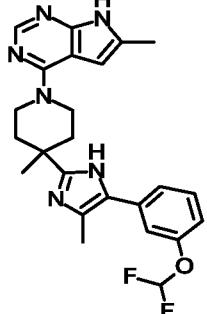
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P-3169		4-[4-[5-(3-methoxyphenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-6-(6-methoxy-3-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine	510.4
P-3170		6-[1-(difluoromethyl)pyrazol-4-yl]-4-[4-[5-(4-ethoxyphenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	533.4
P-3171		4-[4-[5-(4-ethoxyphenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-6-(6-methoxy-3-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine	524.4

P-3172		4-[4-[4-[5-(6-methoxy-3-pyridyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	503.3
P-3173		4-[4-[4-[5-(5-fluoro-6-methoxy-3-pyridyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	507.3
P-3174		4-[4-[5-(4-chlorophenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-6-methyl-7H-pyrrolo[2,3-d]pyrimidine	431.2
P-3175		4-[4-[5-(4-chlorophenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-6-[1-(difluoromethyl)pyrazol-4-yl]-7H-pyrrolo[2,3-d]pyrimidine	523.3

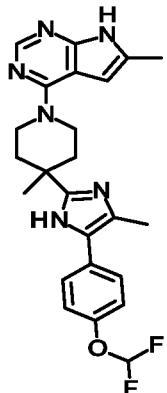
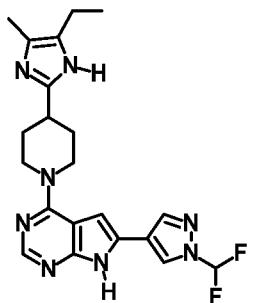
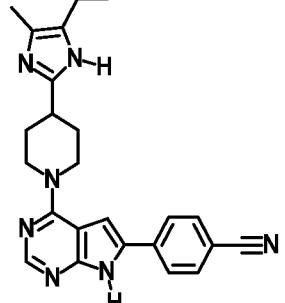
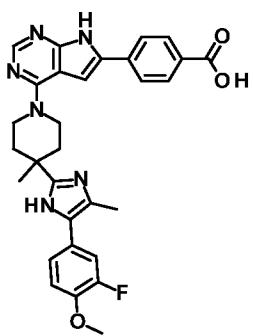
P-3176	 <p>4-[4-[5-(4-chlorophenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-6-(6-methoxy-3-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine</p>	514.3
P-3177	 <p>4-[4-[4-methyl-4-[4-methyl-5-[4-(trifluoromethyl)phenyl]-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile</p>	540.3*
P-3178	 <p>6-(6-methoxy-3-pyridyl)-4-[4-methyl-4-[4-methyl-5-[4-(trifluoromethyl)phenyl]-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine</p>	546.3*
P-3179	 <p>6-[1-(difluoromethyl)pyrazol-4-yl]-4-[4-methyl-4-[4-methyl-5-[4-(trifluoromethyl)phenyl]-1H-imidazol-2-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine</p>	555.3*

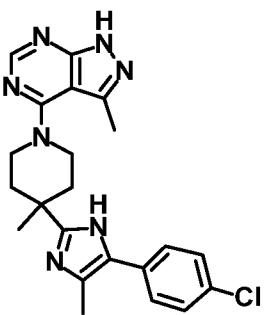
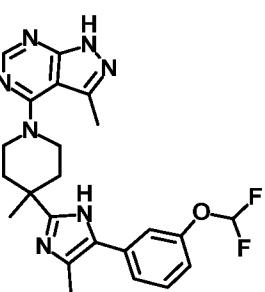
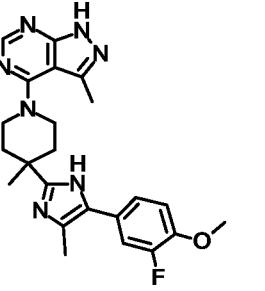
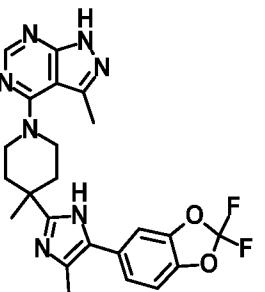
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P-3181		4-[4-[4-[5-(5-fluoro-6-methoxy-3-pyridyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	523.4
P-3182		6-[1-(difluoromethyl)pyrazol-4-yl]-4-[4-[5-(6-methoxy-3-pyridyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	530.4
P-3183		4-[4-[5-(3-fluoro-4-methoxy-phenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-6-methyl-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	435.3

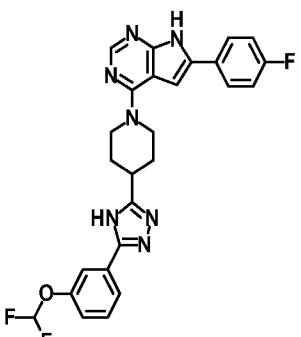
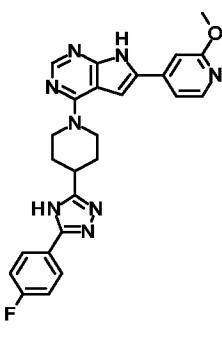
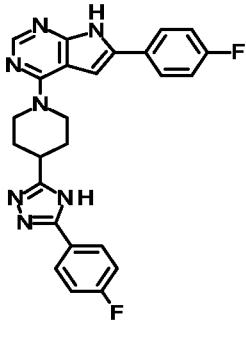
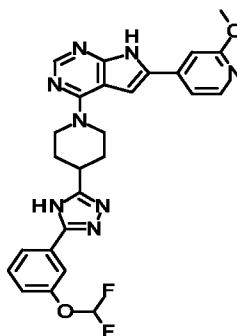
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P-3185		4-[4-[4-(5-fluoro-6-methoxy-3-pyridyl)-5-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-6-methyl-7H-pyrrolo[2,3-d]pyrimidine	436.3
P-3186		4-[4-[4-(6-methoxy-3-pyridyl)-5-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-6-methyl-7H-pyrrolo[2,3-d]pyrimidine	418.3
P-3187		6-[1-(difluoromethyl)pyrazol-4-yl]-4-[4-[5-(3-fluoro-4-methoxy-phenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	537.4

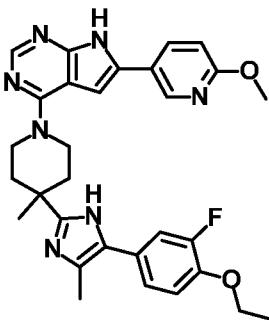
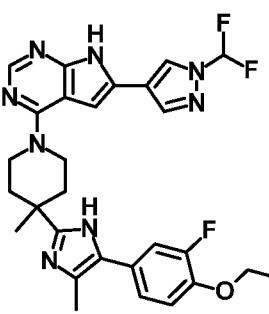
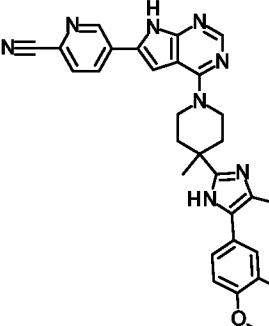
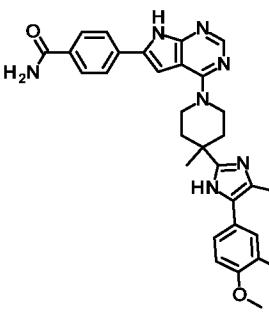
P-3188	 <p>4-[4-[5-(3-fluoro-4-methoxy-phenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-6-(6-methoxy-3-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine</p>	528.4
P-3189	 <p>4-[4-[5-[4-(difluoromethyl)phenyl]-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-6-[1-(difluoromethyl)pyrazol-4-yl]-7H-pyrrolo[2,3-d]pyrimidine</p>	539.4
P-3190	 <p>4-[4-[5-[4-(difluoromethyl)phenyl]-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-6-(6-methoxy-3-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine</p>	530.4
P-3191	 <p>4-[4-[5-[3-(difluoromethoxy)phenyl]-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-6-methyl-7H-pyrrolo[2,3-d]pyrimidine</p>	453.3

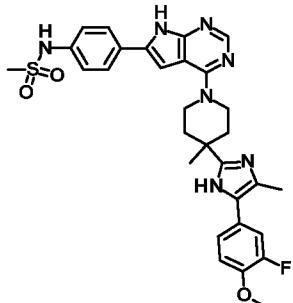
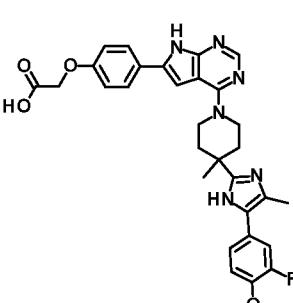
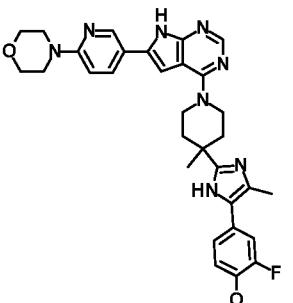
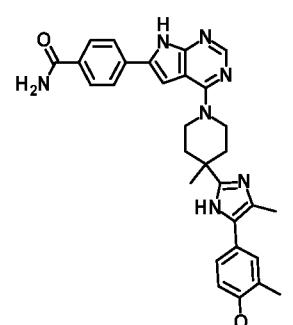
P-3192	<p>4-[4-[5-[3-(difluoromethoxy)phenyl]-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-6-[1-(difluoromethyl)pyrazol-4-yl]-7H-pyrrolo[2,3-d]pyrimidine</p>	555.4
P-3193	<p>4-[4-[5-[3-(difluoromethoxy)phenyl]-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-6-(6-methoxy-3-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine</p>	546.4
P-3194	<p>4-[4-[4-[5-[3-(difluoromethoxy)phenyl]-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile</p>	540.4
P-3195	<p>4-[4-[4-[5-[4-(difluoromethoxy)phenyl]-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile</p>	540.4

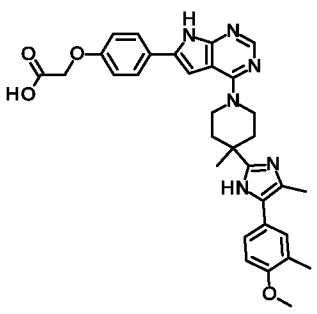
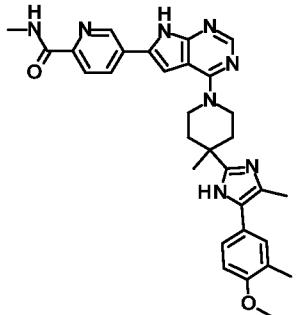
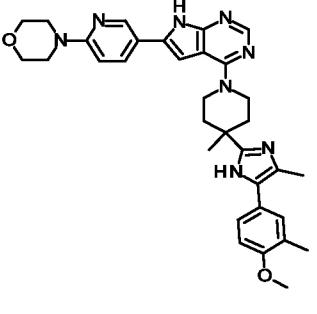
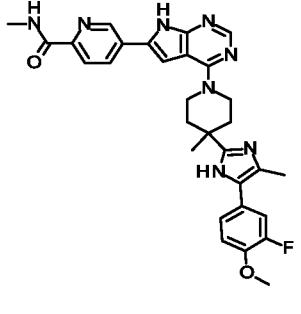
P-3196		4-[4-[5-[4-(difluoromethoxy)phenyl]-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-6-methyl-7H-pyrrolo[2,3-d]pyrimidine	453.2
P-3197		6-[1-(difluoromethyl)pyrazol-4-yl]-4-[4-(5-ethyl-4-methyl-1H-imidazol-2-yl)-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	427.2
P-3198		4-[4-[4-(5-ethyl-4-methyl-1H-imidazol-2-yl)-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzonitrile	412.25
P-3199		4-[4-[5-(3-fluoro-4-methoxy-phenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzoic acid	541.4

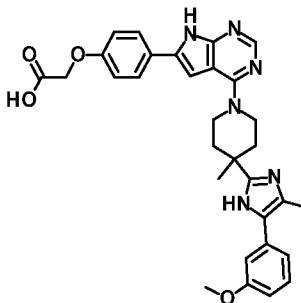
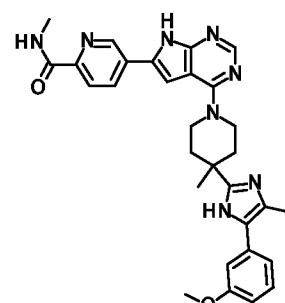
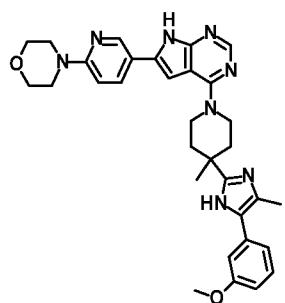
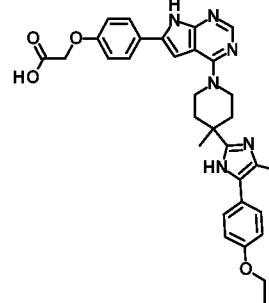
P-3200		4-[4-[5-(4-chlorophenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-3-methyl-1H-pyrazolo[3,4-d]pyrimidine	422.3
P-3201		4-[4-[5-[3-(difluoromethoxy)phenyl]-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-3-methyl-1H-pyrazolo[3,4-d]pyrimidine	454.3
P-3202		4-[4-[5-(3-fluoro-4-methoxy-phenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-3-methyl-1H-pyrazolo[3,4-d]pyrimidine	436.4
P-3203		4-[4-[5-(2,2-difluoro-1,3-benzodioxol-5-yl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-3-methyl-1H-pyrazolo[3,4-d]pyrimidine	468.3

P-3204		4-[4-[5-[3-(difluoromethoxy)phenyl]-4H-1,2,4-triazol-3-yl]-1-piperidyl]-6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidine	506.7
P-3205		4-[4-[5-(4-fluorophenyl)-4H-1,2,4-triazol-3-yl]-1-piperidyl]-6-(2-methoxy-4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine	471.0
P-3206		6-(4-fluorophenyl)-4-[4-[5-(4-fluorophenyl)-4H-1,2,4-triazol-3-yl]-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	458.7
P-3207		4-[4-[5-[3-(difluoromethoxy)phenyl]-4H-1,2,4-triazol-3-yl]-1-piperidyl]-6-(2-methoxy-4-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine	519.6

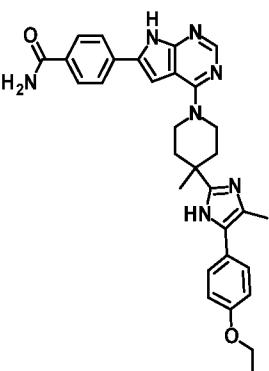
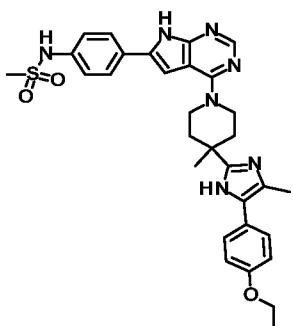
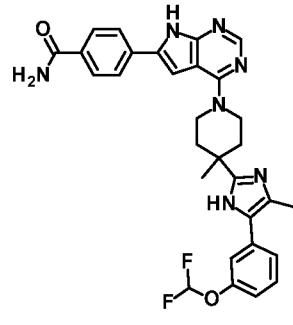
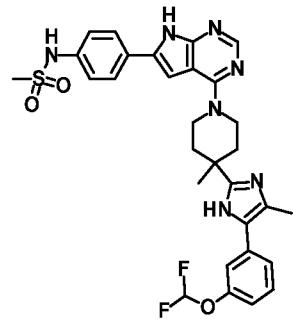
P-3209		4-[4-[5-(4-ethoxy-3-fluoro-phenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-6-(6-methoxy-3-pyridyl)-7H-pyrrolo[2,3-d]pyrimidine	542.4
P-3210		6-[1-(difluoromethyl)pyrazol-4-yl]-4-[4-[5-(4-ethoxy-3-fluoro-phenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	551.4
P-3211		5-[4-[4-[5-(3-fluoro-4-methoxy-phenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]pyridine-2-carbonitrile	523.6
P-3212		4-[4-[4-[5-(3-fluoro-4-methoxy-phenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzamide	540.4

P-3213		N-[4-[4-[5-(3-fluoro-4-methoxy-phenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]phenyl]methanesulfonamide	590.6
P-3214		2-[4-[4-[5-(3-fluoro-4-methoxy-phenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]phenoxy]acetic acid	571.3
P-3215		4-[5-[4-[5-(3-fluoro-4-methoxy-phenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]-2-pyridyl]morpholine	583.3
P-3216		4-[4-[5-(4-methoxy-3-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzamide	536.2

P-3217		2-[4-[4-[5-(4-methoxy-3-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]phenoxy]acetic acid	567.4
P-3218		5-[4-[4-[5-(4-methoxy-3-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]-N-methyl-pyridine-2-carboxamide	551.5
P-3219		4-[5-[4-[4-[5-(4-methoxy-3-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]-2-pyridyl]morpholine	579.4
P-3220		5-[4-[4-[5-(3-fluoro-4-methoxy-phenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]-N-methyl-pyridine-2-carboxamide	555.4

P-3221		2-[4-[4-[5-(3-methoxyphenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]phenoxy]acetic acid	553.3
P-3222		5-[4-[4-[5-(3-methoxyphenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]-N-methyl-pyridine-2-carboxamide	537.4
P-3223		4-[5-[4-[4-[5-(3-methoxyphenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]-2-pyridyl]morpholine	565.6
P-3224		2-[4-[4-[5-(4-ethoxyphenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]phenoxy]acetic acid	567.4

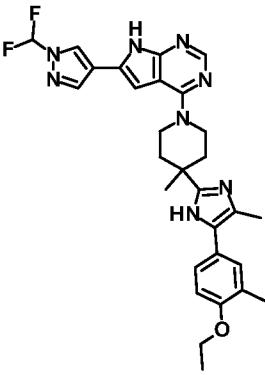
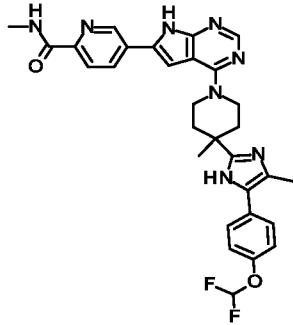
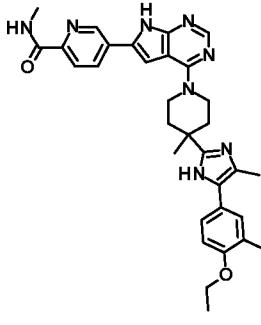
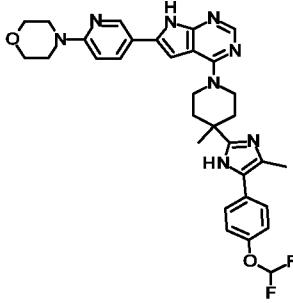
P-3225		4-[4-[4-[5-(3-methoxyphenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzamide	522.4
P-3226		5-[4-[4-[5-(4-ethoxyphenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]-N-methyl-pyridine-2-carboxamide	551.5
P-3227		4-[5-[4-[4-[5-(4-ethoxyphenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]-2-pyridyl]morpholine	579.4
P-3228		N-[4-[4-[4-[5-(4-methoxy-3-methylphenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]phenyl]methanesulfonamide	586.4

P-3229		4-[4-[4-[5-(4-ethoxyphenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzamide	536.2
P-3230		N-[4-[4-[4-[5-(4-ethoxyphenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]phenyl]methanesulfonamide	586.4
P-3231		4-[4-[4-[5-[3-(difluoromethoxy)phenyl]-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzamide	558.1
P-3232		N-[4-[4-[4-[5-[3-(difluoromethoxy)phenyl]-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]phenyl]methanesulfonamide	608.3

P-3233		2-[4-[4-[5-[3-(difluoromethoxy)phenyl]-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]phenoxy]acetic acid	589.4
P-3234		N-[4-[4-[5-(3-methoxyphenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]methanesulfonamide	572.2
P-3235		5-[4-[4-[5-[4-(difluoromethyl)phenyl]-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]-N-methyl-pyridine-2-carboxamide	557.2
P-3236		5-[4-[4-[5-[3-(difluoromethoxy)phenyl]-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]-N-methyl-pyridine-2-carboxamide	573.4

P-3237		4-[5-[4-[4-[5-[4-(difluoromethyl)phenyl]-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]-2-pyridyl]morpholine	585.5
P-3238		4-[5-[4-[4-[5-[3-(difluoromethoxy)phenyl]-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]-2-pyridyl]morpholine	601.4
P-3239		4-[4-[4-[5-[4-(difluoromethyl)phenyl]-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzamide	542.2
P-3240		2-[4-[4-[4-[5-[4-(difluoromethyl)phenyl]-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]phenoxy]acetic acid	573.1

P-3241		2-[4-[4-[5-[4-(difluoromethoxy)phenyl]-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]phenoxy]acetic acid	589.4
P-3242		4-[4-[5-[4-(difluoromethoxy)phenyl]-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-6-[1-(difluoromethyl)pyrazol-4-yl]-7H-pyrrolo[2,3-d]pyrimidine	555.1
P-3243		4-[4-[4-[5-(4-ethoxy-3-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzamide	550.6
P-3244		2-[4-[4-[5-(4-ethoxy-3-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]phenoxy]acetic acid	581.2

P-3245		6-[1-(difluoromethyl)pyrazol-4-yl]-4-[4-[5-(4-ethoxy-3-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	547.3
P-3246		5-[4-[4-[5-[4-(difluoromethoxy)phenyl]-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]-N-methyl-pyridine-2-carboxamide	573.4
P-3247		5-[4-[4-[5-(4-ethoxy-3-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]-N-methyl-pyridine-2-carboxamide	565.6
P-3248		4-[5-[4-[4-[5-[4-(difluoromethoxy)phenyl]-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]-2-pyridyl]morpholine	601.4

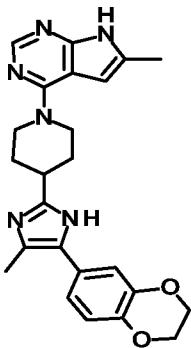
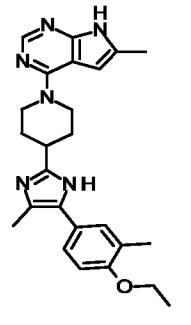
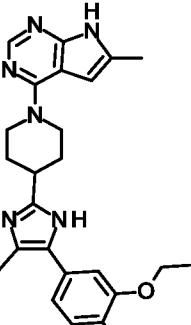
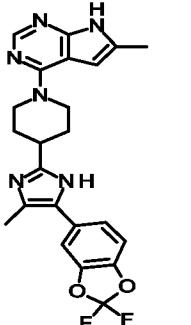
P-3249		4-[5-[4-[5-(4-ethoxy-3-methylphenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]-2-pyridyl]morpholine	593.6
P-3250		5-[4-[5-(4-methoxy-3-methylphenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]pyridine-2-carbonitrile	519.4
P-3251		5-[4-[5-(4-ethoxyphenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]pyridine-2-carbonitrile	519.4
P-3252		N-[4-[4-[5-[4-(difluoromethyl)phenyl]-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]phenyl]methanesulfonamide	592.4

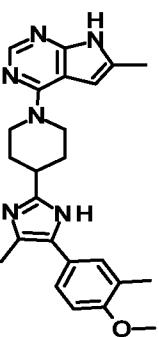
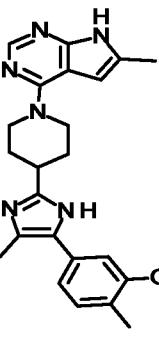
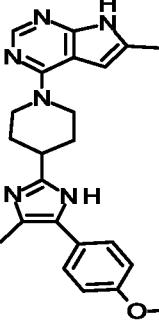
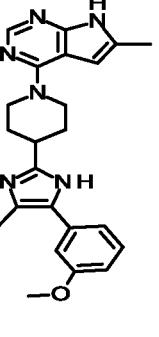
P-3253		4-[4-[5-[4-(difluoromethoxy)phenyl]-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]benzamide	558.1
P-3254		N-[4-[4-[5-[4-(difluoromethoxy)phenyl]-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]phenyl]methanesulfonamide	608.3
P-3255		5-[4-[5-[3-(difluoromethoxy)phenyl]-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]pyridine-2-carbonitrile	541.3
P-3256		5-[4-[5-(3-methoxyphenyl)-4-methyl-1H-imidazol-2-yl]-4-methyl-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]pyridine-2-carbonitrile	505.3

* MS(ESI) [M-H⁺] observed.

Table 2.

No.	Compound	Name	MS(ESI) [M+H ⁺] ⁺ or [M-H ⁻] ⁻ observed
P-3004		6-methyl-4-[4-(4-methyl-5-phenyl-1H-imidazol-2-yl)-1-piperidyl]-7H-pyrrolo[2,3-d]pyrimidine	373.0
P-3005		4-[4-[5-(4-fluorophenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-methyl-7H-pyrrolo[2,3-d]pyrimidine	391.2
P-3120		4-[4-[5-(1,3-benzodioxol-5-yl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-methyl-7H-pyrrolo[2,3-d]pyrimidine	417.3

P-3121		4-[4-[5-(2,3-dihydro-1,4-benzodioxin-6-yl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-methyl-7H-pyrrolo[2,3-d]pyrimidine	431.3
P-3125		4-[4-[5-(4-ethoxy-3-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-methyl-7H-pyrrolo[2,3-d]pyrimidine	431.3
P-3126		4-[4-[5-(3-ethoxy-4-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-methyl-7H-pyrrolo[2,3-d]pyrimidine	431.3
P-3127		4-[4-[5-(2,2-difluoro-1,3-benzodioxol-5-yl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-methyl-7H-pyrrolo[2,3-d]pyrimidine	453.3

P-3128		4-[4-[5-(4-methoxy-3-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-methyl-7H-pyrrolo[2,3-d]pyrimidine	417.1
P-3129		4-[4-[5-(3-methoxy-4-methyl-phenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-methyl-7H-pyrrolo[2,3-d]pyrimidine	417.2
P-3130		4-[4-[5-(4-methoxyphenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-methyl-7H-pyrrolo[2,3-d]pyrimidine	402.9
P-3131		4-[4-[5-(3-methoxyphenyl)-4-methyl-1H-imidazol-2-yl]-1-piperidyl]-6-methyl-7H-pyrrolo[2,3-d]pyrimidine	403.1

Example 7: Compound Properties

[0237] 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.

[0238] 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. Pat. Publ. No. 20040002534, 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.

[0239] 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

[0240] 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. IC₅₀ 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 30 mM. These were diluted 30 µl into 130 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 30 µl in 1x kinase buffer (50 mM HEPES, pH 7.2, 5 mM MgCl₂, 5 mM MnCl₂, 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 30 minutes at room

temperature before adding 5 μ l of acceptor beads (PY30 coated beads (Perkin Elmer Life Science) final concentration 1 μ g/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 PY30 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 IC₅₀.

[0241] 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 30 mM. These were diluted 30 μ l into 130 μ l of DMSO (4 mM) and 1 μ l was added to an assay plate. These were then serially diluted 1:3 (50 μ l to 100 μ l DMSO) for a total of 8 points. Plates were prepared such that each kinase reaction is 30 μ l in 1x kinase buffer (25 mM HEPES, pH 7.5, 2 mM MgCl₂, 2 mM MnCl₂, 0.01% Tween-30, 1 mM DTT, and 0.001% BSA), 5% DMSO and 100 μ M 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 μ l of donor beads (Streptavidin coated beads (Perkin Elmer Life Science) final concentration 10 μ g/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 30 minutes at room temperature before adding 5 μ l of acceptor beads (PY30 coated beads (Perkin Elmer Life Science) final concentration 10 μ g/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 PY30 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 IC₅₀.

[0242] 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).

[0243] 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.

[0244] For protein expression, the plasmid containing the Kit gene was transformed into *E. coli* strains BL31(DE3)RIL and transformants selected for growth on LB agar plates containing appropriate antibiotics. Single colonies were grown overnight at 37°C in 300 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.

[0245] 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 (immobilized metal ion affinity chromatography). 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).

[0246] 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 MnCl₂, 0.1 mg/ml poly (Glu, Tyr) 4:1, 10 mM MgAcetate and γ -³³P-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

[0247] The c-kit mutant D816V (or kinase domain thereof) is an active kinase in AlphaScreen. IC₅₀ 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 30 mM. These were diluted 30 µl into 130 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 30 µl in 1x kinase buffer (25 mM HEPES, pH 7.2, 8 mM MgCl₂, 2 mM MnCl₂, 50 mM NaCl, 0.01% Brij, 1mM 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 30 minutes at room temperature before adding 5 µl of acceptor beads (PY30 coated beads (Perkin Elmer Life Science) final concentration 7.5 µg/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 PY30 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 IC₅₀.

Protein Expression and Purification

[0248] 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 OD₆₀₀ 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 30 minutes. Cells were re-suspended in 0.1M KPO₄ pH 8.0, 250 mM NaCl, 10% Glycerol, 0.75% NP-40, 25mM 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 30,000 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 300 (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

[0249] 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 IC₅₀ values. BaF3-FL KIT D816V cells were seeded at 1 x 10⁴ 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% CO₂ 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 µL 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 IC₅₀ value.

[0250] 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.

[0251] 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.

[0252] 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 < IC₅₀ ≤ 1 μM; ++ = 1 μM < IC₅₀ ≤ 10 μM ; + = 10 μM < IC₅₀ < 300 μM.

Compound number	Biochemical activity (IC ₅₀ μM)	
	Kit	Kit D816V
P-3001	+++	
P-3002	+++	+++
P-3003	+++	+++
P-3004	+	++
P-3005	++	++
P-3006	+++	+++
P-3007	++	+++
P-3008	+++	+++

P-3009	+++	+++
P-3010	+++	+++
P-3204	+	+++
P-3011	++	+++
P-3205	+	++
P-3206	++	+++
P-3207	++	++
P-3014	++	+++
P-3015	+++	+++
P-3016	++	+++
P-3017	+++	+++
P-3018	++	+++
P-3019	+	+++
P-3020	++	+++
P-3021	+++	+++
P-3022	++	+++
P-3023	+++	+++
P-3024	++	+++
P-3025	++	+++
P-3026	++	+++
P-3027	++	+++
P-3028	+++	+++
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P-3038	+++	+++
P-3039	++	+++
P-3040	+++	+++
P-3041	+++	+++
P-3042	++	+++
P-3043	+++	+++
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P-3045	+	+++
P-3046	+++	+++
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P-3069	+++	+++
P-3070	+++	+++
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P-3110	+	+++
P-3111	+	+++
P-3112	+++	+++
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P-3141	++	+++
P-3142	++	+++
P-3143	++	+++
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P-3246	+++	+++
P-3247	+++	+++
P-3248	+++	+++
P-3249	+++	+++
P-3250	+++	+++
P-3251	+++	+++
P-3252	+++	+++
P-3253	+++	+++
P-3254	+++	+++
P-3255	++	+++
P-3256	+++	+++

[0253] Compounds P-3001 to P-3011, P-3014 to P-3207 and P-3209 to P-3256, e.g., compounds P-3001, P-3002, P-3003, P-3004, P-3005, P-3006, P-3007, P-3008, P-3009, P-3010, P-3011, P-3014, P-3015, P-3016, P-3017, P-3018, P-3019, P-3020, P-3021, P-3022, P-3023, P-3024, P-3025, P-3026, P-3027, P-3028, P-3029, P-3030, P-3031, P-3032, P-3033, P-3034, P-3035, P-3036, P-3037, P-3038, P-3039, P-3040, P-3041, P-3042, P-3043, P-3044, P-3045, P-3046, P-3047, P-3048, P-3049, P-3050, P-3051, P-3052, P-3053, P-3054, P-3055, P-3056, P-3057, P-3058, P-3059, P-3060, P-3061, P-3062, P-3063, P-3064, P-3065, P-3066, P-3067, P-3068, P-3069, P-3070, P-3071, P-3072, P-3073, P-3074, P-3075, P-3076, P-3077, P-3078, P-3079, P-3080, P-3081, P-3082, P-3083, P-3084, P-3085, P-3086, P-3087, P-3088, P-3089, P-3090, P-3091, P-3092, P-3093, P-3094, P-3095, P-3096, P-3097, P-3098, P-3099, P-3100, P-3101, P-3102, P-3104, P-3105, P-3106, P-3107, P-3108,

P-3109, P-3110, P-3111, P-3112, P-3113, P-3114, P-3115, P-3116, P-3117, P-3118, P-3119, P-3120, P-3121, P-3122, P-3123, P-3124, P-3125, P-3126, P-3127, P-3128, P-3129, P-3130, P-3131, P-3132, P-3133, P-3134, P-3135, P-3136, P-3137, P-3138, P-3139, P-3140, P-3141, P-3142, P-3143, P-3144, P-3145, P-3146, P-3147, P-3148, P-3149, P-3150, P-3151, P-3152, P-3153, P-3154, P-3155, P-3156, P-3157, P-3158, P-3159, P-3160, P-3161, P-3162, P-3163, P-3164, P-3165, P-3166, P-3167, P-3168, P-3169, P-3170, P-3171, P-3172, P-3173, P-3174, P-3175, P-3176, P-3177, P-3178, P-3179, P-3180, P-3181, P-3182, P-3183, P-3184, P-3185, P-3186, P-3187, P-3188, P-3189, P-3190, P-3191, P-3192, P-3193, P-3194, P-3195, P-3196, P-3197, P-3198, P-3199, P-3200, P-3201, P-3202, P-3203, P-3204, P-3205, P-3206, P-3207, P-3209, P-3210, P-3211, P-3212, P-3213, P-3214, P-3215, P-3216, P-3217, P-3218, P-3219, P-3220, P-3221, P-3222, P-3223, P-3224, P-3225, P-3226, P-3227, P-3228, P-3229, P-3230, P-3231, P-3232, P-3233, P-3234, P-3235, P-3236, P-3237, P-3238, P-3239, P-3240, P-3241, P-3242, P-3243, P-3244, P-3245, P-3246, P-3247, P-3248, P-3249, P-3250, P-3251, P-3252, P-3253, P-3254, P-3255 or P-3256 had IC₅₀ of less than 10 μM in at least one of the c-kit cell assays described above in Example 7.

SEQUENCE LISTING

SEQ ID NO: 1 Sequence NP_000313

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SEQ ID NO:2 Sequence NM_000222

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[0254] 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.

[0255] 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 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.

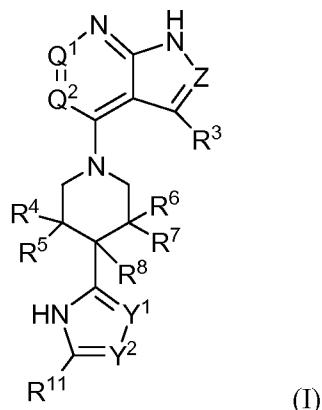
[0256] While this disclosure has been disclosed with reference to specific embodiments, it is apparent that other embodiments and variations of this disclosure may be devised by others skilled in the art without departing from the true spirit and scope of the disclosure.

[0257] 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.

[0258] 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):



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

Z is N or CR¹;

Q¹ is N or CR², wherein R² is H, halogen, CH₃, CH₃O, or CN, wherein CH₃ or CH₃O is optionally substituted with from 1 to 3 halogens;

Q² is N or CH;

R³ is H, F, CH₃, CH₃O, CHF₂, CH₂F, CF₃, CHF₂O, CH₂FO or CF₃O;

R⁴, R⁵, R⁶ and R⁷ are each independently H, C₁₋₄alkyl or C₁₋₄haloalkyl;

Y¹ is N or CR⁹, wherein R⁹ is H, C₁₋₄alkyl or C₁₋₄haloalkyl;

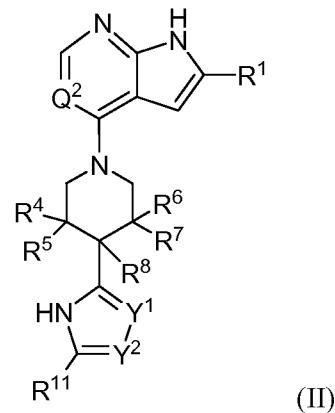
Y² is N or CR¹⁰;

wherein R¹⁰ and R¹¹ are each independently optionally substituted C₁₋₄alkyl, C₁₋₄haloalkyl, optionally substituted C₃₋₆cycloalkyl, optionally substituted aryl or optionally substituted heteroaryl, wherein two adjacent substituents on an aryl or heteroaryl ring are optionally taken together with the atoms to which they attach to form an optionally substituted fused 5- or 6-membered ring having from 0-2 heteroatoms selected from O, N or S; and

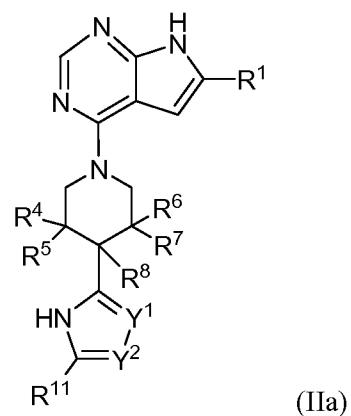
(i) R¹ is optionally substituted aryl or optionally substituted heteroaryl; and R⁸ is H, C₁₋₄alkyl or C₁₋₄haloalkyl; or

(ii) R¹ is optionally substituted C₁₋₆alkyl; and R⁸ is C₁₋₄alkyl or C₁₋₄haloalkyl.

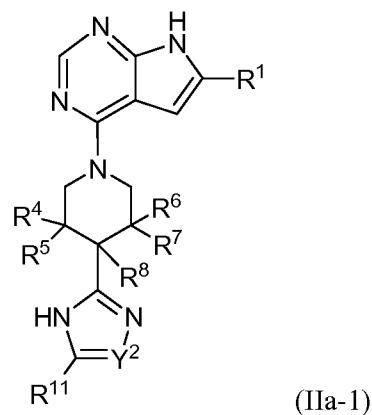
2. The compound of claim 1, having formula (II):



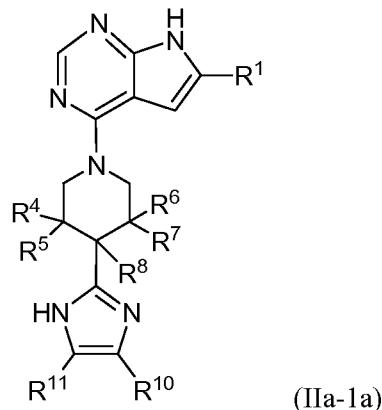
3. The compound of claim 1, having formula (IIa):



4. The compound of any of claims 1-3, having formula (IIa-1):



5. The compound of any of claims 1-4, having formula (IIa-1a):



6. The compound of claim **1**, wherein Q¹ is CH.
7. The compound of claim **1**, wherein Z is CR¹.
8. The compound of any of claims **1**, **6** or **7**, wherein Q² is N.
9. The compound of any of claims **1** and **6-8**, wherein Y¹ is N.
10. The compound of any of claims **1** and **6-9**, wherein Y² is CR¹⁰.
11. The compound of any of claims **1** and **6-10**, wherein Y² is CR¹⁰ and one of R¹⁰ or R¹¹ is C₁₋₄alkyl or C₁₋₄haloalkyl and the other is optionally substituted aryl or optionally substituted heteroaryl.
12. The compound of any of claims **1-11**, wherein R¹ is C₁₋₆alkyl, aryl or heteroaryl, each of which is optionally substituted with from 1-3 R^a substituents independently selected from C₁₋₆alkyl, C₁₋₆alkoxy, C₂₋₆alkenyl, C₂₋₆alkynyl, aryl, aryl-C₁₋₄alkyl, heteroaryl, heteroaryl-C₁₋₄alkyl, C₃₋₆cycloalkyl, C₃₋₆cycloalkyl-C₁₋₄alkyl, C₃₋₆cycloalkenyl, CH₂=CH-, C₃₋₆cycloalkyl-C₂₋₄alkenyl, C₃₋₆cycloalkyl-C₂₋₄alkynyl, heterocycloalkyl, heterocycloalkyl-C₁₋₄alkyl or R^b; or two adjacent R^a substituents on an aromatic ring are taken together with the atoms to which they are attached form a 5- or 6-membered ring having from 0-2 heteroatoms selected from O, N or S; wherein each R^b is independently selected from halogen, CN, -OH, -NH₂, -NO₂, -C(O)OH, -C(S)OH, -C(O)NH₂, -C(S)NH₂, -S(O)₂NH₂, -NHC(O)NH₂, -NHC(S)NH₂, -NHS(O)₂NH₂, -C(NH)NH₂, -OR^c, -SR^c, -OC(O)R^c, -OC(S)R^c, -C(O)R^c, -C(S)R^c, -C(O)OR^c, -C(S)OR^c, -S(O)R^c, -S(O)₂R^c, -C(O)NHR^c, -C(S)NHR^c, -C(O)NRR^cR^c, -C(S)NRR^cR^c, -S(O)NHR^c, -S(O)₂NR^cR^c, -C(NH)NHR^c, -C(NH)NR^cR^c, -NHC(O)R^c, -NHC(S)R^c, -NR^cC(O)R^c, -NR^cC(S)R^c, -NHS(O)₂R^c, -NR^cS(O)₂R^c, -NHC(O)NHR^c, -NHC(S)NHR^c, -NR^cC(O)NH₂, -NR^cC(S)NH₂, -NR^cC(O)NR^c, -NR^cC(S)NR^c, -NHC(O)NR^cR^c, -NHC(S)NR^cR^c, -NR^cC(O)NR^cR^c, -NR^cC(S)NR^cR^c, -NHS(O)₂NHR^c, -NR^cS(O)₂NHR^c, -NHS(O)₂NR^cR^c, -NR^cS(O)₂NR^cR^c, -NHR^c, R^c or -NR^cR^c, wherein each R^c is independently selected from C₁₋₆alkyl, aryl, aryl-C₁₋₂alkyl, C₃₋₆cycloalkyl, C₃₋₆cycloalkyl-C₁₋₄alkyl, heteroaryl, heteroaryl-C₁₋₄alkyl, heterocycloalkyl or heterocycloalkyl-C₁₋₄alkyl; or two R^c groups when

attached to the same nitrogen atom are taken together with the nitrogen atom to which they are attached form a 4-, 5- or 6-membered ring; wherein the aliphatic or aromatic portion of each R^a is further optionally substituted with from 1-3 R^d groups independently selected from halogen, CN, -OH, -NH₂, -NO₂, -C(O)OH, -C(S)OH, -C(O)NH₂, -C(S)NH₂, -S(O)₂NH₂, -NHC(O)NH₂, -NHC(S)NH₂, -NHS(O)₂NH₂, -C(NH)NH₂, -OR^e, -SR^e, -OC(O)R^e, -OC(S)R^e, -P(=O)HR^e, -P(=O)R^eR^e, -PH(=O)OR^e, -P(=O)(OR^e)₂, -OP(=O)(OR^e)₂, -C(O)R^e, -C(S)R^e, -C(O)OR^e, -C(S)OR^e, -S(O)R^e, -S(O)₂R^e, -C(O)NHR^e, -C(S)NHR^e, -C(O)NR^eR^e, -C(S)NR^eR^e, -S(O)₂NHR^e, -S(O)NR^eR^e, -C(NH)NHR^e, -C(NH)NR^eR^e, -NHC(O)R^e, -NHC(S)R^e, -NR^eC(O)R^e, -NR^eC(S)R^e, -NHS(O)₂R^e, -NR^eS(O)₂R^e, -NHC(O)NHR^e, -NHC(S)NHR^e, -NR^eC(O)NH₂, -NR^eC(S)NH₂, -NR^eC(O)NHR^e, -NR^eC(S)NHR^e, -NHC(O)NR^eR^e, -NHC(S)NR^eR^e, -NR^eC(O)NR^eR^e, -NR^eC(S)NR^eR^e, -NHS(O)₂NHR^e, -NR^eS(O)₂NH₂, -NHS(O)₂NHR^e, -NHC(O)NR^eR^e, -NHC(S)NR^eR^e, -NR^eS(O)₂NRR^e, -NHR^e, -NR^eR^e or R^e; wherein each R^e is independently C₁₋₆alkyl or aryl; or two R^e groups when attached to the same nitrogen atom are taken together with the nitrogen atom to which they are attached form a 4- to 6-membered ring; wherein each R^c is further optionally substituted with from 1-3 R^f substituents independently selected from halogen, CN, -OH, -NH₂, -NO₂, -C(O)OH, -C(S)OH, -C(O)NH₂, -C(S)NH₂, -S(O)₂NH₂, -NHC(O)NH₂, -NHC(S)NH₂, -NHS(O)₂NH₂, -C(NH)NH₂, -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(O)NR^gR^g, -S(O)₂NHR^g, -S(O)₂NR^gR^g, -NHC(O)R^g, -NR^gC(O)R^g, -NR^gS(O)₂R^g, -NHC(O)NHR^g, -NR^gC(O)NH₂, -NR^gC(O)NHR^g, -NHC(O)NR^gR^g, -NHC(S)NR^gR^g, -NR^gC(O)NR^gR^g, -NHS(O)₂NHR^g, -NR^gS(O)₂NH₂, -NR^gS(O)₂NHR^g, -NHS(O)₂NR^gR^g, -NR^gS(O)₂NR^gR^g, -NHR^g, -NR^gR^g or R^g, wherein each R^g is independently C₁₋₆alkyl.

13. The compound of claim **12**, wherein R¹ is C₁₋₆alkyl, phenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 4-pyrazolyl or 3-pyrazolyl, each of which is optionally substituted with from 1-3 R^c or 1-3 R^d groups.

14. The compound of claim **1-11**, wherein R¹ is C₁₋₆alkyl, phenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 4-pyrazolyl or 3-pyrazolyl, each of which is optionally substituted with from 1-3 R¹² substituents independently selected from halogen, CN, C₁₋₆alkyl, C₁₋₆alkoxy, C₃₋₆cycloalkyl, C₃₋₆cycloalkylalkyl, C₁₋₆haloalkyl, C₁₋₆haloalkoxy, heterocycloalkyl, heterocycloalkylalkyl, -NHR^g, -N(R^g)₂, -C(O)NH₂, -C(O)NHR^g, -C(O)NHR^gR^g, -COOH, -COOR^g, -SO₂NH₂, -SO₂NHR^g, -SO₂NR^gR^g, -NHSO₂R^g, -NHC(O)R^g or -OC(O)R^g.

15. The compound of claim **14**, wherein R¹² is selected from halogen, CN, C₁₋₆alkyl, C₁₋₆alkoxy, -CF₃, -CH₂F, CH₂F, -OCF₃, -OCHF₂, -OCH₂F, -NHR^g, -N(R^g)₂, 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, C(O)NH₂, -C(O)NHCH₃, -C(O)NH(CH₃)₂, -COOH, -COOCH₃, -SO₂NH₂, -SO₂NHCH₃, -SO₂N(CH₃)₂, -NHSO₂CH₃, -NHC(O)CH₃ or -OC(O)CH₃.

16. The compound of any of claims **1-15**, wherein one of R¹⁰ or R¹¹ is optionally substituted C₁₋₄alkyl, optionally substituted C₃₋₆cycloalkyl or C₁₋₄haloalkyl and the other R¹⁰ or R¹¹ is optionally substituted aryl or optionally substituted heteroaryl.

17. The compound of any of claims **1-16**, wherein one of R¹⁰ or R¹¹ is C₁₋₆alkyl, aryl-C₁₋₄alkyl, heteroaryl-C₁₋₄alkyl, C₃₋₆cycloalkyl, C₃₋₆cycloalkyl-C₁₋₄alkyl or C₁₋₆haloalkyl and the other R¹⁰ or R¹¹ is aryl or heteroaryl, each of which is optionally substituted with from 1-3 R^c or 1-3 R^d substituents; or two adjacent R^c substituents or R^d substituents on an aromatic ring are taken together with the atoms to which they are attached from an optionally substituted 5- or 6-membered ring having from 0-2 heteroatoms selected from O, N or S.

18. The compound of any of claims **1-17**, wherein one of R¹⁰ or R¹¹ is -CH₃, -CH₂CH₃, -CF₃, or cyclopropyl, and the other R¹⁰ or R¹¹ is phenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-thiophenyl, 2,3-dihydro-1,4-benzodioxin-6-yl, 1,3-benzodioxol-5-yl, or 2,2-difluoro-1,3-benzodioxol-5-yl, wherein at each occurrence, the other R¹⁰ or R¹¹ is optionally substituted with from 1-3 R¹².

19. The compound of any of claims **1-18**, wherein R⁴, R⁵, R⁶ and R⁷ are H.

20. The compound of any of claims **1-19**, wherein R⁸ is H, methyl or ethyl.

21. A pharmaceutical composition comprising a compound of any of claims **1-20** and a pharmaceutically acceptable carrier or excipient.

22. The pharmaceutical composition of claim **21**, further comprising another therapeutic agent.

23. A method for modulating a protein kinase, said method comprising: administering to a subject a compound of any of claims **1-20** or a composition of claim **21** or **22**, wherein said protein kinase is a c-kit protein kinase or a mutant c-kit protein kinase.

24. 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 **1-20**, wherein the protein kinase is a c-kit protein or a mutant c-kit protein kinase.

25. The method of claim **24**, wherein the disease or condition is selected from a cancer, gastrointestinal stromal tumors or mastocytosis.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2015/018537

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1, 6, 8-25(all partially)

Remark on Protest

The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2015/018537

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04 A61K31/437 A61P35/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data, BIOSIS, CHEM ABS Data, COMPENDEX, EMBASE, INSPEC

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2008/140947 A1 (LILLY CO ELI [US]; DALLY ROBERT DEAN [US]; HUANG JIANPING [US]; JOSEPH) 20 November 2008 (2008-11-20) page 46; claim 1; compounds 16, 17 -----	1,6,8-25
A	WO 2008/075109 A1 (ASTEX THERAPEUTICS LTD [GB]; CANCER RES INST ROYAL [GB]; CANCER REC TE) 26 June 2008 (2008-06-26) claim 1 -----	1,6,8-25
X,P	WO 2014/039714 A2 (PLEXXIKON INC [US]) 13 March 2014 (2014-03-13) claim 1 -----	1,6,8-25



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier application or patent but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 April 2015	13/07/2015
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Bareyt, Sébastien

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2015/018537

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1, 6, 8-25(all partially)

related to compounds of formula I wherein Z is N

2. claims: 2-5, 7(completely); 1, 6, 8-25(partially)

related to compounds of formula I wherein Z is CR1
