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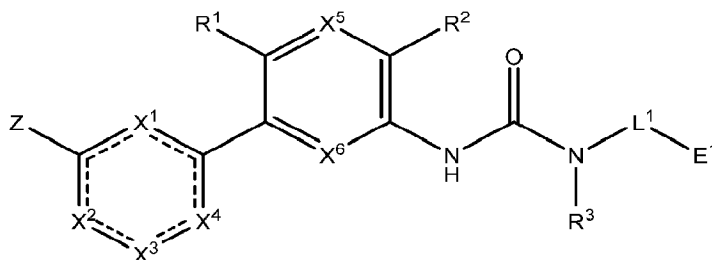
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(54) **Titre : INHIBITEURS DE KINASE RAF ET LEURS PROCEDES D'UTILISATION**

(54) **Title:** RAF KINASE INHIBITORS AND METHODS OF USE THEREOF



(I)

(57) **Abrégé/Abstract:**

Described herein are compounds (I) that are RAF inhibitors and their use in the treatment of disorders such as cancers.

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Abstract:

Described herein are compounds (I) that are RAF inhibitors and their use in the treatment of disorders such as cancers.

RAF KINASE INHIBITORS AND METHODS OF USE THEREOF**CROSS REFERENCE**

[0001] This application claims priority to U.S. Provisional Application No. 63/287,866 filed December 9, 2021 and U.S. Provisional Application No. 63/393,440, filed July 29, 2022, each of which is incorporated herein by reference in its entirety.

BACKGROUND

[0002] The BRAF V600X (i.e., V600E) mutant form of BRAF is known to be oncogenic, and there are multiple BRAF inhibitors now marketed to inhibit the signaling of oncogenic BRAF V600E in melanoma and other cancers. BRAF V600E signals as a monomer and is constitutively active independent of upstream control by RAS. The marketed BRAF V600E inhibitors include vemurafenib, dabrafenib, and encorafenib.

[0003] Other than BRAF V600X mutants, almost all other oncogenic forms of BRAF signal through the formation of homodimers (BRAF-BRAF dimer) or heterodimers (*e.g.*, BRAF-CRAF dimer) that are refractory to BRAF inhibitors such as vemurafenib, dabrafenib, and encorafenib. Such dimers are formed in cancers driven by BRAF fusions, atypical BRAF mutations, or RAS mutant cancers.

[0004] Oncogenic BRAF fusions originate from genomic rearrangements placing the 3-prime portion of the BRAF gene encoding the kinase domain behind another gene at the 5-prime position. The rearrangements result in the expression of oncoproteins that express constitutive kinase activity due to loss of the N-terminal auto-inhibitory domain of BRAF resulting from the genomic rearrangements. These BRAF fusions exhibit constitutive kinase activity due to spontaneous dimerization and as such are capable of aberrant signaling in cancer cells independent of upstream effectors or regulatory mechanisms. Additionally, some 5-prime translocated rearrangement genes contribute the N-terminal domains to be capable of further inducing dimerization, thereby enhancing activating dimerization of the BRAF fusion protein kinase domain. Since the expression of these genomic rearrangements are controlled by the promoter of the 5-prime partner, often there is overexpression of the BRAF fusion transcript due to efficient or excessive promoter activity. BRAF fusions are among the most common kinase translocations in solid tumors. Since their first description in 2005 as oncogenes in papillary thyroid carcinoma, hundreds of tumors in which the BRAF kinase domain is fused to one of more than 110 different 5-prime partner genes have been identified across at least 15 different tumor types. BRAF fusions are found in papillary thyroid

carcinoma, astrocytomas, melanomas, and have also been identified in drug resistant EGFR mutant lung cancers. BRAF fusion proteins signal by dimerization in a RAS-independent manner and are resistant to many BRAF inhibitors such as vemurafenib and dabrafenib, that are not capable of inhibiting both protomers of the signaling homodimer BRAF fusions. Rare CRAF fusion proteins have also been demonstrated to be tumor drivers. Such CRAF fusion proteins signal as CRAF-CRAF homodimers.

[0005] Other so-called atypical BRAF mutations also lead to spontaneous dimerization and signaling independent of RAS control. Like BRAF fusions, these atypical BRAF mutants signal as aberrant homodimers.

[0006] RAS mutant cancers comprise approximately 26-30% of all human cancers. RAS mutant cancers signal through the RAS → RAF → MEK → ERK signaling pathway. In this signaling cascade, kinase-inactive RAF monomers (comprising ARAF, BRAF, and CRAF isoforms) are recruited to oncogenic RAS where RAS induces the formation of kinase-active signaling RAF dimers. A predominant RAF heterodimer that is recruited to mutant RAS is the BRAF/CRAF heterodimer.

[0007] A combinatorial siRNA screening approach identified RAF as a dominant node in RAS mutant cancers, and that codepletion of both BRAF and CRAF, together with depletion of the autophagy gene ATG7, gave the best synthetic lethal inhibition of RAS mutant signaling, and additionally afforded the best therapeutic window for inhibiting signaling in RAS mutant cells versus normal, RAS wildtype cells. Additionally, it has been reported that inhibition of the RAF → MEK → ERK pathway in combination with autophagy-inhibiting agents effectively blocked RAS mutant cancer growth *in vitro* and *in vivo*.

[0008] Vertical inhibition of the RAF→ MEK→ ERK pathway through pan inhibition of RAF (specifically BRAF + CRAF) and ERK kinase activities where shown to illicit high synergy in blocking MAPK pathway signaling in KRAS-mutant pancreatic cancer cells, organoid studies, as well as in murine models of KRAS mutant pancreatic cancer. Vertical inhibition of RAF (BRAF + CRAF) and MEK kinase activities was also shown to be synergistic in KRAS mutant tumors.

[0009] The importance of inhibiting both BRAF and CRAF isoforms, as well as the requirement of inhibitor successfully binding to and inhibiting both protomers of signaling RAF dimers, has been well demonstrated. Failure of a RAF inhibitor, especially BRAF inhibitors, to successfully bind to and inhibit both protomers of signaling RAF dimers in RAS mutant cancers leads to paradoxical pathway stimulation rather than the desired pathway

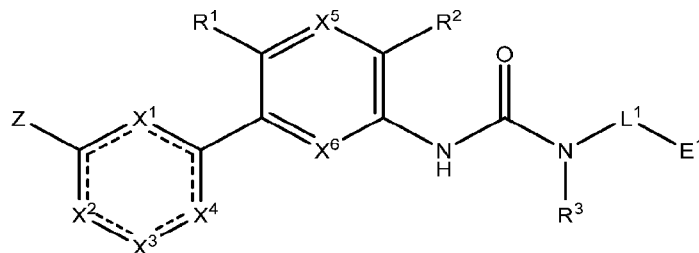
inhibition. Such BRAF inhibitors are contraindicated for the treatment of RAS mutant cancers.

[00010] There is a need to identify RAF inhibitors that can inhibit multiple RAF isoforms, and in particular to inhibit both BRAF and CRAF isoforms, and especially to inhibit both RAF protomers present in signaling BRAF/BRAF homodimers and BRAF/CRAF heterodimers. Such pan RAF inhibitors find utility in the treatment of BRAF V600X driven cancers, atypical BRAF mutated cancers, BRAF fusion cancers, CRAF fusion cancers, and RAS mutant cancers.

SUMMARY

[00011] Described herein, in part, are compounds that are RAF inhibitors, *e.g.*, BRAF or CRAF inhibitors and methods of use thereof, such as the treatment of cancers driven by oncogenic forms of RAS or BRAF. In an embodiment, the compounds of the disclosure inhibit both BRAF and CRAF isoforms. In another embodiment, the compounds of the disclosure inhibit both RAF protomers present in signaling BRAF/BRAF homodimers and BRAF/CRAF heterodimers.

[00012] In an embodiment, described herein is a compound represented by Formula I:



Formula I

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^1 and X^4 are each independently CR^5 or N;

X^5 and X^6 are each independently CH, CF, or N;

X^2 is N, CH, C=O, C-O-L²-E², C-L²-E², C-N(R⁴)-L²-E², or N-L²-E²;

X^3 is C-O-L³-E³, C-L³-E³, C-N(R⁴)-L³-E³, CH, C=O, N, or N-L³-E³,

provided that not more than two of X^1 , X^2 , X^3 , and X^4 are N;

provided that when X^2 is N, X^3 is C-O-L³-E³, C-L³-E³, C-N(R⁴)-L³-E³, N, or

CH;

provided that when X^3 is N, X^2 is N, CH, C-O-L²-E², C-L²-E², or C-N(R⁴)-L²-

E²;

provided that when X^2 is $C=O$, X^3 is $N-L^3-E^3$;

provided that when X^3 is $C=O$, X^2 is $N-L^2-E^2$;

L^1 is selected from a direct bond and a C_1 - C_6 alkyl optionally substituted with $(E^{11})_m$, or when taken together with R^3 and the N atom to which L^1 and R^3 are attached form an optionally substituted heterocycle having from 4 to 8 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

L^2 is a direct bond or a C_1 - C_6 alkyl optionally substituted with $(E^{21})_p$;

L^3 is a direct bond or a C_1 - C_6 alkyl optionally substituted with $(E^{31})_p$;

E^1 is selected from the group consisting of H, hydroxy, alkoxy, cyano, haloalkoxy, halogen,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, amine, alkylamine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of aryl, alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, heterocyclyl, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, and heterocyclyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, alkoxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E^{11} , at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{11} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

E² is selected from the group consisting of H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, sulfone, hydroxy, alkoxy, alkoxyalkyl, cyano, sulfonyl, and

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E²¹, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; or wherein two occurrences of E²¹ taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

E³ is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, sulfonyl, haloalkoxy, H, alkyl, acyl, amine, aminoalkyl, amide, haloalkyl, cyano, sulfone,

optionally substituted heterocyclyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted heteroaryl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

optionally substituted cycloalkyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E³¹, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E³¹ taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is L⁷-E⁷ wherein:

L⁷ is a direct bond

E⁷ is selected from the group consisting of:

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, cycloalkyl, alkoxy, alkoxyalkyl, amine, acyl, carbamoyl, formyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, urea, amine, amidine, acyl, carbamoyl, formyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

each occurrence of m is independently 0, 1, 2, 3, or 4;

each occurrence of p is independently 0, 1, or 2;

R¹ is selected from the group consisting of H, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, and halogen;

R² is selected from the group consisting of H and F;

R³ is selected from the group consisting of H, C₁-C₅alkyl, and C₃-C₆cycloalkyl;

R⁴, at each occurrence, is independently H or alkyl; and

R⁵, at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen;

with the proviso that

when E⁷ is morpholinyl, X² and X⁴ are both N, X³ is C-L³-E³, and L³ is a direct bond, then E³ is not heteroaryl;

when E⁷ is morpholinyl, X¹ and X⁴ are both N, X³ is C-L³-E³, and L³ is a direct bond, then E³ is not heteroaryl;

when E⁷ is morpholinyl, X¹, X⁴, X⁵, and X⁶ are CH, R¹ is -CH₃, X² is N, and X³ is C-L³-E³, then L³-E³ is not optionally substituted C₁-C₈ alkyl, optionally substituted C₃-C₆ cycloalkyl, optionally substituted C₄-C₈ cycloalkylalkyl, optionally substituted C₃-C₆ heterocyclyl, optionally substituted C₄-C₈ heterocyclylalkyl, optionally substituted 5- or 6-membered heteroaryl, or amide;

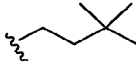
when X¹, X⁴, X⁵, and X⁶ are CH, R¹ is -CH₃, X² is N, X³ is C-L³-E³, L³ is a direct bond, and E³ is morpholinyl, then E⁷ is not optionally substituted C₃-C₆ heterocyclyl or optionally substituted 5- or 6-membered heteroaryl;

when E⁷ is morpholinyl, X¹ is CH, X² is N, X³ is C-O-L³-E³, X⁴ is CH, X⁶ is CH, CD, or CF, and R³ is H, then L¹-E¹ is not optionally substituted alkyl, optionally substituted C₃-C₆ cycloalkyl, optionally substituted C₃-C₆ cycloalkylalkyl, optionally substituted C₄-C₆ heterocyclyl, or optionally substituted heterocyclylalkyl; when E⁷ is morpholinyl, X¹ is CH,

X^2 is C-O- L^2 - E^2 , X^3 is N, X^4 is CH, X^6 is CH, CD, or CF, and R^3 is H, then L^1 - E^1 is not optionally substituted alkyl, optionally substituted C₃-C₆ cycloalkyl, optionally substituted C₃-C₆ cycloalkylalkyl, optionally substituted C₄-C₆ heterocyclyl, or optionally substituted heterocyclylalkyl;

when E^7 is morpholinyl, X^1 is CH, X^2 is N, X^3 is C-O- L^3 - E^3 , X^4 is CH, and X^6 is CH, CD, or CF, then L^1 is not taken together with R^3 and the N atom to which L^1 and R^3 are attached form an optionally substituted heterocycle having from 4 to 8 atoms in the ring structure;

when E^7 is morpholinyl, X^1 is CH, X^2 is C-O- L^2 - E^2 , X^3 is N, X^4 is CH, and X^6 is CH, CD, or CF, then L^1 is not taken together with R^3 and the N atom to which L^1 and R^3 are attached form an optionally substituted heterocycle having from 4 to 8 atoms in the ring structure;

when L^1 - E^1 is , R^1 is methyl, R^2 is H, R^3 is H, X^1 is N or CH, X^4 is N or CH, X^5 is N or CH, X^6 is CH, E^7 is a substituent selected from the group consisting of oxetanyl, tetrahydrofuranyl, and tetrahydropyranyl, and

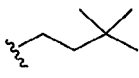
X^2 is selected from the group consisting of:

- (i) C- L^2 - E^2 , wherein L^2 - E^2 is selected from H;
- (ii) C-O- L^2 - E^2 , wherein O- L^2 - E^2 is selected from the group consisting of methoxy, ethoxy, isopropoxy, 2-methoxyethoxy, 2-hydroxyethoxy, (tetrahydro-2*H*-pyran-4-yl)oxy, and (1-ethylpiperidin-4-yl)oxy;
- (iii) C-N(R^4)- L^2 - E^2 , wherein N(R^4)- L^2 - E^2 is selected from the group consisting of (2-methoxyethyl)amino, (2-hydroxyethyl)(methyl)amino, and (1-hydroxypropan-2-yl)amino; and

(iv) N,

then X^3 is not selected from the group consisting of:

- (i) C- L^3 - E^3 , wherein L^3 - E^3 is selected from the group consisting of H, methyl, 3-hydroxyoxetan-3-yl, 4-hydroxy-piperidin-1-yl, 4-amino-4-methylpiperidin-1-yl, and 2-oxooxazolidin-3-yl;
- (ii) C-O- L^3 - E^3 , wherein O- L^3 - E^3 is selected from the group consisting of methoxy, 2-hydroxyethoxy, and 2,3-dihydroxypropoxy;
- (iii) C-N(R^4)- L^3 - E^3 , wherein N(R^4)- L^3 - E^3 is selected from the group consisting of bis(2-hydroxyethyl)amino and (2-hydroxyethyl)amino; and
- (iv) N;

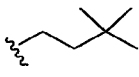
when L¹-E¹ is , R¹ is methyl, R² is H, R³ is H, X¹ is N or CH, X⁴ is N or CH, X⁵ is N or CH, X⁶ is CH, X³ is C-L³-E³, L³ is a direct bond, E³ is selected from the group consisting of oxetanyl, tetrahydrofuranyl, and tetrahydropyranyl, and

X² is selected from the group consisting of:

- (i) C-L²-E², wherein L²-E² is selected from H;
- (ii) C-O-L²-E², wherein O-L²-E² is selected from the group consisting of methoxy, ethoxy, isopropoxy, 2-methoxyethoxy, 2-hydroxyethoxy, (tetrahydro-2H-pyran-4-yl)oxy, and (1-ethylpiperidin-4-yl)oxy;
- (iii) C-N(R⁴)-L²-E², wherein N(R⁴)-L²-E² is selected from the group consisting of (2-methoxyethyl)amino, (2-hydroxyethyl)(methyl)amino, and (1-hydroxypropan-2-yl)amino; and

(iv) N,

then E⁷ is not selected from the group consisting of: 3-hydroxyoxetan-3-yl, 4-hydroxy-piperidin-1-yl, 4-amino-4-methylpiperidin-1-yl, and 2-oxooxazolidin-3-yl;§

when L¹-E¹ is , R¹ is methyl, R² is H, R³ is H, X¹ is N or CH, X⁴ is N or CH, X⁵ is N or CH, X⁶ is CH, E⁷ is a substituent selected from the group consisting of oxetanyl, tetrahydrofuranyl, and tetrahydropyranyl, X² is C=O, and X³ is N-L³-E³, then L³-E³ is not selected from the group consisting of: H, methyl, hydroxy-ethyl, hydroxy-propyl, and 2,3-dihydroxypropyl; and

when E⁷ is 5- or 6- membered optionally substituted heteroaryl or 5- or 6-membered optionally substituted heterocyclyl, X¹ and X⁴ are each independently N, CH, or CF, X⁵ is CH, X⁶ is CH, CD, or CF, X² is N, and X³ is C-O-L³-E³ or C-N(R⁴)-L³-E³, then L¹ is not taken together with R³ and the N atom to which L¹ and R³ are attached form an optionally substituted heterocycle having from 4 to 7 atoms in the ring structure.

[00013] In another embodiment, described herein is a pharmaceutical composition comprising a compound described herein (*e.g.*, a compound of the disclosure as described herein) and a pharmaceutically acceptable carrier or excipient.

[00014] In another embodiment, described herein is a method of treating a cancer in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound described herein (*e.g.*, a compound of the disclosure as described herein).

[00015] In another embodiment, described herein is a method of treating a disorder selected from the group consisting of histiocytosis, melanoma, multiple myeloma, thyroid cancer, ovarian cancer, colorectal cancer, colon cancer, pancreatic cancer, lung cancer, bladder cancer, gastrointestinal stromal tumors, solid tumors, blood-borne cancers, hairy cell leukemia, acute myelogenous leukemia (AML), and other cancers caused by activation of the RAS → RAF → MEK → ERK signaling pathway in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound described herein (*e.g.*, a compound of the disclosure as described herein).

DETAILED DESCRIPTION

[00016] The features and other details of the disclosure will now be more particularly described. Certain terms employed in the specification, examples and appended claims are collected here. These definitions should be read in light of the remainder of the disclosure and as understood by a person of skill in the art. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by a person of ordinary skill in the art.

Definitions

[00017] The definitions set forth in this application are intended to clarify terms used throughout this application.

[00018] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in art to which the subject matter herein belongs. As used in the specification and the appended claims, unless specified to the contrary, the following terms have the meaning indicated in order to facilitate the understanding of the present disclosure.

[00019] When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such substituent. Combinations of substituents, positions of substituents and/or variables are permissible only if such combinations result in stable compounds.

[00020] As used herein, the singular forms "a", "an", and "the" encompass plural references unless the context clearly indicates otherwise.

[00021] As used herein, the term "herein" means the entire application.

[00022] As used herein, "deuterated" mean that at least one hydrogen atom is replaced by deuterium. In any sample of a deuterated compound, some discrete molecules of the compound will likely have hydrogen, rather than deuterium, at the specified position. However, the percent of molecules of the deuterated compound which have deuterium at the specified position will be much greater than would naturally occur. The deuterium at the deuterated position is enriched.

[00023] As used herein, the terms "optional" or "optionally" mean that the subsequently described event or circumstance may occur or may not occur, and that the description includes instances where the event or circumstance occurs as well as instances in which it does not. For example, "optionally substituted alkyl" refers to the alkyl may be substituted as well as where the alkyl is not substituted.

[00024] It is understood that substituents and substitution patterns on the disclosed compounds can be selected by one of ordinary skilled person in the art to result chemically stable compounds which can be readily synthesized by techniques known in the art, as well as those methods set forth below, from readily available starting materials. If a substituent is itself substituted with more than one group, it is understood that these multiple groups may be on the same carbon or on different carbons, so long as a stable structure result.

[00025] As used herein, the term "optionally substituted" refers to the replacement of one to six hydrogen atoms in a given structure with the radical of a specified substituent including, but not limited to: hydroxyl, hydroxyalkyl, alkoxy, halogen, alkyl, aryl, cycloalkyl, heterocyclyl, amino, aminoalkyl, cyano, haloalkyl, haloalkoxy, -OC(=O)-CH₂-Oalkyl. Preferably, "optionally substituted" refers to the replacement of one to four hydrogen atoms in a given structure with the substituents mentioned above. More preferably, one to three hydrogen atoms are replaced by the substituents as mentioned above. It is understood that the substituent can be further substituted.

[00026] As used herein, the term "substituted" refers to moieties having substituents replacing a hydrogen on one or more carbons of the backbone. It will be understood that "substitution" or "substituted with" includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, *e.g.*, which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc. As used herein, the term "substituted" is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched, and unbranched, carbocyclic, and heterocyclic, aromatic, and non-aromatic

substituents of organic compounds. The permissible substituents can be one or more and the same or different for appropriate organic compounds. For purposes of this application, the heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms.

[00027] Substituents can include any substituents described herein, for example, Such substituents, if not otherwise specified, can include, for example, a halogen, a hydroxyl, a carbonyl (such as a carboxyl, an alkoxy carbonyl, a formyl, or an acyl), a thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), an alkoxy, a phosphoryl, a phosphate, a phosphonate, a phosphinate, an amino, an amido, an amidine, an imine, a cyano, a nitro, an azido, a sulfhydryl, an alkylthio, a sulfate, a sulfonate, a sulfamoyl, a sulfonamido, a sulfonyl, a heterocyclyl, an aralkyl, a heteroaralkyl, or an aromatic or heteroaromatic moiety. It will be understood by those skilled in the art that substituents can themselves be substituted, if appropriate. For instance, the substituents of a substituted alkyl may include substituted and unsubstituted forms of amino, azido, imino, amido, phosphoryl (including phosphonate and phosphinate), sulfonyl (including sulfate, sulfonamido, sulfamoyl and sulfonate), and silyl groups, as well as ethers, alkylthios, carbonyls (including ketones, aldehydes, carboxylates, and esters), -CF₃, -CN, and the like. Unless specifically stated as "unsubstituted," references to chemical moieties herein are understood to include substituted variants. For example, reference to an "aryl" group or moiety implicitly includes both substituted and unsubstituted variants.

[00028] As used herein, the term "alkyl" refers to a straight chained or branched non-aromatic hydrocarbon which is completely saturated. Typically, a straight chained or branched alkyl group has from 1 to about 20 carbon atoms, preferably from 1 to about 10, *e.g.*, may be C₁-C₁₀alkyl or *e.g.*, C₁-C₆alkyl unless otherwise defined. Examples of straight chained and branched alkyl groups include, but are not limited to, methyl, ethyl, 1-propyl (n-propyl), 2-propyl, n-butyl, sec-butyl, tertbutyl, 1-pentyl, 2-pentyl, 3-pentyl, neo-pentyl, 1-hexyl, 2-hexyl, 3-hexyl, 1-heptyl, 2-heptyl, 3-heptyl, 4-heptyl, 1-octyl, 2-octyl, 3-octyl or 4-octyl and the like. Moreover, the term "alkyl" used throughout the specification, examples, and claims is intended to include both "unsubstituted alkyls" and "substituted alkyls", the latter of which refers to alkyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. The "alkyl" group may be optionally substituted.

[00029] The term "C_x-C_y" when used in conjunction with a chemical moiety, such as, acyl, acyloxy, alkyl, alkenyl, alkynyl, or alkoxy is meant to include groups that contain from

x to y carbons in the chain. For example, the term "C_x-C_y" refers to substituted or unsubstituted saturated hydrocarbon groups, including straight-chain alkyl and branched-chain alkyl groups that contain from x to y carbons in the chain, including haloalkyl groups such as trifluoromethyl and 2,2,2-trifluoroethyl, etc. C₀ alkyl indicates a hydrogen where the group is in a terminal position, a bond if internal.

[00030] As used herein, the term "hydrocarbyl" refers to a group that is bonded through a carbon atom that does not have a =O or =S substituent, and typically has at least one carbon-hydrogen bond and a primarily carbon backbone but may optionally include heteroatoms. Thus, groups like methyl, ethoxyethyl, 2-pyridyl, and trifluoromethyl are considered to be hydrocarbyl for the purposes of this application, but substituents such as acetyl (which has a =O substituent on the linking carbon) and ethoxy (which is linked through oxygen, not carbon) are not. Hydrocarbyl groups include, but are not limited to aryl, heteroaryl, carbocycle, heterocyclyl, alkyl, alkenyl, alkynyl, and combinations thereof. The "hydrocarbyl" group may be optionally substituted.

[00031] As used herein, the term "alkoxy" refers to a straight or branched, saturated aliphatic (alkyl) hydrocarbon radical bonded to an oxygen atom that is attached to a core structure. Preferably, alkoxy groups have one to six carbon atoms, i.e., may be C₁-C₆ alkoxy. Examples of alkoxy groups include but are not limited to methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, pentoxy, 3-methyl butoxy, and the like. The "alkoxy" group may be optionally substituted.

[00032] As used herein, the term "alkoxyalkyl" refers to an alkyl group (as defined above) substituted with an alkoxy group and may be represented by the general formula alkyl-O-alkyl. Examples of alkoxyalkyl groups include but are not limited to methyl-O-ethylene-, ethyl-O-ethylene-. The "alkoxyalkyl" group may be optionally substituted.

[00033] As used herein, the term "haloalkyl" refers to alkyl group (as defined above) is substituted with one or more halogens. A monohaloalkyl radical, for example, may have a chlorine, bromine, iodine, or fluorine atom. Dihalo and polyhaloalkyl radicals may have two or more of the same or different halogen atoms. Examples of haloalkyl include, but are not limited to, chloromethyl, dichloromethyl, trichloromethyl, dichloroethyl, dichloropropyl, fluoromethyl, difluoromethyl, trifluoromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl and the like. The "haloalkyl" group may be optionally substituted.

[00034] As used herein, the term "haloalkoxy" refers to radicals wherein one or more of the hydrogen atoms of the alkoxy group are substituted with one or more halogens.

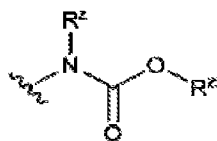
Representative examples of "haloalkoxy" groups include, but not limited to, difluoromethoxy (-OCHF₂), trifluoromethoxy (-OCF₃) or trifluoroethoxy (-OCH₂CF₃). The "haloalkoxy" group may be optionally substituted.

[00035] As used herein, the term "aryl" includes substituted or unsubstituted single-ring aromatic groups in which each atom of the ring is carbon. Preferably the ring is a 5- to 7-membered ring, more preferably a 6-membered ring. The term "aryl" also includes polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings (fused rings) wherein at least one of the rings is aromatic, *e.g.*, the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryl, and/or heterocyclyls. The term "fused" means that the second ring is attached or formed by having two adjacent atoms in common with the first ring. The term "fused" is equivalent to the term "condensed". Examples of aryl groups include but are not limited to phenyl, naphthyl, phenanthryl, phenol, aniline, or indanyl and the like. Unless otherwise specified, all aryl groups described herein may be optionally substituted.

[00036] As used herein, the terms "polycyclyl", "polycycle", and "polycyclic" refer to two or more rings (*e.g.*, cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryl, and/or heterocyclyls) in which one or more atoms are common to two adjoining rings, *e.g.*, the rings are "fused rings". Each of the rings of the polycycle can be substituted or unsubstituted. In certain embodiments, each ring of the polycycle contains from 3 to 10 atoms in the ring, preferably from 5 to 7.

[00037] As used herein, the term "acyl" refers to a group -C(=O)-R^w wherein R^w is optionally substituted alkyl. Examples of "acyl" include, but are not limited to, instances where R^w is C₁-C₁₀alkyl (C₁-C₁₀acyl) or C₁-C₆alkyl (C₁-C₆acyl). In some embodiments, each occurrence of the optionally substituted substituent is independently selected from the group consisting of H, OH, alkoxy, cyano, F, and amino. Additional examples of "acyl" include -C(=O)-CH₃, -C(=O)-CH₂-CH₃, -C(=O)-CH₂-CH₂-CH₃, or -C(=O)-CH(CH₃)₂.

[00038] As used herein, the term "carbamoyl" refers to a group represented by

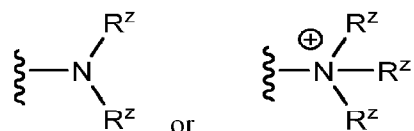


wherein R^z independently represents a hydrogen or optionally substituted hydrocarbyl group, or R^z groups taken together with the -N-C(=O)-O- moiety to which they are attached

complete a heterocycle having from 5 to 8 atoms in the ring structure which may be optionally substituted.

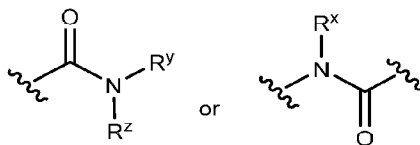
[00039] As used herein, the term “formyl” refers to a group $-\text{C}(=\text{O})\text{H}$.

[00040] As used herein, the terms "amine" and "amino" refer to both unsubstituted and substituted amines and salts thereof, *e.g.*, a moiety that can be represented by



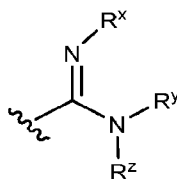
[00041] wherein R^Z independently represent a hydrogen or optionally substituted hydrocarbyl group, or R^Z groups are taken together with the N atom to which they are attached complete a heterocycle having from 4 to 8 atoms in the ring structure which may be optionally substituted.

[00042] As used herein, the terms "amide" and “amido” each refer to a group represented by



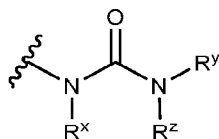
wherein R^X , R^Y , and R^Z each independently represents a hydrogen or optionally substituted hydrocarbyl group, or R^Y , and R^Z groups are taken together with the N atom to which they are attached complete a heterocycle having from 4 to 8 atoms in the ring structure which may be optionally substituted.

[00043] As used herein, the term “amidine” refers to a group represented by



wherein R^X , R^Y , and R^Z each independently represents a hydrogen or optionally substituted hydrocarbyl group, or R^Y , and R^Z groups are taken together with the N atom to which they are attached complete a heterocycle having from 4 to 8 atoms in the ring structure which may be optionally substituted.

[00044] As used herein, the term "urea" refers to a group represented by



wherein R^x , R^y , and R^z each independently represents a hydrogen or optionally substituted hydrocarbyl group, or R^y and R^z are taken together with the N atom to which they are attached complete a heterocycle having from 4 to 8 atoms in the ring structure which may be optionally substituted.

[00045] As used herein, the terms "alkylamino" and "alkylamine" refer to an amino group, as defined above, substituted with at least one alkyl group.

[00046] As used herein, the term "aminoalkyl" refers to an alkyl group substituted with an amino group.

[00047] As used herein, the term "amidoalkyl" refers to an alkyl group substituted with an amido group.

[00048] As used herein, the term "cyanoalkyl" refers to an alkyl group substituted with a cyano group.

[00049] As used herein, the term "alkylthio" refers to a thiol group substituted with an alkyl group and may be represented by the general formula alkyl-S-.

[00050] As used herein, the term "thioalkyl" refers to an alkyl group substituted with a thiol group.

[00051] As used herein, the term "hydroxyalkyl" refers to an alkyl group substituted with a hydroxy group.

[00052] As used herein, the term "cycloalkyl" alone or in combination with other term(s) refers to a cyclic hydrocarbon which is completely saturated. "Cycloalkyl" includes monocyclic, bicyclic, and tricyclic rings. Typically, a monocyclic cycloalkyl group has from 3 to about 10 carbon atoms, more typically 3 to 8 carbon atoms (*e.g.*, C₃-C₁₀cycloalkyl or *e.g.*, C₃-C₆cycloalkyl) unless otherwise defined. Examples of monocyclic cycloalkyls include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and the like. The second ring of a bicyclic cycloalkyl or, the second or third rings of a tricyclic cycloalkyl, may be selected from saturated, unsaturated, and aromatic rings. Cycloalkyl includes bicyclic and tricyclic molecules in which one, two or three or more atoms are shared between the two rings. The term "fused cycloalkyl" refers to a bicyclic or tricyclic cycloalkyl in which each of the rings shares two adjacent atoms with the other ring. The second ring of a fused bicyclic cycloalkyl or, the second or third rings of a fused tricyclic cycloalkyl, may be selected from saturated,

unsaturated, and aromatic rings. A "cycloalkenyl" group is a cyclic hydrocarbon containing one or more double bonds. Cycloalkyls can be further substituted with alkyls, alkenyls, alkoxys, alkylthios, aminoalkyls, carbonyl-substituted alkyls, -CF₃, -CN, and the like. A cycloalkyl may alternatively be polycyclic with more than two rings. Examples of polycyclic cycloalkyls include bridged, fused, and spirocyclic carbocyclyls.

[00053] As used interchangeably herein, the term "cycloalkylalkyl" or "carbocyclylalkyl" refers to an alkyl group substituted with a cycloalkyl group. Carbocyclyl and/or alkyl of carbocyclylalkyls can be further substituted as defined above for cycloalkyl and alkyl, respectively.

[00054] As used herein, the terms "carbocycle," or "carbocyclic" include bicyclic molecules in which one, two or three or more atoms are shared between the two rings. The term "fused carbocycle" refers to a bicyclic carbocycle in which each of the rings shares two adjacent atoms with the other ring. Each ring of a fused carbocycle may be selected from saturated, unsaturated, and aromatic rings. In an exemplary embodiment, an aromatic ring, *e.g.*, phenyl, may be fused to a saturated or unsaturated ring, *e.g.*, cyclohexane, cyclopentane, or cyclohexene. Any combination of saturated, unsaturated, and aromatic bicyclic rings, as valence permits, is included in the definition of carbocyclic. Exemplary "carbocycles" include cyclopentane, cyclohexane, bicyclo[2.2.1]heptane, 1,5-cyclooctadiene, 1,2,3,4-tetrahydronaphthalene, bicyclo[4.2.0]oct-3-ene, naphthalene and adamantane. Exemplary fused carbocycles include decalin, 4,5-naphthalene, 1,2,3,4-tetrahydronaphthalene, bicyclo[4.2.0]octane, 4,5,6,7-tetrahydro-1*H*-indene and bicyclo[4.1.0]hept-3-ene. "Carbocycles" may be substituted at any one or more positions capable of bearing a hydrogen atom.

[00055] As used herein, the term "cyano" refers to -CN group.

[00056] As used herein, the term "hydroxy" or "hydroxyl" refers to -OH group.

[00057] As used herein, the term "halo" or "halogen" alone or in combination with other term(s) means chloro, fluoro, bromo, and iodo.

[00058] As used herein, the term "heteroatom" refers an atom of any element other than carbon or hydrogen. Exemplary heteroatoms are nitrogen (N), oxygen (O), sulfur (S), and silicon (Si).

[00059] As used herein, the terms "heterocyclyl", "heterocycloalkyl", "heterocycle", and "heterocyclic" refer to a non-aromatic, saturated or partially saturated, including monocyclic, polycyclic (*e.g.*, bicyclic, tricyclic) bridged, or fused, ring system of 3 to 15 member having at least one heteroatom or heterogroup selected from O, N, S, S(O), S(O)₂,

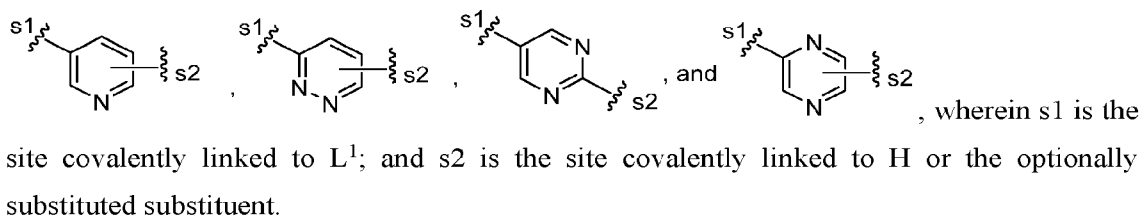
NH, or C(O) with the remaining ring atoms being independently selected from the group consisting of carbon, oxygen, nitrogen, and sulfur. Examples of "heterocyclyl" include, but are not limited to azetidiny, oxetanyl, imidazolidiny, pyrrolidiny, oxazolidiny, thiazolidiny, pyrazolidiny, tetrahydrofuranyl, piperidiny, piperaziny, tetrahydropyranyl, morpholiny, thiomorpholiny, 1,4-dioxanyl, dioxidothiomorpholiny, oxapiperaziny, oxapiperidiny, tetrahydrofuryl, tetrahydropyranyl, tetrahydrothiophenyl, dihydropyranyl, indoliny, indolinylmethyl, 2-azabicyclo[2.2.2]octanyl, azociny, chromanyl, xanthenyl and N-oxides thereof. Attachment of a heterocycloalkyl substituent can occur via either a carbon atom or a heteroatom. A heterocycloalkyl group can be optionally substituted with one or more suitable groups by one or more aforesaid groups. Preferably "heterocyclyl" refers to 4- to 6-membered ring selected from the group consisting of, imidazolidiny, pyrrolidiny, oxazolidiny, thiazolidiny, pyrazolidiny, tetrahydrofuranyl, piperidiny, piperaziny, tetrahydropyranyl, morpholiny, thiomorpholiny, 1,4-dioxanyl and N-oxides thereof. More preferably, "heterocycloalkyl" includes azetidiny, pyrrolidiny, morpholiny and piperidiny. All heterocycloalkyl are optionally substituted by one or more aforesaid groups.

[00060] As used herein, "heterocyclylalkyl" refers to an alkyl group substituted with a heterocyclyl. If the heterocyclyl is a nitrogen-containing heterocyclyl, the heterocyclyl is optionally attached to the alkyl radical at the nitrogen atom. Heterocyclyl and/or alkyl of heterocyclylalkyls can be further substituted as defined above for heterocyclyl and alkyl, respectively.

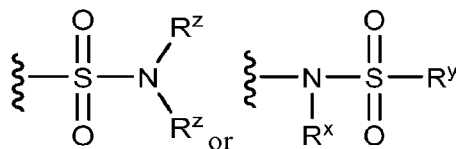
[00061] As used herein, the term "heteroaryl" refers to substituted or unsubstituted aromatic single ring structures, preferably 5- to 7-membered rings, more preferably 5- to 6-membered rings, whose ring structures include at least one heteroatom, preferably one to four heteroatoms, more preferably one or two heteroatoms. The term "heteroaryl" also refers to substituted or unsubstituted aromatic or partly aromatic ring systems containing at least one heteroatom and having two or more cyclic rings (bicyclic, tricyclic, or polycyclic), containing 8 to 20 ring atoms, suitably 5 to 10 ring atoms, which may be linked covalently, or fused in which two or more atoms are common to two adjoining rings wherein at least one of the rings is heteroaromatic, *e.g.*, the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryl, and/or heterocyclyl. The rings may contain an N or S atom, wherein the N or S atom is optionally oxidized, or the N atom is optionally quaternized. All heteroaryl are optionally substituted. Any suitable ring position of the heteroaryl moiety may be covalently linked to a defined chemical structure. Examples of heteroaryl include, but are not limited to: furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, cinnoliny,

isoxazolyl, thiazolyl, isothiazolyl, 1H-tetrazolyl, oxadiazolyl, thiadiazolyl, triazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzofuranyl, benzothieryl, benzotriazinyl, phthalazinyl, thianthrene, dibenzofuranyl, dibenzothieryl, benzimidazolyl, indolyl, isoindolyl, indazolyl, quinolynyl, isoquinolynyl, quinazolynyl, quinoxalynyl, purinyl, pteridinyl, 9H-carbazolyl, alpha-carboline, indolizynyl, benzoisothiazolyl, benzoxazolyl, pyrrolopyridyl, furopyridinyl, purinyl, benzothiadiazolyl, benzoxadiazolyl, benzotriazolyl, benzotriadiazolyl, 7-azaindolyl, 7-azaindazolyl, pyrrolopyridinyl, pyrrolopyrimidinyl, oxazolonepyridinyl, oxazolonepyrimidinyl, imidazolonepyridinyl, imidazolonepyrimidinyl, pyrazolopyridinyl, pyrazolopyrimidinyl, tetrahydronaphthyridinyl, tetrahydropyridolpyriminyl, dihydronaphthyridinonyl, naphthyridinonyl, oxazinanonepyridinyl, oxazinanonepyrimidinyl, carbazolyl, dibenzothieryl, acridinyl, and the like.

[00062] With respect to E¹ as described herein, E¹ is not a ring selected from the group consisting of



[00063] As used herein, the term "sulfonamide" is represented by:



wherein R^x, R^y and R^z, at each occurrence, independently represents a hydrogen, optionally substituted hydrocarbyl group, or R^z groups taken together with the N atom to which they are attached complete a heterocycle having from 4 to 8 atoms in the ring structure which may be optionally substituted.

[00064] As used herein, the term "sulfone" refers to the group -S(O)₂-R⁶ wherein R⁶ represents an optionally substituted hydrocarbyl.

[00065] As used herein, Z-H is an alcohol or amine wherein H is directly connected to an oxygen or nitrogen within the Z moiety.

[00066] As used herein, Z-B(OR)₂ is a boronic acid or boronic ester wherein boronate is directly bonded to a carbon within the Z moiety.

[00067] A “combination therapy” is a treatment that includes the administration of two or more therapeutic agents, *e.g.*, a compound of the disclosure and a MAPK pathway inhibitor, to a patient in need thereof.

[00068] “Disease,” “disorder,” and “condition” are used interchangeably herein.

[00069] “Individual,” “patient,” or “subject” are used interchangeably and include any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, and most preferably humans. The compounds described herein can be administered to a mammal, such as a human, but can also be administered to other mammals such as an animal in need of veterinary treatment, *e.g.*, domestic animals (*e.g.*, dogs, cats, and the like), farm animals (*e.g.*, cows, sheep, pigs, horses, and the like) and laboratory animals (*e.g.*, rats, mice, guinea pigs, and the like).

[00070] The MAPK pathway as used herein is the signal transduction pathway comprising RAS→RAF→MEK→ERK.

[00071] A “MAPK pathway inhibitor” is an inhibitor of the MAP kinase signaling pathway. Inhibitors of this pathway include RAS inhibitors (*e.g.*, AMG-510, MRTX 849), RAF inhibitors (*e.g.*, dabrafenib, vemurafenib, LY3009120, encorafenib), MEK inhibitors (*e.g.*, trametinib, binimetinib, selumetinib, cobimetinib), and ERK inhibitors (*e.g.*, ulixertinib, SCH772984, LY3214996). The terms “MAPK pathway inhibitor” and “MAPK kinase inhibitor” are used interchangeably herein.

[00072] “Pharmaceutically or pharmacologically acceptable” include molecular entities and compositions that do not produce an adverse, allergic, or other untoward reaction when administered to an animal, or a human, as appropriate. For human administration, preparations should meet sterility, pyrogenicity, and general safety and purity standards as required by FDA Office of Biologics standards.

[00073] The term “pharmaceutically acceptable carrier” or “pharmaceutically acceptable excipient” as used herein refers to any and all solvents, dispersion media, coatings, isotonic and absorption delaying agents, and the like, that are compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is well known in the art. The compositions may also contain other active compounds providing supplemental, additional, or enhanced therapeutic functions.

[00074] The term “pharmaceutical composition” as used herein refers to a composition comprising at least one compound as disclosed herein formulated together with one or more pharmaceutically acceptable carriers.

[00075] The term "pharmaceutically acceptable salt(s)" as used herein refers to salts of acidic or basic groups that may be present in compounds used in the compositions. Compounds included in the present compositions that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. The acids that may be used to prepare pharmaceutically acceptable acid addition salts of such basic compounds are those that form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, including, but not limited to, malate, oxalate, chloride, bromide, iodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, isonicotinate, acetate, lactate, salicylate, citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, *p*-toluenesulfonate and pamoate (i.e., 1,1'-methylene-*bis*-(2-hydroxy-3-naphthoate)) salts. Compounds included in the present compositions that are acidic in nature are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include alkali metal or alkaline earth metal salts, particularly calcium, magnesium, sodium, lithium, zinc, potassium, and iron salts. Compounds included in the present compositions that include a basic or acidic moiety may also form pharmaceutically acceptable salts with various amino acids. The compounds of the disclosure may contain both acidic and basic groups; for example, one amino and one carboxylic acid group. In such a case, the compound can exist as an acid addition salt, a zwitterion, or a base salt.

[00076] The compounds of the disclosure may contain one or more chiral centers and, therefore, exist as stereoisomers. The term "stereoisomers" when used herein consist of all enantiomers or diastereomers. These compounds may be designated by the symbols "R" or "S," depending on the configuration of substituents around the stereogenic carbon atom, but the skilled artisan will recognize that a structure may denote a chiral center implicitly. These compounds may also be designated by "(+)" and "(-)" based on their optical rotation properties. The presently described compounds encompasses various stereoisomers of these compounds and mixtures thereof. Mixtures of enantiomers or diastereomers may be designated by the symbol "(±)" in nomenclature, but the skilled artisan will recognize that a structure may denote a chiral center implicitly.

[00077] In the present specification, the term "therapeutically effective amount" means the amount of the subject compound that will elicit the biological or medical response of a tissue, system, or animal, (e.g., mammal or human) that is being sought by the researcher,

veterinarian, medical doctor or other clinician. The compounds described herein are administered in therapeutically effective amounts to treat a disorder.

[00078] “Treating” includes any effect, *e.g.*, lessening, reducing, modulating, or eliminating, that results in the improvement of the condition, disease, disorder, and the like.

[00079] The disclosure also embraces isotopically labeled compounds which are identical to those recited herein, except 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 the disclosed compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, and chlorine, such as ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , and ^{36}Cl , respectively. For example, a compound of the disclosure may have one or more H atom replaced with deuterium.

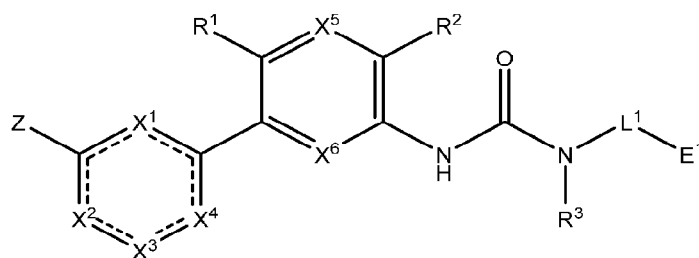
[00080] Individual enantiomers and diastereomers of the disclosed compounds can be prepared synthetically from commercially available starting materials that contain asymmetric or stereogenic centers, or by preparation of racemic mixtures followed by resolution methods well known to those of ordinary skill in the art. These methods of resolution are exemplified by (1) attachment of a mixture of enantiomers to a chiral auxiliary, separation of the resulting mixture of diastereomers by recrystallization or chromatography and liberation of the optically pure product from the auxiliary, (2) salt formation employing an optically active resolving agent, (3) direct separation of the mixture of optical enantiomers on chiral liquid chromatographic columns or (4) kinetic resolution using stereoselective chemical or enzymatic reagents. Racemic mixtures can also be resolved into their component enantiomers by well-known methods, such as chiral-phase liquid chromatography or crystallizing the compound in a chiral solvent. Stereoselective syntheses, a chemical or enzymatic reaction in which a single reactant forms an unequal mixture of stereoisomers during the creation of a new stereocenter or during the transformation of a pre-existing one, are well known in the art. Stereoselective syntheses encompass both enantio- and diastereoselective transformations and may involve the use of chiral auxiliaries. For examples, see Carreira and Kvaerno, *Classics in Stereoselective Synthesis*, Wiley-VCH: Weinheim, 2009.

[00081] As used herein, “compounds of the disclosure”, comprise compounds of Formula I, Formula I-A, Formula I-B, Formula I-C, Formula I-CA, Formula I-D, Formula I-DA, Formula I-E, Formula I-EA, Formula I-F, Formula I-FA, Formula I-FB, Formula I-G, Formula I-GA, Formula I-H, Formula I-HA, Formula I-J, Formula I-JA, Formula I-JB,

Formula I-JC, Formula I-K, Formula I-KA, Formula I-L, Formula I-LA, Formula I-M, Formula I-MA, Formula I-N, Formula I-NA, Formula I-O, Formula I-OA, Formula I-P, Formula I-PA, Formula I-Q, Formula I-QA, Formula I-R, Formula I-RA, Formula I-S, Formula I-SA, Formula I-T, and Formula I-TA.

Compounds

[00082] In an embodiment, provided herein is a compound represented by Formula I:



Formula I

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^1 and X^4 are each independently CR^5 or N;

X^5 and X^6 are each independently CH, CF, or N;

X^2 is N, CH, C=O, C-O- L^2 - E^2 , C- L^2 - E^2 , C-N(R^4)- L^2 - E^2 , or N- L^2 - E^2 ;

X^3 is C-O- L^3 - E^3 , C- L^3 - E^3 , C-N(R^4)- L^3 - E^3 , CH, C=O, N, or N- L^3 - E^3 ,

provided that not more than two of X^1 , X^2 , X^3 , and X^4 are N;

provided that when X^2 is N, X^3 is C-O- L^3 - E^3 , C- L^3 - E^3 , C-N(R^4)- L^3 - E^3 , N, or

CH;

provided that when X^3 is N, X^2 is N, CH, C-O- L^2 - E^2 , C- L^2 - E^2 , or C-N(R^4)- L^2 -

E^2 ;

provided that when X^2 is C=O, X^3 is N- L^3 - E^3 ;

provided that when X^3 is C=O, X^2 is N- L^2 - E^2 ;

L^1 is selected from a direct bond and a C_1 - C_6 alkyl optionally substituted with $(E^{11})_m$, or when taken together with R^3 and the N atom to which L^1 and R^3 are attached form an optionally substituted heterocycle having from 4 to 8 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

L^2 is a direct bond or a C_1 - C_6 alkyl optionally substituted with $(E^{21})_p$;

L³ is a direct bond or a C₁-C₆alkyl optionally substituted with (E³¹)_p;

E¹ is selected from the group consisting of H, hydroxy, alkoxy, cyano, haloalkoxy, halogen,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, amine, alkylamine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of aryl, alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, heterocyclyl, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, and heterocyclyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, alkoxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E¹¹, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E¹¹ taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

E² is selected from the group consisting of H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, sulfone, hydroxy, alkoxy, alkoxyalkyl, cyano, sulfonyl, and

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E²¹, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E²¹ taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

E³ is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, sulfonyl, haloalkoxy, H, alkyl, acyl, amine, aminoalkyl, amide, haloalkyl, cyano, sulfone, optionally substituted heterocyclyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted heteroaryl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

optionally substituted cycloalkyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E³¹, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E³¹ taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is L⁷-E⁷ wherein:

L⁷ is a direct bond

E⁷ is selected from the group consisting of:

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, cycloalkyl, alkoxy, alkoxyalkyl, amine, acyl, carbamoyl, formyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, urea, amine, amidine, acyl, carbamoyl, formyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

each occurrence of m is independently 0, 1, 2, 3, or 4;

each occurrence of p is independently 0, 1, or 2;

R¹ is selected from the group consisting of H, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, and halogen;

R² is selected from the group consisting of H and F;

R³ is selected from the group consisting of H, C₁-C₅alkyl, and C₃-C₅cycloalkyl;

R⁴, at each occurrence, is independently H or alkyl; and

R⁵, at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen;

with the proviso that

when E⁷ is morpholinyl, X² and X⁴ are both N, X³ is C-L³-E³, and L³ is a direct bond, then E³ is not heteroaryl;

when E⁷ is morpholinyl, X¹ and X⁴ are both N, X³ is C-L³-E³, and L³ is a direct bond, then E³ is not heteroaryl;

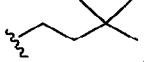
when E⁷ is morpholinyl, X¹, X⁴, X⁵, and X⁶ are CH, R¹ is -CH₃, X² is N, and X³ is C-L³-E³, then L³-E³ is not optionally substituted C₁-C₈ alkyl, optionally substituted C₃-C₆ cycloalkyl, optionally substituted C₄-C₈ cycloalkylalkyl, optionally substituted C₃-C₆ heterocyclyl, optionally substituted C₄-C₈ heterocyclylalkyl, optionally substituted 5- or 6-membered heteroaryl, or amide;

when X¹, X⁴, X⁵, and X⁶ are CH, R¹ is -CH₃, X² is N, X³ is C-L³-E³, L³ is a direct bond, and E³ is morpholinyl, then E⁷ is not optionally substituted C₃-C₆ heterocyclyl or optionally substituted 5- or 6-membered heteroaryl;

when E⁷ is morpholinyl, X¹ is CH, X² is N, X³ is C-O-L³-E³, X⁴ is CH, X⁶ is CH, CD, or CF, and R³ is H, then L¹-E¹ is not optionally substituted alkyl, optionally substituted C₃-C₆ cycloalkyl, optionally substituted C₃-C₆ cycloalkylalkyl, optionally substituted C₄-C₆ heterocyclyl, or optionally substituted heterocyclylalkyl; when E⁷ is morpholinyl, X¹ is CH, X² is C-O-L²-E², X³ is N, X⁴ is CH, X⁶ is CH, CD, or CF, and R³ is H, then L¹-E¹ is not optionally substituted alkyl, optionally substituted C₃-C₆ cycloalkyl, optionally substituted C₃-C₆ cycloalkylalkyl, optionally substituted C₄-C₆ heterocyclyl, or optionally substituted heterocyclylalkyl;

when E⁷ is morpholinyl, X¹ is CH, X² is N, X³ is C-O-L³-E³, X⁴ is CH, and X⁶ is CH, CD, or CF, then L¹ is not taken together with R³ and the N atom to which L¹ and R³ are attached form an optionally substituted heterocycle having from 4 to 8 atoms in the ring structure;

when E^7 is morpholinyl, X^1 is CH, X^2 is C-O- L^2 - E^2 , X^3 is N, X^4 is CH, and X^6 is CH, CD, or CF, then L^1 is not taken together with R^3 and the N atom to which L^1 and R^3 are attached form an optionally substituted heterocycle having from 4 to 8 atoms in the ring structure;

when L^1 - E^1 is , R^1 is methyl, R^2 is H, R^3 is H, X^1 is N or CH, X^4 is N or CH, X^5 is N or CH, X^6 is CH, E^7 is a substituent selected from the group consisting of oxetanyl, tetrahydrofuranyl, and tetrahydropyranyl, and

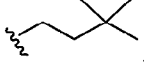
X^2 is selected from the group consisting of:

- (i) C- L^2 - E^2 , wherein L^2 - E^2 is selected from H;
- (ii) C-O- L^2 - E^2 , wherein O- L^2 - E^2 is selected from the group consisting of methoxy, ethoxy, isopropoxy, 2-methoxyethoxy, 2-hydroxyethoxy, (tetrahydro-2H-pyran-4-yl)oxy, and (1-ethylpiperidin-4-yl)oxy;
- (iii) C-N(R^4)- L^2 - E^2 , wherein N(R^4)- L^2 - E^2 is selected from the group consisting of (2-methoxyethyl)amino, (2-hydroxyethyl)(methyl)amino, and (1-hydroxypropan-2-yl)amino; and

(iv) N,

then X^3 is not selected from the group consisting of:

- (i) C- L^3 - E^3 , wherein L^3 - E^3 is selected from the group consisting of H, methyl, 3-hydroxyoxetan-3-yl, 4-hydroxy-piperidin-1-yl, 4-amino-4-methylpiperidin-1-yl, and 2-oxooxazolidin-3-yl;
- (ii) C-O- L^3 - E^3 , wherein O- L^3 - E^3 is selected from the group consisting of methoxy, 2-hydroxyethoxy, and 2,3-dihydroxypropoxy;
- (iii) C-N(R^4)- L^3 - E^3 , wherein N(R^4)- L^3 - E^3 is selected from the group consisting of bis(2-hydroxyethyl)amino and (2-hydroxyethyl)amino; and
- (iv) N;

when L^1 - E^1 is , R^1 is methyl, R^2 is H, R^3 is H, X^1 is N or CH, X^4 is N or CH, X^5 is N or CH, X^6 is CH, X^3 is C- L^3 - E^3 , L^3 is a direct bond, E^3 is selected from the group consisting of oxetanyl, tetrahydrofuranyl, and tetrahydropyranyl, and

X^2 is selected from the group consisting of:

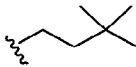
- (i) C- L^2 - E^2 , wherein L^2 - E^2 is selected from H;

(ii) C-O-L²-E², wherein O-L²-E² is selected from the group consisting of methoxy, ethoxy, isopropoxy, 2-methoxyethoxy, 2-hydroxyethoxy, (tetrahydro-2H-pyran-4-yl)oxy, and (1-ethylpiperidin-4-yl)oxy;

(iii) C-N(R⁴)-L²-E², wherein N(R⁴)-L²-E² is selected from the group consisting of (2-methoxyethyl)amino, (2-hydroxyethyl)(methyl)amino, and (1-hydroxypropan-2-yl)amino; and

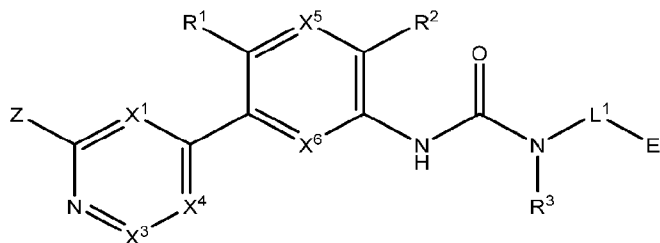
(iv) N,

then E⁷ is not selected from the group consisting of: 3-hydroxyoxetan-3-yl, 4-hydroxy-piperidin-1-yl, 4-amino-4-methylpiperidin-1-yl, and 2-oxooxazolidin-3-yl;

when L¹-E¹ is , R¹ is methyl, R² is H, R³ is H, X¹ is N or CH, X⁴ is N or CH, X⁵ is N or CH, X⁶ is CH, E⁷ is a substituent selected from the group consisting of oxetanyl, tetrahydrofuranyl, and tetrahydropyranyl, X² is C=O, and X³ is N-L³-E³, then L³-E³ is not selected from the group consisting of: H, methyl, hydroxy-ethyl, hydroxy-propyl, and 2,3-dihydroxypropyl; and

when E⁷ is 5- or 6- membered optionally substituted heteroaryl or 5- or 6-membered optionally substituted heterocyclyl, X¹ and X⁴ are each independently N, CH, or CF, X⁵ is CH, X⁶ is CH, CD, or CF, X² is N, and X³ is C-O-L³-E³ or C-N(R⁴)-L³-E³, then L¹ is not taken together with R³ and the N atom to which L¹ and R³ are attached form an optionally substituted heterocycle having from 4 to 7 atoms in the ring structure.

[00083] In some embodiments, the compound is represented by Formula I-A:



Formula I-A

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X¹ and X⁴ are each independently CH, CR⁵, or N;

X³ is C-O-L³-E³, C-L³-E³, C-N(R⁴)-L³-E³, CH or N;

X⁵ and X⁶ are each independently CH, CF, or N;

provided that not more than one of X¹, X³, and X⁴ are N;

L¹ is selected from a direct bond and a C₁-C₆alkyl optionally substituted with (E¹¹)_m, or when taken together with R³ and the N atom to which L¹ and R³ are attached form an optionally substituted heterocycle having from 4 to 8 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

L³ is a direct bond or a C₁-C₆ alkyl optionally substituted with (E³¹)_p;

E¹ is selected from the group consisting of H, hydroxy, alkoxy, cyano, haloalkoxy, halogen,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, amine, alkylamine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of aryl, alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, heterocyclyl, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano and heterocyclyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, alkoxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E¹¹, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; or wherein two occurrences of E¹¹ taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

E³ is selected from the group consisting of H, alkyl, acyl, amine, aminoalkyl, amide, haloalkyl, cyano, sulfone, haloalkoxy, hydroxy, alkoxy, alkoxyalkyl, sulfonyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy,

alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E^{31} , at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{31} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is L^7-E^7 wherein:

L^7 is a direct bond;

E^7 is selected from the group consisting of:

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, cycloalkyl, alkoxy, alkoxyalkyl, amine, acyl, carbamoyl, formyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, urea, amine, amidine, acyl, carbamoyl, formyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

each occurrence of m is independently 0, 1, 2, 3, or 4;

each occurrence of p is independently 0, 1, or 2;

R^1 is selected from the group consisting of H, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, and halogen;

R^2 is selected from the group consisting of H and F;

R^3 is selected from the group consisting of H, C_1 - C_5 alkyl, and C_3 - C_5 cycloalkyl;

R^4 , at each occurrence, is independently H or alkyl; and

R^5 , at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen;

with the proviso that

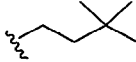
when E^7 is morpholinyl, X^4 is N, X^3 is $C-L^3-E^3$, and L^3 is a direct bond, then E^3 is not heteroaryl;

when E^7 is morpholinyl, X^1 , X^4 , X^5 , and X^6 are CH, R^1 is $-CH_3$, and X^3 is $C-L^3-E^3$, then L^3-E^3 is not optionally substituted C_1 - C_8 alkyl, optionally substituted C_3 - C_6 cycloalkyl, optionally substituted C_4 - C_8 cycloalkylalkyl, optionally substituted C_3 - C_6 heterocyclyl, optionally substituted C_4 - C_8 heterocyclalkyl, optionally substituted 5- or 6-membered heteroaryl, or amide;

when X^1 , X^4 , X^5 , and X^6 are CH, R^1 is $-CH_3$, X^3 is $C-L^3-E^3$, L^3 is a direct bond, and E^3 is morpholinyl, then E^7 is not optionally substituted C_3 - C_6 heterocyclyl or optionally substituted 5- or 6-membered heteroaryl;

when E^7 is morpholinyl, X^1 is CH, X^3 is $C-O-L^3-E^3$, X^4 is CH, X^6 is CH or CF, and R^3 is H, then L^1-E^1 is not optionally substituted alkyl, optionally substituted C_3 - C_6 cycloalkyl, optionally substituted C_3 - C_6 cycloalkylalkyl, optionally substituted C_4 - C_6 heterocyclyl, or optionally substituted heterocyclalkyl;

when E^7 is morpholinyl, X^1 is CH, X^3 is $C-O-L^3-E^3$, X^4 is CH, and X^6 is CH, CD, or CF, then L^1 is not taken together with R^3 and the N atom to which L^1 and R^3 are attached form an optionally substituted heterocycle having from 4 to 8 atoms in the ring structure;

when L^1-E^1 is , R^1 is methyl, R^2 is H, R^3 is H, X^1 is N or CH, X^4 is N or CH, X^5 is N or CH, X^6 is CH, and E^7 is a substituent selected from the group consisting of oxetanyl, tetrahydrofuranyl, and tetrahydropyranyl,

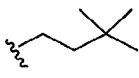
then X^3 is not selected from the group consisting of:

(i) $C-L^3-E^3$, wherein L^3-E^3 is selected from the group consisting of H, methyl, 3-hydroxyoxetan-3-yl, 4-hydroxy-piperidin-1-yl, 4-amino-4-methylpiperidin-1-yl, and 2-oxooxazolidin-3-yl;

(ii) $C-O-L^3-E^3$, wherein $O-L^3-E^3$ is selected from the group consisting of methoxy, 2-hydroxyethoxy, and 2,3-dihydroxypropoxy;

(iii) $C-N(R^4)-L^3-E^3$, wherein $N(R^4)-L^3-E^3$ is selected from the group consisting of bis(2-hydroxyethyl)amino and (2-hydroxyethyl)amino; and

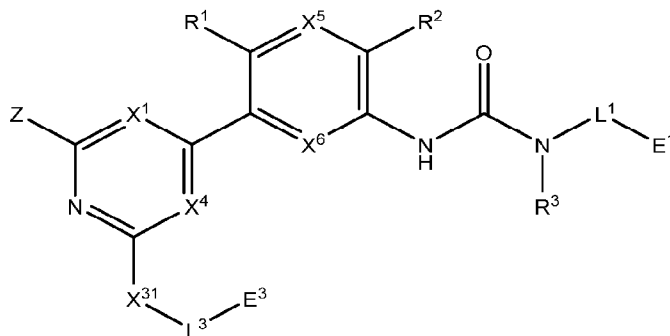
(iv) N;

when L^1-E^1 is , R^1 is methyl, R^2 is H, R^3 is H, X^1 is N or CH, X^4 is N or CH, X^5 is N or CH, X^6 is CH, X^3 is C- L^3 - E^3 , L^3 is a direct bond, and E^3 is selected from the group consisting of oxetanyl, tetrahydrofuranyl, and tetrahydropyranyl,

then E^7 is not selected from the group consisting of: 3-hydroxyoxetan-3-yl, 4-hydroxy-piperidin-1-yl, 4-amino-4-methylpiperidin-1-yl, and 2-oxooxazolidin-3-yl; and

when E^7 is 5- or 6- membered optionally substituted heteroaryl or 5- or 6-membered optionally substituted heterocyclyl, X^1 and X^4 are each independently N, CH, or CF, X^5 is CH, X^6 is CH, CD, or CF, X^2 is N, and X^3 is C-O- L^3 - E^3 or C-N(R^4)- L^3 - E^3 , then L^1 is not taken together with R^3 and the N atom to which L^1 and R^3 are attached form an optionally substituted heterocycle having from 4 to 7 atoms in the ring structure.

[00084] In some embodiments, the compound is represented by Formula I-B:



Formula I-B

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^1 and X^4 are each independently CH, CR^5 , or N;

provided that not more than one of X^1 and X^4 are N;

X^5 and X^6 are each independently CH, CF, or N;

X^{31} is O or N(R^4);

L^1 is selected from a direct bond and a C_1 - C_6 alkyl optionally substituted with $(E^{11})_m$, or when taken together with R^3 and the N atom to which L^1 and R^3 are attached form an optionally substituted heterocycle having from 4 to 8 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

L^3 is a direct bond or a C_1 - C_6 alkyl optionally substituted with $(E^{31})_p$;

E¹ is selected from the group consisting of H, hydroxy, alkoxy, cyano, haloalkoxy, halogen,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, amine, alkylamine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of aryl, alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, heterocyclyl, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano and heterocyclyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, alkoxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E¹¹, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E¹¹ taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

E³ is selected from the group consisting of haloalkoxy, H, alkyl, acyl, amine, aminoalkyl, amide, haloalkyl, cyano, sulfone, hydroxy, alkoxy, alkoxyalkyl, cyano, sulfonyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E^{31} , at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{31} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is L^7-E^7 wherein:

L^7 is a direct bond;

E^7 is selected from the group consisting of:

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, cycloalkyl, alkoxy, alkoxyalkyl, amine, acyl, carbamoyl, formyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, urea, amine, amidine, acyl, carbamoyl, formyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

each occurrence of m is independently 0, 1, 2, 3, or 4;

each occurrence of p is independently 0, 1, or 2;

R^1 is selected from the group consisting of H, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, and halogen;

R^2 is selected from the group consisting of H and F;

R^3 is selected from the group consisting of H, C_1 - C_5 alkyl, and C_3 - C_5 cycloalkyl;

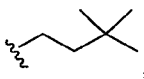
R^4 , at each occurrence, is independently H or alkyl; and

R^5 , at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen;

with the proviso that

when E^7 is morpholinyl, X^1 is CH, X^{31} is O, X^4 is CH, X^6 is CH or CF, and R^3 is H, then L^1-E^1 is not optionally substituted alkyl, optionally substituted C_3 - C_6 cycloalkyl, optionally substituted C_3 - C_6 cycloalkylalkyl, optionally substituted C_4 - C_6 heterocyclyl, or optionally substituted heterocyclylalkyl;

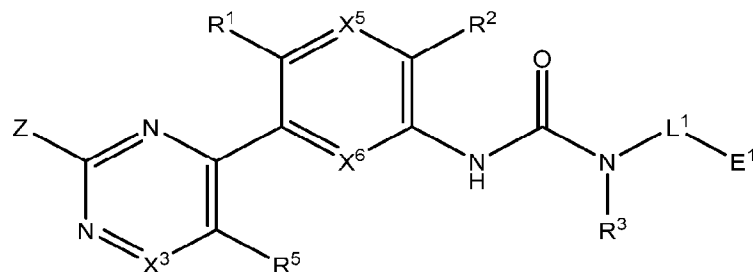
when E^7 is morpholinyl, X^1 is CH, X^{31} is O, X^4 is CH, and X^6 is CH, CD, or CF, then L^1 is not taken together with R^3 and the N atom to which L^1 and R^3 are attached form an optionally substituted heterocycle having from 4 to 8 atoms in the ring structure;

when L^1-E^1 is , R^1 is methyl, R^2 is H, R^3 is H, X^1 is N or CH, X^4 is N or CH, X^5 is N or CH, X^6 is CH, and E^7 is a substituent selected from the group consisting of oxetanyl, tetrahydrofuranyl, and tetrahydropyranyl,

then $X^{31}-L^3-E^3$ is not selected from the group consisting of: methoxy, 2-hydroxyethoxy, 2,3-dihydroxypropoxy, bis(2-hydroxyethyl)amino, and (2-hydroxyethyl)amino; and

when E^7 is 5- or 6- membered optionally substituted heteroaryl or 5- or 6-membered optionally substituted heterocyclyl, X^1 and X^4 are each independently N, CH, or CF, X^5 is CH, and X^6 is CH, CD, or CF, then L^1 is not taken together with R^3 and the N atom to which L^1 and R^3 are attached form an optionally substituted heterocycle having from 4 to 7 atoms in the ring structure.

[00085] In some embodiments, the compound is represented by Formula I-C:



Formula I-C

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^3 is C-O- L^3-E^3 , C- L^3-E^3 , C-N(R^4)- L^3-E^3 , or CH;

X^5 and X^6 are each independently CH, CF, or N;

L^1 is selected from a direct bond and a C₁-C₆alkyl optionally substituted with $(E^{11})_m$, or when taken together with R^3 and the N atom to which L^1 and R^3 are attached form an optionally substituted heterocycle having from 4 to 8 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

L^3 is a direct bond or a C₁-C₆ alkyl optionally substituted with $(E^{31})_p$;

E¹ is selected from the group consisting of H, hydroxy, alkoxy, cyano, haloalkoxy, halogen,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, amine, alkylamine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of aryl, alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, heterocyclyl, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano and heterocyclyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, alkoxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently H, alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E¹¹, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E¹¹ taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

E³ is selected from the group consisting of haloalkoxy, H, alkyl, acyl, amine, aminoalkyl, amide, haloalkyl, cyano, sulfone, hydroxy, alkoxy, alkoxyalkyl, cyano, sulfonyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently H, alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently H, alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E^{31} , at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{31} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is L^7-E^7 wherein:

L^7 is a direct bond;

E^7 is selected from the group consisting of:

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, cycloalkyl, alkoxy, alkoxyalkyl, amine, acyl, carbamoyl, formyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, urea, amine, amidine, acyl, carbamoyl, formyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

each occurrence of m is independently 0, 1, 2, 3, or 4;

each occurrence of p is independently 0, 1, or 2;

R^1 is selected from the group consisting of H, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, and halogen;

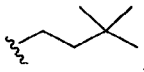
R^2 is selected from the group consisting of H and F;

R^3 is selected from the group consisting of H, C_1 - C_5 alkyl, and C_3 - C_5 cycloalkyl;

R^4 , at each occurrence, is independently H or alkyl; and

R^5 , at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen,

with the proviso that

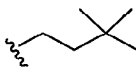
when L^1-E^1 is , R^1 is methyl, R^2 is H, R^3 is H, X^4 is CH, X^5 is N or CH, X^6 is CH, and E^7 is a substituent selected from the group consisting of oxetanyl, tetrahydrofuranyl, and tetrahydropyranyl,

then X^3 is not selected from the group consisting of:

(i) C-L³-E³, wherein L³-E³ is selected from the group consisting of H, methyl, 3-hydroxyoxetan-3-yl, 4-hydroxy-piperidin-1-yl, 4-amino-4-methylpiperidin-1-yl, and 2-oxooxazolidin-3-yl;

(ii) C-O-L³-E³, wherein O-L³-E³ is selected from the group consisting of methoxy, 2-hydroxyethoxy, and 2,3-dihydroxypropoxy; and

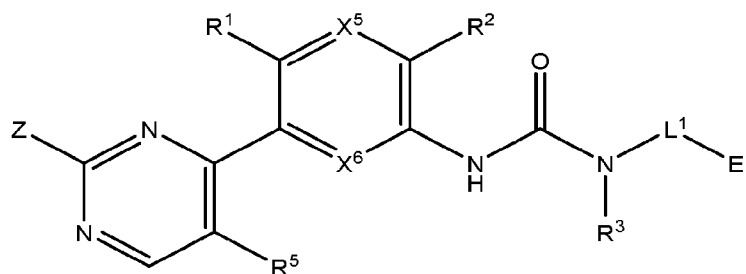
(iii) C-N(R⁴)-L³-E³, wherein N(R⁴)-L³-E³ is selected from the group consisting of bis(2-hydroxyethyl)amino and (2-hydroxyethyl)amino; and

when L¹-E¹ is , R¹ is methyl, R² is H, R³ is H, X⁴ is CH, X⁵ is N or CH, X⁶ is CH, X³ is C-L³-E³, L³ is a direct bond, and E³ is selected from the group consisting of oxetanyl, tetrahydrofuranyl, and tetrahydropyranyl,

then E⁷ is not selected from the group consisting of: 3-hydroxyoxetan-3-yl, 4-hydroxy-piperidin-1-yl, 4-amino-4-methylpiperidin-1-yl, and 2-oxooxazolidin-3-yl; and

when E⁷ is 5- or 6- membered optionally substituted heteroaryl or 5- or 6-membered optionally substituted heterocyclyl, R⁵ is H or F, X⁵ is CH, X⁶ is CH, CD, or CF, and X³ is C-O-L³-E³ or C-N(R⁴)-L³-E³, then L¹ is not taken together with R³ and the N atom to which L¹ and R³ are attached form an optionally substituted heterocycle having from 4 to 7 atoms in the ring structure.

[00086] In some embodiments, the compound is represented by Formula I-CA:



Formula I-CA

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X⁵ and X⁶ are each independently CH, CF, or N;

L¹ is selected from a direct bond and a C₁-C₆alkyl optionally substituted with (E¹¹)_m, or when taken together with R³ and the N atom to which L¹ and R³ are attached form an optionally substituted heterocycle having from 4 to 8 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently selected from the

group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E¹ is selected from the group consisting of hydroxy, alkoxy, cyano, haloalkoxy, halogen,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, amine, alkylamine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of aryl, alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, heterocyclyl, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano and heterocyclyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, alkoxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently H, alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E¹¹, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E¹¹ taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is L⁷-E⁷ wherein:

L⁷ is a direct bond;

E⁷ is optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, urea, amine, amidine, acyl, carbamoyl, formyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

each occurrence of m is independently 0, 1, 2, 3, or 4;

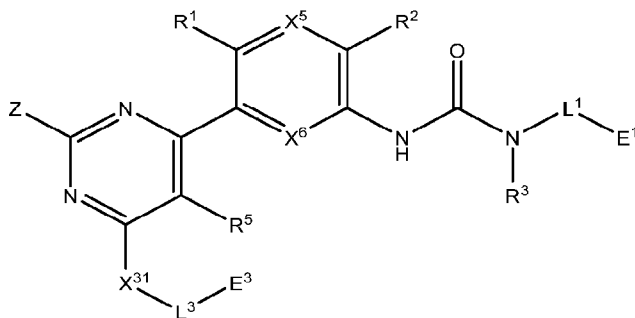
R¹ is selected from the group consisting of H, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, and halogen;

R^2 is selected from the group consisting of H and F;

R^3 is selected from the group consisting of H, C₁-C₅ alkyl, and C₃-C₅ cycloalkyl; and

R^5 , at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen.

[00087] In some embodiments, the compound is represented by Formula I-D:



Formula I-D

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^{31} is O or N(R⁴);

X^5 and X^6 are each independently CH, CF, or N;

L^1 is selected from a direct bond and a C₁-C₆alkyl optionally substituted with (E¹¹)_m, or when taken together with R³ and the N atom to which L¹ and R³ are attached form an optionally substituted heterocycle having from 4 to 8 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

L^3 is a direct bond or a C₁-C₆ alkyl optionally substituted with (E³¹)_p;

E¹ is selected from the group consisting of H, hydroxy, alkoxy, cyano, haloalkoxy, halogen,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, amine, alkylamine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of aryl, alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, heterocyclyl, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano and heterocyclyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, alkoxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E^{11} , at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; or wherein two occurrences of E^{11} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

E^3 is selected from the group consisting of haloalkoxy, H, alkyl, acyl, amine, aminoalkyl, amide, haloalkyl, cyano, sulfone, hydroxy, alkoxy, alkoxyalkyl, cyano, sulfonyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E^{31} , at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{31} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is L^7-E^7 wherein:

L^7 is a direct bond;

E^7 is selected from the group consisting of:

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, cycloalkyl, alkoxy, alkoxyalkyl, amine, acyl, carbamoyl, formyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, urea, amine, amidine, acyl, carbamoyl, formyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

each occurrence of m is independently 0, 1, 2, 3, or 4;

each occurrence of p is independently 0, 1, or 2;

R^1 is selected from the group consisting of H, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, and halogen;

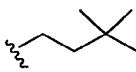
R^2 is selected from the group consisting of H and F;

R^3 is selected from the group consisting of H, C_1 - C_5 alkyl, and C_3 - C_5 cycloalkyl;

R^4 , at each occurrence, is independently H or alkyl; and

R^5 , at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen,

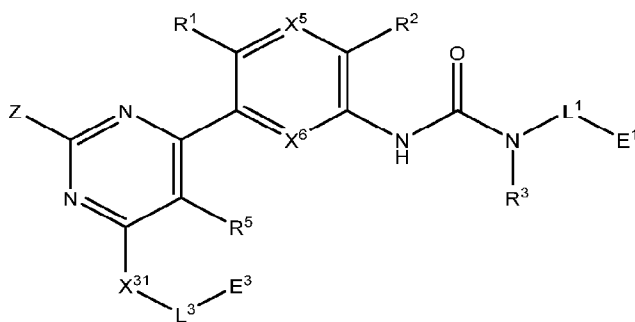
with the proviso that

when L^1 - E^1 is , R^1 is methyl, R^2 is H, R^3 is H, X^4 is CH, X^5 is N or CH, X^6 is CH, and E^7 is a substituent selected from the group consisting of oxetanyl, tetrahydrofuranyl, and tetrahydropyranyl,

then X^{31} - L^3 - E^3 is not selected from the group consisting of methoxy, 2-hydroxyethoxy, 2,3-dihydroxypropoxy, bis(2-hydroxyethyl)amino, and (2-hydroxyethyl)amino; and

when E^7 is 5- or 6- membered optionally substituted heteroaryl or 5- or 6-membered optionally substituted heterocyclyl, R^5 is H or F, X^5 is CH, and X^6 is CH, CD, or CF, then L^1 is not taken together with R^3 and the N atom to which L^1 and R^3 are attached form an optionally substituted heterocycle having from 4 to 7 atoms in the ring structure.

[00088] In some embodiments, the compound is represented by Formula I-DA:



Formula I-DA

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^{31} is O or N(R^4);

X^5 and X^6 are each independently CH, CF, or N;

L^1 is selected from a direct bond and a C_1 - C_6 alkyl optionally substituted with $(E^{11})_m$, or when X^5 is N, L^1 may be taken together with R^3 and the N atom to which L^1 and R^3 are attached form an optionally substituted heterocycle having from 4 to 8 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

L^3 is a direct bond or a C_1 - C_6 alkyl optionally substituted with $(E^{31})_p$;

E^1 is selected from the group consisting of hydroxy, alkoxy, cyano, haloalkoxy, halogen,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, amine, alkylamine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of aryl, alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, heterocyclyl, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano and heterocyclyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, alkoxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E¹¹, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E¹¹ taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

E³ is selected from the group consisting of haloalkoxy, alkyl, acyl, amine, aminoalkyl, amide, haloalkyl, cyano, sulfone, hydroxy, alkoxy, alkoxyalkyl, cyano, sulfonyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E³¹, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E³¹ taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is L⁷-E⁷ wherein:

L⁷ is a direct bond;

E⁷ is optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, urea, amine, amidine, acyl, carbamoyl, formyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

each occurrence of m is independently 0, 1, 2, 3, or 4;

each occurrence of p is independently 0, 1, or 2;

R¹ is selected from the group consisting of H, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, and halogen;

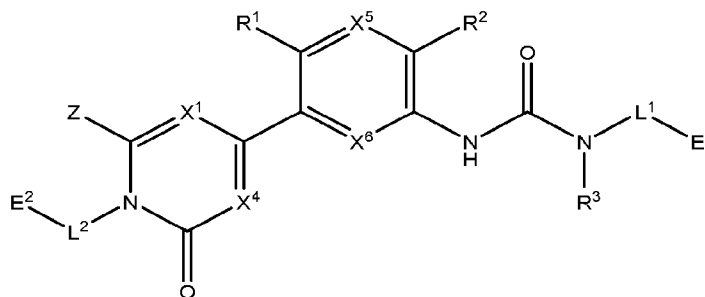
R² is selected from the group consisting of H and F;

R³ is selected from the group consisting of H, C₁-C₅ alkyl, and C₃-C₅ cycloalkyl;

R⁴, at each occurrence, is independently H or alkyl; and

R⁵, at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen.

[00089] In some embodiments, the compound is represented by Formula I-E:



Formula I-E

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X¹ and X⁴ are each independently CH, CR⁵, or N;

provided that not more than one of X¹ and X⁴ are N;

X⁵ and X⁶ are each independently CH, CF, or N;

L¹ is selected from a direct bond and a C₁-C₆alkyl optionally substituted with (E¹¹)_m, or when taken together with R³ and the N atom to which L¹ and R³ are attached form an optionally substituted heterocycle having from 4 to 8 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

L² is a direct bond or a C₁-C₆ alkyl optionally substituted with (E²¹)_p;

E¹ is selected from the group consisting of H, hydroxy, alkoxy, cyano, haloalkoxy, halogen,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, amine, alkylamine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of aryl, alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, heterocyclyl, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano and heterocyclyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, alkoxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of H, alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E¹¹, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E¹¹ taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

E² is selected from the group consisting of H, alkyl, amine, haloalkoxy, haloalkyl, sulfone, hydroxy, alkoxy, alkoxyalkyl, cyano, sulfonyl, and

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E²¹, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E²¹ taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is L⁷-E⁷ wherein:

L⁷ is a direct bond;

E⁷ is selected from the group consisting of:

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, cycloalkyl,

alkoxy, alkoxyalkyl, amine, acyl, carbamoyl, formyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, urea, amine, amidine, acyl, carbamoyl, formyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

each occurrence of m is independently 0, 1, 2, 3, or 4;

each occurrence of p is independently 0, 1, or 2;

R¹ is selected from the group consisting of H, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, and halogen;

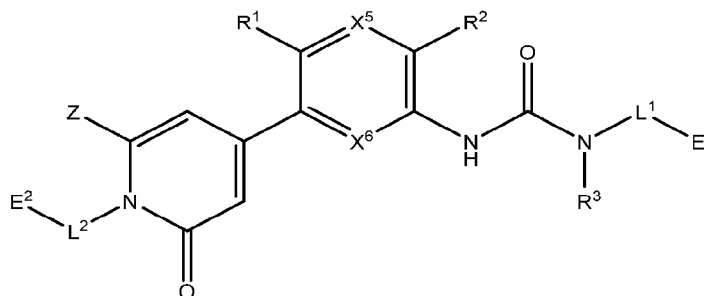
R² is selected from the group consisting of H and F;

R³ is selected from the group consisting of H, C₁-C₅ alkyl, and C₃-C₅ cycloalkyl;

R⁴, at each occurrence, is independently H or alkyl; and

R⁵, at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen.

[00090] In some embodiments, the compound is represented by Formula I-EA:



Formula I-EA

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X⁵ and X⁶ are each independently CH, CF, or N;

L¹ is selected from a direct bond and a C₁-C₆alkyl optionally substituted with (E¹¹)_m, or when taken together with R³ and the N atom to which L¹ and R³ are attached form an optionally substituted heterocycle having from 4 to 8 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

L² is a direct bond;

E¹ is selected from the group consisting of hydroxy, alkoxy, cyano, haloalkoxy, halogen,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, amine, alkylamine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of aryl, alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, heterocyclyl, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano and heterocyclyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, alkoxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of H, alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E¹¹, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E¹¹ taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

E² is alkyl;

Z is L⁷-E⁷ wherein:

L⁷ is a direct bond;

E⁷ is optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, urea, amine, amidine, acyl, carbamoyl, formyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

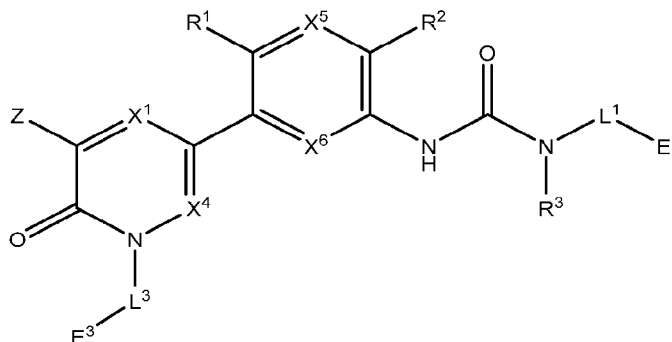
each occurrence of m is independently 0, 1, 2, 3, or 4;

R¹ is selected from the group consisting of H, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, and halogen;

R² is selected from the group consisting of H and F;

R^3 is selected from the group consisting of H, C₁-C₅ alkyl, and C₃-C₅ cycloalkyl; and R^5 , at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen.

[00091] In some embodiments, the compound is represented by Formula I-F:



Formula I-F

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^1 and X^4 are each independently CH, CR⁵, or N;

provided that not more than one of X^1 and X^4 are N;

X^5 and X^6 are each independently CH, CF, or N;

L^1 is selected from a direct bond and a C₁-C₆alkyl optionally substituted with (E¹¹)_m, or when taken together with R^3 and the N atom to which L^1 and R^3 are attached form an optionally substituted heterocycle having from 4 to 8 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl; L^3 is a direct bond or a C₁-C₆ alkyl optionally substituted with (E³¹)_p;

E^1 is selected from the group consisting of H, hydroxy, alkoxy, cyano, haloalkoxy, halogen,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, amine, alkylamine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of aryl, alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, heterocyclyl, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano and heterocyclyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, alkoxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E¹¹, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E¹¹ taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

E³ is selected from the group consisting of haloalkoxy, H, alkyl, acyl, amine, aminoalkyl, amide, haloalkyl, cyano, sulfone, hydroxy, alkoxy, alkoxyalkyl, cyano, sulfonyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, or cyano, cyanoalkyl, heterocyclyl, and

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E³¹, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E³¹ taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is L⁷-E⁷ wherein:

L^7 is a direct bond;

E^7 is selected from the group consisting of:

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, cycloalkyl, alkoxy, alkoxyalkyl, amine, acyl, carbamoyl, formyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, urea, amine, amidine, acyl, carbamoyl, formyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

each occurrence of m is independently 0, 1, 2, 3, or 4;

each occurrence of p is independently 0, 1, or 2;

R^1 is selected from the group consisting of H, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, and halogen;

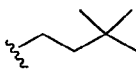
R^2 is selected from the group consisting of H and F;

R^3 is selected from the group consisting of H, C_1 - C_5 alkyl, and C_3 - C_5 cycloalkyl;

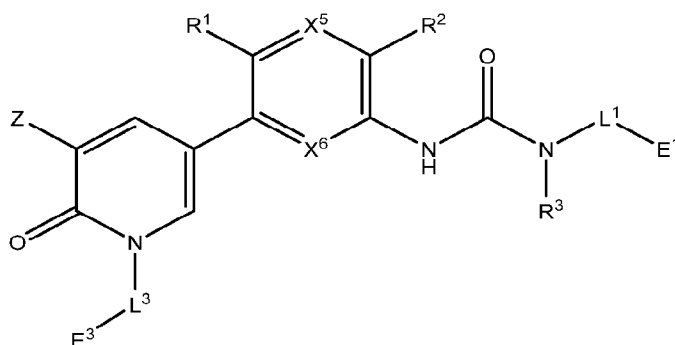
R^4 , at each occurrence, is independently H or alkyl; and

R^5 , at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen;

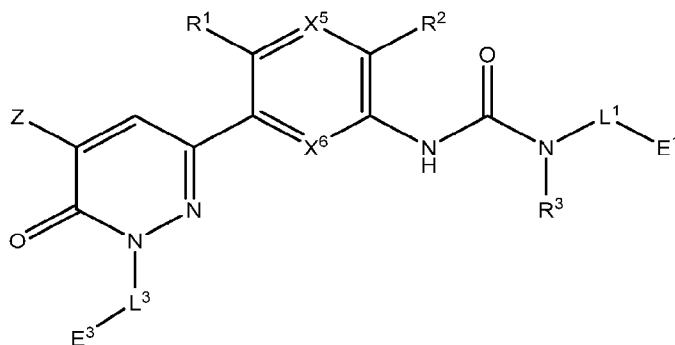
with the proviso that

when L^1 - E^1 is , R^1 is methyl, R^2 is H, R^3 is H, X^1 is N or CH, X^4 is N or CH, X^5 is N or CH, X^6 is CH, and E^7 is a substituent selected from the group consisting of oxetanyl, tetrahydrofuranyl, and tetrahydropyranyl, then L^3 - E^3 is not selected from the group consisting of: H, methyl, hydroxy-ethyl, hydroxy-propyl, and 2,3-dihydroxypropyl.

[00092] In some embodiment, the compound is represented by Formula I-FA or Formula I-FB:



Formula I-FA



Formula I-FB

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^5 and X^6 are each independently CH, CF, or N;

L^1 is selected from a direct bond and a C_1 - C_6 alkyl optionally substituted with $(E^{11})_m$, or when taken together with R^3 and the N atom to which L^1 and R^3 are attached form an optionally substituted heterocycle having from 4 to 8 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

L^3 is a direct bond;

E^1 is selected from the group consisting of hydroxy, alkoxy, cyano, haloalkoxy, halogen,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, amine, alkylamine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of aryl, alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, heterocyclyl, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano and heterocyclyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, alkoxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E¹¹, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E¹¹ taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

E³ is alkyl;

Z is L⁷-E⁷ wherein:

L⁷ is a direct bond;

E⁷ is optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, cycloalkyl, alkoxy, alkoxyalkyl, amine, acyl, carbamoyl, formyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone;

each occurrence of m is independently 0, 1, 2, 3, or 4;

R¹ is selected from the group consisting of H, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, and halogen;

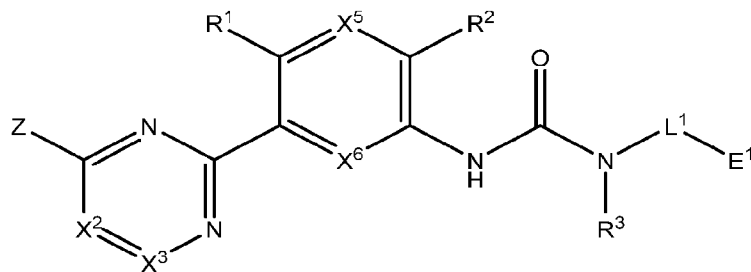
R² is selected from the group consisting of H and F;

R³ is selected from the group consisting of H, C₁-C₅ alkyl, and C₃-C₅ cycloalkyl;; and

R⁵, at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen;

with the proviso that E⁷ is not oxetanyl, tetrahydrofuranyl, or tetrahydropyranyl.

[00093] In some embodiments, the compound is represented by Formula I-G:



Formula I-G

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^2 is C-O- L^2 - E^2 , C- L^2 - E^2 , C-N(R^4)- L^2 - E^2 , or CH;

X^3 is C-O- L^3 - E^3 , C- L^3 - E^3 , C-N(R^4)- L^3 - E^3 , or CH;

X^5 and X^6 are each independently CH, CF, or N;

L^1 is selected from a direct bond and a C₁-C₆alkyl optionally substituted with (E^{11})_m, or when taken together with R^3 and the N atom to which L^1 and R^3 are attached form an optionally substituted heterocycle having from 4 to 8 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

L^2 is a direct bond or a C₁-C₆ alkyl optionally substituted with (E^{21})_p;

L^3 is a direct bond or a C₁-C₆ alkyl optionally substituted with (E^{31})_p;

E^1 is selected from the group consisting of H, hydroxy, alkoxy, cyano, haloalkoxy, halogen,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, amine, alkylamine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of aryl, alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, heterocyclyl, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano and heterocyclyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide,

amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, alkoxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E¹¹, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E¹¹ taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

E² is selected from the group consisting of H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and sulfone, hydroxy, alkoxy, alkoxyalkyl, cyano, sulfonyl, and

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E²¹, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E²¹ taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

E³ is selected from the group consisting of haloalkoxy, H, alkyl, acyl, amine, aminoalkyl, amide, haloalkyl, cyano, sulfone, hydroxy, alkoxy, alkoxyalkyl, cyano, sulfonyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E^{31} , at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; or wherein two occurrences of E^{31} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is L^7-E^7 wherein:

L^7 is a direct bond;

E^7 is selected from the group consisting of:

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, cycloalkyl, alkoxy, alkoxyalkyl, amine, acyl, carbamoyl, formyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, urea, amine, amidine, acyl, carbamoyl, formyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

each occurrence of m is independently 0, 1, 2, 3, or 4;

each occurrence of p is independently 0, 1, or 2;

R^1 is selected from the group consisting of H, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, and halogen;

R^2 is selected from the group consisting of H and F;

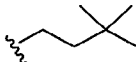
R^3 is selected from the group consisting of H, C_1 - C_5 alkyl, and C_3 - C_5 cycloalkyl;

R^4 , at each occurrence, is independently H or alkyl; and

R^5 , at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen,

with the proviso that

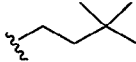
when E^7 is morpholinyl, X^3 is $C-L^3-E^3$, and L^3 is a direct bond, then E^3 is not heteroaryl;

when L^1-E^1 is , R^1 is methyl, R^2 is H, R^3 is H, X^5 is N or CH, X^6 is CH, E^7

is a substituent selected from the group consisting of oxetanyl, tetrahydrofuranyl, and tetrahydropyranyl, and

X^2 is selected from the group consisting of:

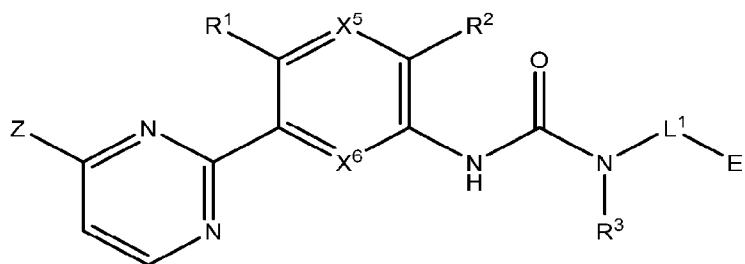
- (i) C-L²-E², wherein L²-E² is selected from H;
- (ii) C-O-L²-E², wherein O-L²-E² is selected from the group consisting of methoxy, ethoxy, isopropoxy, 2-methoxyethoxy, 2-hydroxyethoxy, (tetrahydro-2*H*-pyran-4-yl)oxy, and (1-ethylpiperidin-4-yl)oxy; and
- (iii) C-N(R⁴)-L²-E², wherein N(R⁴)-L²-E² is selected from the group consisting of (2-methoxyethyl)amino, (2-hydroxyethyl)(methyl)amino, and (1-hydroxypropan-2-yl)amino; then X³ is not selected from the group consisting of:
 - (i) C-L³-E³, wherein L³-E³ is selected from the group consisting of H, methyl, 3-hydroxyoxetan-3-yl, 4-hydroxy-piperidin-1-yl, 4-amino-4-methylpiperidin-1-yl, and 2-oxooxazolidin-3-yl;
 - (ii) C-O-L³-E³, wherein O-L³-E³ is selected from the group consisting of methoxy, 2-hydroxyethoxy, and 2,3-dihydroxypropoxy; and
 - (iii) C-N(R⁴)-L³-E³, wherein N(R⁴)-L³-E³ is selected from the group consisting of bis(2-hydroxyethyl)amino and (2-hydroxyethyl)amino; and

when L¹-E¹ is , R¹ is methyl, R² is H, R³ is H, X⁵ is N or CH, X⁶ is CH, X³ is C-L³-E³, L³ is a direct bond, E³ is selected from the group consisting of oxetanyl, tetrahydrofuranyl, and tetrahydropyranyl, and

X² is selected from the group consisting of:

- (i) C-L²-E², wherein L²-E² is selected from H;
- (ii) C-O-L²-E², wherein O-L²-E² is selected from the group consisting of methoxy, ethoxy, isopropoxy, 2-methoxyethoxy, 2-hydroxyethoxy, (tetrahydro-2*H*-pyran-4-yl)oxy, and (1-ethylpiperidin-4-yl)oxy; and
- (iii) C-N(R⁴)-L²-E², wherein N(R⁴)-L²-E² is selected from the group consisting of (2-methoxyethyl)amino, (2-hydroxyethyl)(methyl)amino, and (1-hydroxypropan-2-yl)amino; then E⁷ is not selected from the group consisting of: 3-hydroxyoxetan-3-yl, 4-hydroxy-piperidin-1-yl, 4-amino-4-methylpiperidin-1-yl, and 2-oxooxazolidin-3-yl.

[00094] In some embodiments, the compound is represented by Formula I-GA:



Formula I-GA

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^5 and X^6 are each independently CH, CF, or N;

L^1 is selected from a direct bond and a C_1 - C_6 alkyl optionally substituted with $(E^{11})_m$, or when taken together with R^3 and the N atom to which L^1 and R^3 are attached form an optionally substituted heterocycle having from 4 to 8 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^1 is selected from the group consisting of hydroxy, alkoxy, cyano, haloalkoxy, halogen,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, amine, alkylamine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of aryl, alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, heterocyclyl, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano and heterocyclyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, alkoxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E^{11} , at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; or wherein two occurrences of E^{11} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is L^7-E^7 wherein:

L^7 is a direct bond;

E^7 is optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, urea, amine, amidine, acyl, carbamoyl, formyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

each occurrence of m is independently 0, 1, 2, 3, or 4;

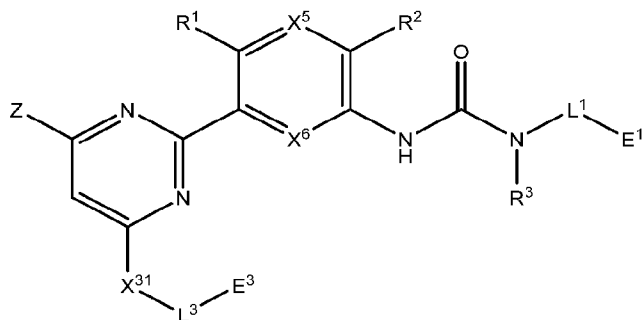
R^1 is selected from the group consisting of H, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, and halogen;

R^2 is selected from the group consisting of H and F;

R^3 is selected from the group consisting of H, C₁-C₅ alkyl, and C₃-C₅ cycloalkyl; and

R^5 , at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen.

[00095] In some embodiments, the compound is represented by Formula I-H:



Formula I-H

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^{31} is O or N(R^4);

X^5 and X^6 are each independently CH, CF, or N;

L^1 is selected from a direct bond and a C₁-C₆alkyl optionally substituted with $(E^{11})_m$, or when taken together with R^3 and the N atom to which L^1 and R^3 are attached form an optionally substituted heterocycle having from 4 to 8 atoms in the ring structure wherein the

optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

L^3 is a direct bond or a C_1 - C_6 alkyl optionally substituted with $(E^{31})_p$;

E^1 is selected from the group consisting of H, hydroxy, alkoxy, cyano, haloalkoxy, halogen,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, amine, alkylamine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of aryl, alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, heterocyclyl, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano and heterocyclyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, alkoxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E^{11} , at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{11} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

E^3 is selected from the group consisting of haloalkoxy, H, alkyl, acyl, amine, aminoalkyl, amide, haloalkyl, cyano, sulfone, hydroxy, alkoxy, alkoxyalkyl, cyano, sulfonyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of H, alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E^{31} , at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{31} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is L^7-E^7 wherein:

L^7 is a direct bond;

E^7 is selected from the group consisting of:

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, cycloalkyl, alkoxy, alkoxyalkyl, amine, acyl, carbamoyl, formyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, urea, amine, amidine, acyl, carbamoyl, formyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

each occurrence of m is independently 0, 1, 2, 3, or 4;

each occurrence of p is independently 0, 1, or 2;

R^1 is selected from the group consisting of H, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, and halogen;

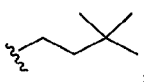
R^2 is selected from the group consisting of H and F;

R^3 is selected from the group consisting of H, C_1 - C_5 alkyl, and C_3 - C_5 cycloalkyl;

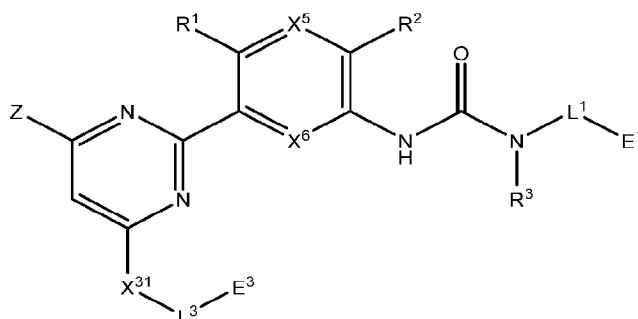
R^4 , at each occurrence, is independently H or alkyl; and

R^5 , at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen,

with the proviso that

when L¹-E¹ is , R¹ is methyl, R² is H, R³ is H, X⁵ is N or CH, X⁶ is CH, E⁷ is a substituent selected from the group consisting of oxetanyl, tetrahydrofuranyl, and tetrahydropyranyl, then X³¹-L³-E³ is not selected from the group consisting of: methoxy, 2-hydroxyethoxy, 2,3-dihydroxypropoxy, bis(2-hydroxyethyl)amino, and (2-hydroxyethyl)amino.

[00096] In some embodiments, the compound is represented by Formula I-HA:



Formula I-HA

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X³¹ is O or N(R⁴);

X⁵ and X⁶ are each independently CH, CF, or N;

L¹ is selected from a direct bond and a C₁-C₆alkyl optionally substituted with (E¹¹)_m, or when taken together with R³ and the N atom to which L¹ and R³ are attached form an optionally substituted heterocycle having from 4 to 8 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

L³ is a direct bond or a C₁-C₆ alkyl optionally substituted with (E³¹)_p;

E¹ is selected from the group consisting of hydroxy, alkoxy, cyano, haloalkoxy, halogen,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, amine, alkylamine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of aryl, alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, heterocyclyl, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano and heterocyclyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, alkoxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E¹¹, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; or wherein two occurrences of E¹¹ taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

E³ is selected from the group consisting of haloalkoxy, H, alkyl, acyl, amine, aminoalkyl, amide, haloalkyl, cyano, sulfone, hydroxy, alkoxy, alkoxyalkyl, cyano, sulfonyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of H, alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E³¹, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E³¹ taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is L⁷-E⁷ wherein:

L^7 is a direct bond;

E^7 is optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, urea, amine, amidine, acyl, carbamoyl, formyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

each occurrence of m is independently 0, 1, 2, 3, or 4;

each occurrence of p is independently 0, 1, or 2;

R^1 is selected from the group consisting of H, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, and halogen;

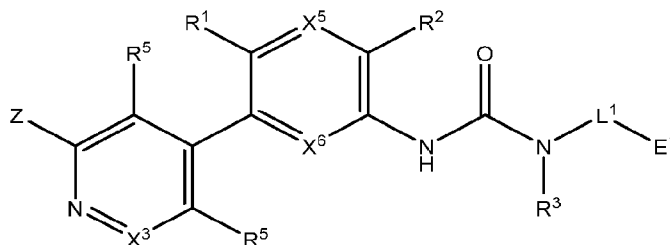
R^2 is selected from the group consisting of H and F;

R^3 is selected from the group consisting of H, C_1 - C_5 alkyl, and C_3 - C_5 cycloalkyl;

R^4 , at each occurrence, is independently H or alkyl; and

R^5 , at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen.

[00097] In some embodiments, the compound is represented by Formula I-J:



Formula I-J

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^3 is $C-O-L^3-E^3$, $C-L^3-E^3$, $C-N(R^4)-L^3-E^3$, CH , or N ;

X^5 and X^6 are each independently CH , CF , or N ;

L^1 is selected from a direct bond and a C_1 - C_6 alkyl optionally substituted with $(E^{11})_m$, or when taken together with R^3 and the N atom to which L^1 and R^3 are attached form an optionally substituted heterocycle having from 4 to 8 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

L^3 is a direct bond or a C_1 - C_6 alkyl optionally substituted with $(E^{31})_p$;

E^1 is selected from the group consisting of H, hydroxy, alkoxy, cyano, haloalkoxy, halogen;

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, amine, alkylamine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of aryl, alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, heterocyclyl, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano and heterocyclyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, alkoxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E¹¹, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; or wherein two occurrences of E¹¹ taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

E³ is selected from the group consisting of haloalkoxy, H, alkyl, acyl, amine, aminoalkyl, amide, haloalkyl, cyano, sulfone, hydroxy, alkoxy, alkoxyalkyl, cyano, sulfonyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, or sulfone,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E^{31} , at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; or wherein two occurrences of E^{31} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is L^7-E^7 wherein:

L^7 is selected from the group consisting of a direct bond;

E^7 is selected from the group consisting of:

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, cycloalkyl, alkoxy, alkoxyalkyl, amine, acyl, carbamoyl, formyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, urea, amine, amidine, acyl, carbamoyl, formyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

each occurrence of m is independently 0, 1, 2, 3, or 4;

each occurrence of p is independently 0, 1, or 2;

R^1 is selected from the group consisting of H, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, and halogen;

R^2 is selected from the group consisting of H and F;

R^3 is selected from the group consisting of H, C_1-C_5 alkyl, and C_3-C_5 cycloalkyl;

R^4 , at each occurrence, is independently H or alkyl; and

R^5 , at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen;

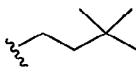
with the proviso that

when E^7 is morpholinyl, R^5 is H, X^5 and X^6 are CH, R^1 is $-CH_3$, and X^3 is $C-L^3-E^3$, then L^3-E^3 is not optionally substituted C_1-C_8 alkyl, optionally substituted C_3-C_6 cycloalkyl, optionally substituted C_4-C_8 cycloalkylalkyl, optionally substituted C_3-C_6 heterocyclyl, optionally substituted C_4-C_8 heterocyclylalkyl, optionally substituted 5- or 6-membered heteroaryl, or amide;

when R^5 is H, X^5 and X^6 are CH, R^1 is $-CH_3$, X^3 is $C-L^3-E^3$, L^3 is a direct bond, and E^3 is morpholinyl, then E^7 is not optionally substituted C_3-C_6 heterocyclyl or optionally substituted 5- or 6-membered heteroaryl;

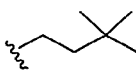
when E^7 is morpholinyl, X^3 is $C-O-L^3-E^3$, R^5 is H, X^6 is CH or CF, and R^3 is H, then L^1-E^1 is not optionally substituted alkyl, optionally substituted C_3-C_6 cycloalkyl, optionally substituted C_3-C_6 cycloalkylalkyl, optionally substituted C_4-C_6 heterocyclyl, or optionally substituted heterocyclalkyl;

when E^7 is morpholinyl, X^3 is $C-O-L^3-E^3$, R^5 is H, and X^6 is CH, CD, or CF, then L^1 is not taken together with R^3 and the N atom to which L^1 and R^3 are attached form an optionally substituted heterocycle having from 4 to 8 atoms in the ring structure;

when L^1-E^1 is , R^1 is methyl, R^2 is H, R^3 is H, R^5 is H, X^5 is N or CH, X^6 is CH, and E^7 is a substituent selected from the group consisting of oxetanyl, tetrahydrofuranyl, and tetrahydropyranyl,

then X^3 is not selected from the group consisting of:

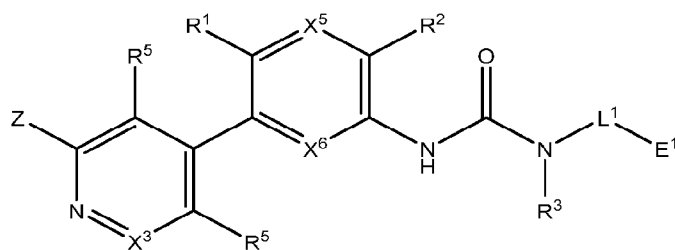
- (i) $C-L^3-E^3$, wherein L^3-E^3 is selected from the group consisting of methyl, 3-hydroxyoxetan-3-yl, 4-hydroxy-piperidin-1-yl, 4-amino-4-methylpiperidin-1-yl, and 2-oxooxazolidin-3-yl;
- (ii) $C-O-L^3-E^3$, wherein $O-L^3-E^3$ is selected from the group consisting of methoxy, 2-hydroxyethoxy, and 2,3-dihydroxypropoxy;
- (iii) $C-N(R^4)-L^3-E^3$, wherein $N(R^4)-L^3-E^3$ is selected from the group consisting of bis(2-hydroxyethyl)amino and (2-hydroxyethyl)amino; and
- (iv) N; and

when L^1-E^1 is , R^1 is methyl, R^2 is H, R^3 is H, R^5 is H, X^5 is N or CH, X^6 is CH, X^3 is $C-L^3-E^3$, L^3 is a direct bond, and E^3 is selected from the group consisting of oxetanyl, tetrahydrofuranyl, and tetrahydropyranyl,

then E^7 is not selected from the group consisting of: 3-hydroxyoxetan-3-yl, 4-hydroxy-piperidin-1-yl, 4-amino-4-methylpiperidin-1-yl, and 2-oxooxazolidin-3-yl; and

when E^7 is 5- or 6- membered optionally substituted heteroaryl or 5- or 6-membered optionally substituted heterocyclyl, R^5 is H or F, X^5 is CH, X^6 is CH, CD, or CF, and X^3 is $C-O-L^3-E^3$ or $C-N(R^4)-L^3-E^3$, then L^1 is not taken together with R^3 and the N atom to which L^1 and R^3 are attached form an optionally substituted heterocycle having from 4 to 7 atoms in the ring structure.

[00098] In some embodiments, the compound is represented by Formula I-JA:



Formula I-JA

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^3 is C-L³-E³ or CH;

X^5 and X^6 are each independently CH, CF, or N;

L¹ is selected from a direct bond and a C₁-C₆alkyl optionally substituted with (E¹¹)_m, or when taken together with R³ and the N atom to which L¹ and R³ are attached form an optionally substituted heterocycle having from 4 to 8 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

L³ is a direct bond;

E¹ is selected from the group consisting of hydroxy, alkoxy, cyano, haloalkoxy, halogen;

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, amine, alkylamine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of aryl, alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, heterocyclyl, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano and heterocyclyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, alkoxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E¹¹, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E¹¹ taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

E³ is selected from the group consisting of alkyl and

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

Z is L⁷-E⁷ wherein:

L⁷ is selected from the group consisting of a direct bond;

E⁷ is optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, urea, amine, amidine, acyl, carbamoyl, formyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

each occurrence of m is independently 0, 1, 2, 3, or 4;

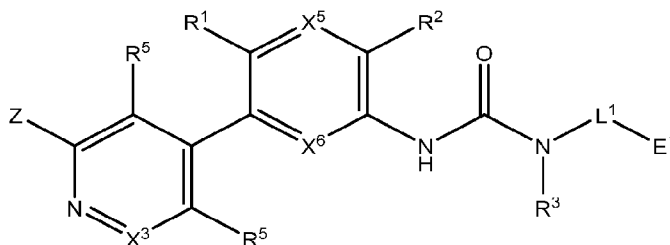
R¹ is selected from the group consisting of H, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, and halogen;

R² is selected from the group consisting of H and F;

R³ is selected from the group consisting of H, C₁-C₅ alkyl, and C₃-C₅ cycloalkyl; and

R⁵, at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen.

[00099] In some embodiments, the compound is represented by Formula I-JB:



Formula I-JB

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^3 is $C-O-L^3-E^3$, $C-L^3-E^3$, $C-N(R^4)-L^3-E^3$, or CH ;

X^5 and X^6 are each independently CH , CF , or N ;

L^1 is selected from a direct bond and a C_1 - C_6 alkyl optionally substituted with $(E^{11})_m$, or when taken together with R^3 and the N atom to which L^1 and R^3 are attached form an optionally substituted heterocycle having from 4 to 8 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

L^3 is a direct bond or a C_1 - C_6 alkyl optionally substituted with $(E^{31})_p$;

E^1 is selected from the group consisting of

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano and heterocyclyl, and

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E^{11} , at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{11} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

E^3 is selected from the group consisting of haloalkoxy, H, alkyl, acyl, amine, aminoalkyl, amide, haloalkyl, cyano, sulfone, hydroxy, alkoxy, alkoxyalkyl, cyano, sulfonyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, or sulfone, and

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E^{31} , at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E³¹ taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is L⁷-E⁷ wherein:

L⁷ is selected from the group consisting of a direct bond;

E⁷ is optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, cycloalkyl, alkoxy, alkoxyalkyl, amine, acyl, carbamoyl, formyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

each occurrence of m is independently 0, 1, 2, 3, or 4;

each occurrence of p is independently 0, 1, or 2;

R¹ is selected from the group consisting of H, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, and halogen;

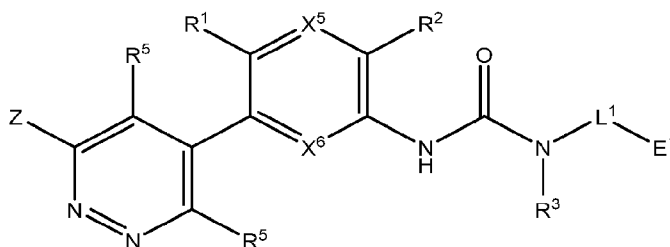
R² is selected from the group consisting of H and F;

R³ is selected from the group consisting of H, C₁-C₅ alkyl, and C₃-C₅ cycloalkyl;

R⁴, at each occurrence, is independently H or alkyl; and

R⁵, at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen.

[000100] In some embodiments, the compound is represented by Formula I-JC:



Formula I-JC

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X⁵ and X⁶ are each independently CH, CF, or N;

L¹ is selected from a direct bond and a C₁-C₆alkyl optionally substituted with (E¹¹)_m, or when taken together with R³ and the N atom to which L¹ and R³ are attached form an optionally substituted heterocycle having from 4 to 8 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently selected from the

group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E¹ is selected from the group consisting of hydroxy, alkoxy, cyano, haloalkoxy, halogen;

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, amine, alkylamine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of aryl, alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, heterocyclyl, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano and heterocyclyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, alkoxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E¹¹, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E¹¹ taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is L⁷-E⁷ wherein:

L⁷ is selected from the group consisting of a direct bond;

E⁷ is optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, urea, amine, amidine, acyl, carbamoyl, formyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

each occurrence of m is independently 0, 1, 2, 3, or 4;

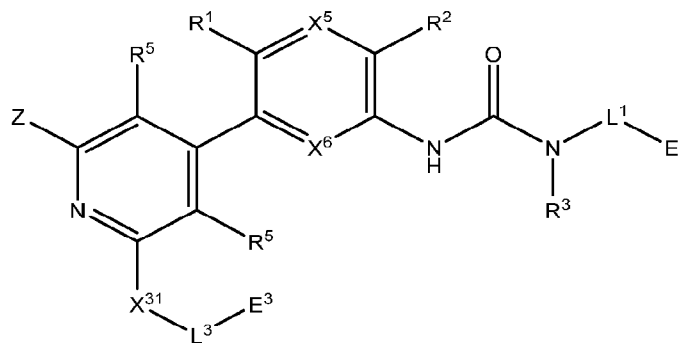
R¹ is selected from the group consisting of H, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, and halogen;

R^2 is selected from the group consisting of H and F;

R^3 is selected from the group consisting of H, C₁-C₅ alkyl, and C₃-C₅ cycloalkyl; and

R^5 , at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen.

[000101] In some embodiments, the compound is represented by Formula I-K:



Formula I-K

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^5 and X^6 are each independently CH, CF, or N;

X^{31} is O or N(R^4);

L^1 is selected from a direct bond and a C₁-C₆alkyl optionally substituted with (E^{11})_m, or when taken together with R^3 and the N atom to which L^1 and R^3 are attached form an optionally substituted heterocycle having from 4 to 8 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

L^3 is a direct bond or a C₁-C₆ alkyl optionally substituted with (E^{31})_p;

E^1 is selected from the group consisting of H, hydroxy, alkoxy, cyano, haloalkoxy, halogen,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, amine, alkylamine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of aryl, alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, heterocyclyl, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano and heterocyclyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, alkoxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E¹¹, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; or wherein two occurrences of E¹¹ taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

E³ is selected from the group consisting of haloalkoxy, H, alkyl, acyl, amine, aminoalkyl, amide, haloalkyl, cyano, sulfone, hydroxy, alkoxy, alkoxyalkyl, cyano, sulfonyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, or sulfone,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, or cyano, cyanoalkyl, heterocyclyl, and

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, hydroxy, or cyano;

E³¹, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E³¹ taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is L⁷-E⁷ wherein:

L^7 is a direct bond;

E^7 is selected from the group consisting of:

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, cycloalkyl, alkoxy, alkoxyalkyl, amine, acyl, carbamoyl, formyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, urea, amine, amidine, acyl, carbamoyl, formyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

each occurrence of m is independently 0, 1, 2, 3, or 4; and

each occurrence of p is independently 0, 1, or 2;

R^1 is selected from the group consisting of H, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, and halogen;

R^2 is selected from the group consisting of H and F;

R^3 is selected from the group consisting of H, C_1 - C_5 alkyl, and C_3 - C_5 cycloalkyl;

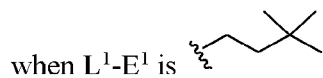
R^4 , at each occurrence, is independently H or alkyl; and

R^5 , at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen;

with the proviso that

when E^7 is morpholinyl, R^5 is H, X^6 is CH, CD, or CF, X^{31} is O, and R^3 is H, then L^1 - E^1 is not optionally substituted alkyl, optionally substituted C_3 - C_6 cycloalkyl, optionally substituted C_3 - C_6 cycloalkylalkyl, optionally substituted C_4 - C_6 heterocyclyl, or optionally substituted heterocyclylalkyl;

when E^7 is morpholinyl, R^5 is H, X^{31} is O, and X^6 is CH, CD, or CF, then L^1 is not taken together with R^3 and the N atom to which L^1 and R^3 are attached form an optionally substituted heterocycle having from 4 to 8 atoms in the ring structure;

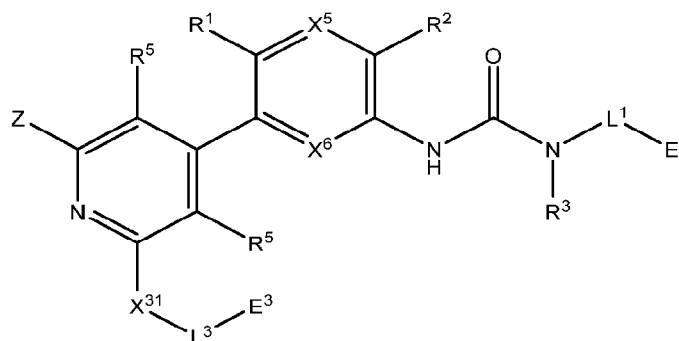


is CH, and E^7 is a substituent selected from the group consisting of oxetanyl, tetrahydrofuranyl, and tetrahydropyranyl,

then X^{31} - L^3 - E^3 is not selected from the group consisting of: methoxy, 2-hydroxyethoxy, 2,3-dihydroxypropoxy; bis(2-hydroxyethyl)amino, and (2-hydroxyethyl)amino;

when E^7 is 5- or 6- membered optionally substituted heteroaryl or 5- or 6-membered optionally substituted heterocyclyl, R^5 is H or F, X^5 is CH, and X^6 is CH, CD, or CF, then L^1 is not taken together with R^3 and the N atom to which L^1 and R^3 are attached form an optionally substituted heterocycle having from 4 to 7 atoms in the ring structure.

[000102] In some embodiments, the compound is represented by Formula I-KA:



Formula I-KA

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^5 and X^6 are each independently CH, CF, or N;

X^{31} is O or N(R^4);

L^1 is selected from a direct bond and a C_1 - C_6 alkyl optionally substituted with $(E^{11})_m$, or when X^5 is N, L^1 may be taken together with R^3 and the N atom to which L^1 and R^3 are attached form an optionally substituted heterocycle having from 4 to 8 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

L^3 is a direct bond or a C_1 - C_6 alkyl optionally substituted with $(E^{31})_p$;

E^1 is selected from the group consisting of hydroxy, alkoxy, cyano, haloalkoxy, halogen,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, amine, alkylamine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of aryl, alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, heterocyclyl, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano and heterocyclyl, the site covalently linked to H or the optionally substituted substituent,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, alkoxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E¹¹, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E¹¹ taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

E³ is selected from the group consisting of haloalkoxy, H, alkyl, acyl, amine, aminoalkyl, amide, haloalkyl, cyano, sulfone, hydroxy, alkoxy, alkoxyalkyl, cyano, sulfonyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, or sulfone,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, or cyano, cyanoalkyl, heterocyclyl, and

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, hydroxy, or cyano;

E³¹, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E³¹ taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is L⁷-E⁷ wherein:

L⁷ is a direct bond;

E⁷ is optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, urea, amine, amidine, acyl, carbamoyl, formyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

each occurrence of m is independently 0, 1, 2, 3, or 4; and

each occurrence of p is independently 0, 1, or 2;

R¹ is selected from the group consisting of H, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, and halogen;

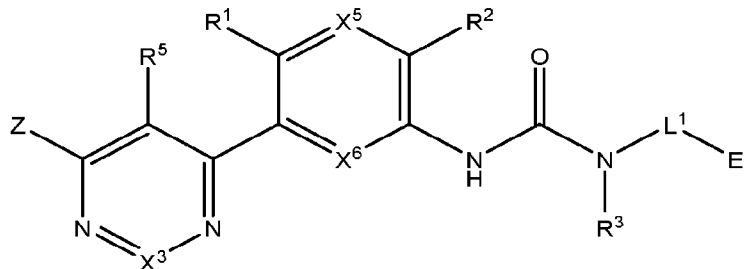
R² is selected from the group consisting of H and F;

R³ is selected from the group consisting of H, C₁-C₅ alkyl, and C₃-C₅ cycloalkyl;

R⁴, at each occurrence, is independently H or alkyl; and

R⁵, at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen.

[000103] In some embodiments, the compound is represented by Formula I-L:



Formula I-L

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X³ is C-O-L³-E³, C-L³-E³, C-N(R⁴)-L³-E³, or CH;

X⁵ and X⁶ are each independently CH, CF, or N;

L¹ is selected from a direct bond and a C₁-C₆alkyl optionally substituted with (E¹¹)_m, or when taken together with R³ and the N atom to which L¹ and R³ are attached form an optionally substituted heterocycle having from 4 to 8 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently selected from the

group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl; L³ is a direct bond or a C₁-C₆ alkyl optionally substituted with (E³¹)_p;

E¹ is selected from the group consisting of H, hydroxy, alkoxy, cyano, haloalkoxy, halogen,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, amine, alkylamine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of aryl, alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, heterocyclyl, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano and heterocyclyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, alkoxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E¹¹, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E¹¹ taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

E³ is selected from the group consisting of haloalkoxy, H, alkyl, acyl, amine, aminoalkyl, amide, haloalkyl, cyano, sulfone, hydroxy, alkoxy, alkoxyalkyl, cyano, sulfonyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, or sulfone,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide,

amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, or cyano, cyanoalkyl, heterocyclyl, and

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E^{31} , at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{31} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is L^7-E^7 wherein:

L^7 is a direct bond

E^7 is selected from the group consisting of:

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, cycloalkyl, alkoxy, alkoxyalkyl, amine, acyl, carbamoyl, formyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, urea, amine, amidine, acyl, carbamoyl, formyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

each occurrence of m is independently 0, 1, 2, 3, or 4;

each occurrence of p is independently 0, 1, or 2;

R^1 is selected from the group consisting of H, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, and halogen;

R^2 is selected from the group consisting of H and F;

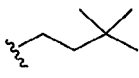
R^3 is selected from the group consisting of H, C_1-C_5 alkyl, and C_3-C_5 cycloalkyl;

R^4 , at each occurrence, is independently H or alkyl; and

R^5 , at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen,

with the proviso that

when E^7 is morpholinyl, X^3 is $C-L^3-E^3$, and L^3 is a direct bond, then E^3 is not heteroaryl;

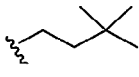
when L^1-E^1 is , R^1 is methyl, R^2 is H, R^3 is H, R^5 is H, X^5 is N or CH, X^6 is CH, and E^7 is a substituent selected from the group consisting of oxetanyl, tetrahydrofuranyl, and tetrahydropyranyl,

then X^3 is not selected from the group consisting of:

(i) $C-L^3-E^3$, wherein L^3-E^3 is selected from the group consisting of H, methyl, 3-hydroxyoxetan-3-yl, 4-hydroxy-piperidin-1-yl, 4-amino-4-methylpiperidin-1-yl, and 2-oxooxazolidin-3-yl;

(ii) $C-O-L^3-E^3$, wherein $O-L^3-E^3$ is selected from the group consisting of methoxy, 2-hydroxyethoxy, and 2,3-dihydroxypropoxy; and

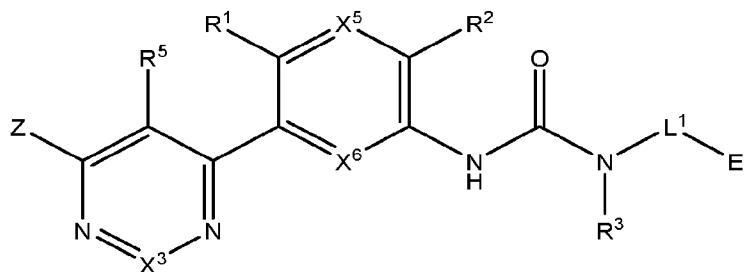
(iii) $C-N(R^4)-L^3-E^3$, wherein $N(R^4)-L^3-E^3$ is selected from the group consisting of bis(2-hydroxyethyl)amino and (2-hydroxyethyl)amino; and

when L^1-E^1 is , R^1 is methyl, R^2 is H, R^3 is H, R^5 is H, X^5 is N or CH, X^6 is CH, X^3 is $C-L^3-E^3$, L^3 is a direct bond, and E^3 is selected from the group consisting of oxetanyl, tetrahydrofuranyl, and tetrahydropyranyl,

then E^7 is not selected from the group consisting of: 3-hydroxyoxetan-3-yl, 4-hydroxy-piperidin-1-yl, 4-amino-4-methylpiperidin-1-yl, and 2-oxooxazolidin-3-yl; and

when E^7 is 5- or 6- membered optionally substituted heteroaryl or 5- or 6-membered optionally substituted heterocyclyl, R^5 is H or F, X^5 is CH, X^6 is CH, CD, or CF, and X^3 is $C-O-L^3-E^3$ or $C-N(R^4)-L^3-E^3$, then L^1 is not taken together with R^3 and the N atom to which L^1 and R^3 are attached form an optionally substituted heterocycle having from 4 to 7 atoms in the ring structure.

[000104] In some embodiments, the compound is represented by Formula I-LA:



Formula I-LA

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X³ is C-L³-E³ or CH;

X⁵ and X⁶ are each independently CH, CF, or N;

L¹ is selected from a direct bond and a C₁-C₆alkyl optionally substituted with (E¹¹)_m, or when taken together with R³ and the N atom to which L¹ and R³ are attached form an optionally substituted heterocycle having from 4 to 8 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

L³ is a direct bond or a C₁-C₆ alkyl optionally substituted with (E³¹)_p;

E¹ is selected from the group consisting of hydroxy, alkoxy, cyano, haloalkoxy, halogen,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, amine, alkylamine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of aryl, alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, heterocyclyl, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano and heterocyclyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, alkoxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E¹¹, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E¹¹ taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

E³ is selected from the group consisting of alkyl and

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E^{31} , at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{31} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is L^7-E^7 wherein:

L^7 is a direct bond

E^7 is optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, urea, amine, amidine, acyl, carbamoyl, formyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

each occurrence of m is independently 0, 1, 2, 3, or 4;

each occurrence of p is independently 0, 1, or 2;

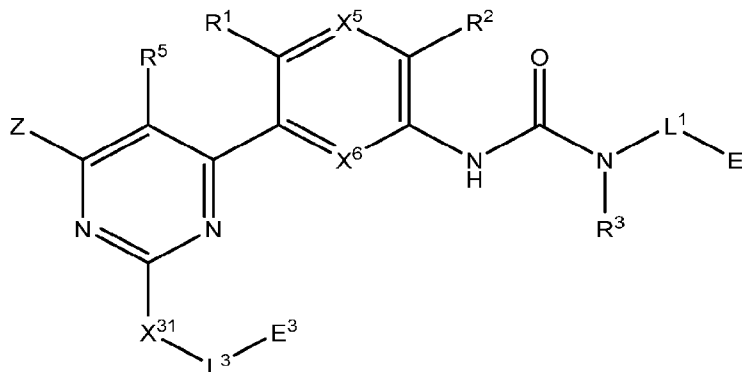
R^1 is selected from the group consisting of H, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, and halogen;

R^2 is selected from the group consisting of H and F;

R^3 is selected from the group consisting of H, C_1 - C_5 alkyl, and C_3 - C_5 cycloalkyl; and

R^5 , at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen.

[000105] In some embodiments, the compound is represented by Formula I-M:



Formula I-M

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X⁵ and X⁶ are each independently CH, CF, or N;

X³¹ is O or N(R⁴);

L¹ is selected from a direct bond and a C₁-C₆alkyl optionally substituted with (E¹¹)_m, or when taken together with R³ and the N atom to which L¹ and R³ are attached form an optionally substituted heterocycle having from 4 to 8 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

L³ is a direct bond or a C₁-C₆ alkyl optionally substituted with (E³¹)_p;

E¹ is selected from the group consisting of H, hydroxy, alkoxy, cyano, haloalkoxy, halogen,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, amine, alkylamine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of aryl, alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, heterocyclyl, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano and heterocyclyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, alkoxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E¹¹, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E¹¹ taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

E³ is selected from the group consisting of haloalkoxy, H, alkyl, acyl, amine, aminoalkyl, amide, haloalkyl, cyano, sulfone, hydroxy, alkoxy, alkoxyalkyl, cyano, sulfonyl,

optionally substituted heterocyclcyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclcyl, and

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E^{31} , at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{31} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclcyl ring having from 3 to 6 atoms in the ring structure;

Z is L^7-E^7 wherein:

L^7 is a direct bond;

E^7 is selected from the group consisting of:

optionally substituted heterocyclcyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, cycloalkyl, alkoxy, alkoxyalkyl, amine, acyl, carbamoyl, formyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, urea, amine, amidine, acyl, carbamoyl, formyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

each occurrence of m is independently 0, 1, 2, 3, or 4;

each occurrence of p is independently 0, 1, or 2;

R^1 is selected from the group consisting of H, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, and halogen;

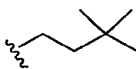
R^2 is selected from the group consisting of H and F;

R^3 is selected from the group consisting of H, C_1 - C_5 alkyl, and C_3 - C_5 cycloalkyl;

R^4 , at each occurrence, is independently H or alkyl; and

R^5 , at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen,

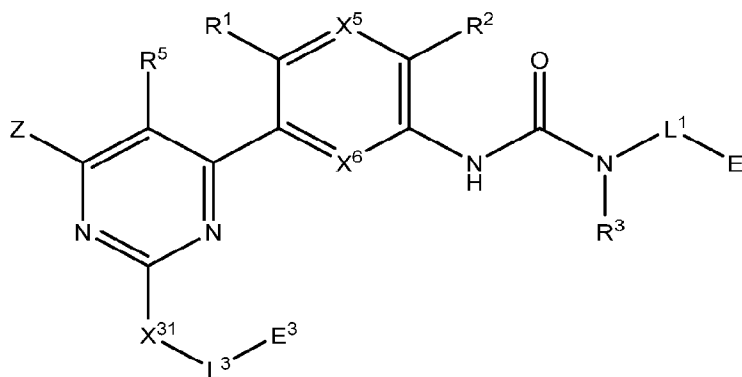
with the proviso that

when L^1-E^1 is , R^1 is methyl, R^2 is H, R^3 is H, R^5 is H, X^5 is N or CH, X^6 is CH, and E^7 is a substituent selected from the group consisting of oxetanyl, tetrahydrofuranyl, and tetrahydropyranyl,

then $X^{31}-L^3-E^3$ is not selected from the group consisting of: methoxy, 2-hydroxyethoxy, 2,3-dihydroxypropoxy, bis(2-hydroxyethyl)amino, and (2-hydroxyethyl)amino; and

when E^7 is 5- or 6- membered optionally substituted heteroaryl or 5- or 6-membered optionally substituted heterocyclyl, R^5 is H or F, X^5 is CH, and X^6 is CH, CD, or CF, then L^1 is not taken together with R^3 and the N atom to which L^1 and R^3 are attached form an optionally substituted heterocycle having from 4 to 7 atoms in the ring structure.

[000106] In some embodiments, the compound is represented by Formula I-MA:



Formula I-MA

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^5 and X^6 are each independently CH, CF, or N;

X^{31} is O or N(R^4);

L^1 is selected from a direct bond and a C_1 - C_6 alkyl optionally substituted with $(E^{11})_m$, or when X^5 is N, L^1 may be taken together with R^3 and the N atom to which L^1 and R^3 are attached form an optionally substituted heterocycle having from 4 to 8 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently

selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

L³ is a direct bond or a C₁-C₆ alkyl optionally substituted with (E³¹)_p;

E¹ is selected from the group consisting of hydroxy, alkoxy, cyano, haloalkoxy, halogen,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, amine, alkylamine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of aryl, alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, heterocyclyl, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano and heterocyclyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, alkoxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E¹¹, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E¹¹ taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

E³ is selected from the group consisting of haloalkoxy, H, alkyl, acyl, amine, aminoalkyl, amide, haloalkyl, cyano, sulfone, hydroxy, alkoxy, alkoxyalkyl, cyano, sulfonyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide,

amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E^{31} , at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{31} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is L^7-E^7 wherein:

L^7 is a direct bond;

E^7 is optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, urea, amine, amidine, acyl, carbamoyl, formyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

each occurrence of m is independently 0, 1, 2, 3, or 4;

each occurrence of p is independently 0, 1, or 2;

R^1 is selected from the group consisting of H, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, and halogen;

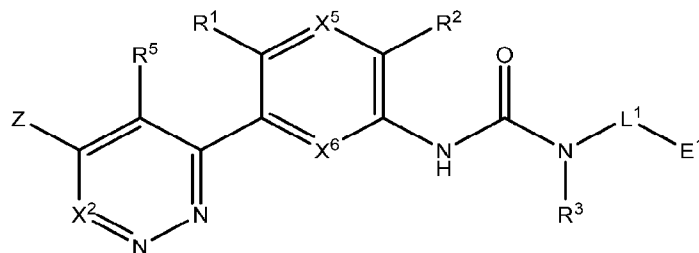
R^2 is selected from the group consisting of H and F;

R^3 is selected from the group consisting of H, C_1 - C_5 alkyl, and C_3 - C_5 cycloalkyl;

R^4 , at each occurrence, is independently H or alkyl; and

R^5 , at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen.

[000107] In some embodiments, the compound is represented by Formula I-N:



Formula I-N

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^2 is C-O-L²-E², C-L²-E², C-N(R⁴)-L²-E², or CH;

X^5 and X^6 are each independently CH, CF, or N;

L^1 is selected from a direct bond and a C₁-C₆alkyl optionally substituted with (E¹¹)_m, or when taken together with R³ and the N atom to which L¹ and R³ are attached form an optionally substituted heterocycle having from 4 to 8 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

L^2 is a direct bond or a C₁-C₆ alkyl optionally substituted with (E²¹)_p;

E¹ is selected from the group consisting of H, hydroxy, alkoxy, cyano, haloalkoxy, halogen,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, amine, alkylamine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of aryl, alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, heterocyclyl, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano and heterocyclyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, alkoxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E¹¹, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E¹¹ taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

E² is selected from the group consisting of H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, sulfone, hydroxy, alkoxy, alkoxyalkyl, cyano, sulfonyl, and

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21} , at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{21} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is L^7-E^7 wherein:

L^7 is a direct bond;

E^7 is selected from the group consisting of:

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, cycloalkyl, alkoxy, alkoxyalkyl, amine, acyl, carbamoyl, formyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, urea, amine, amidine, acyl, carbamoyl, formyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

each occurrence of m is independently 0, 1, 2, 3, or 4;

each occurrence of p is independently 0, 1, or 2;

R^1 is selected from the group consisting of H, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, and halogen;

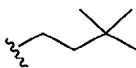
R^2 is selected from the group consisting of H and F;

R^3 is selected from the group consisting of H, C_1 - C_5 alkyl, and C_3 - C_5 cycloalkyl;

R^4 , at each occurrence, is independently H or alkyl; and

R^5 , at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen,

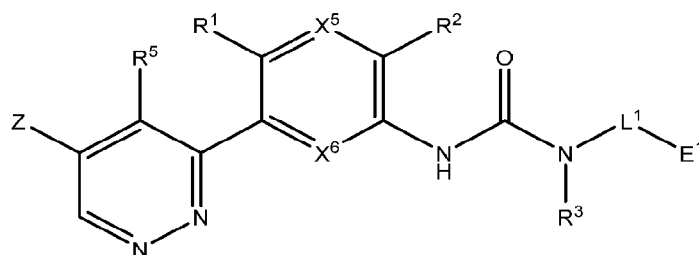
with the proviso that

when L^1-E^1 is , R^1 is methyl, R^2 is H, R^3 is H, R^5 is H, X^5 is N or CH, X^6 is CH, E^7 is a substituent selected from the group consisting of oxetanyl, tetrahydrofuranyl, and tetrahydropyranyl, then

X^2 is not selected from the group consisting of:

- (i) $C-L^2-E^2$, wherein L^2-E^2 is selected from H;
- (ii) $C-O-L^2-E^2$, wherein $O-L^2-E^2$ is selected from the group consisting of methoxy, ethoxy, isopropoxy, 2-methoxyethoxy, 2-hydroxyethoxy, (tetrahydro-2H-pyran-4-yl)oxy, and (1-ethylpiperidin-4-yl)oxy; and
- (iii) $C-N(R^4)-L^2-E^2$, wherein $N(R^4)-L^2-E^2$ is selected from the group consisting of (2-methoxyethyl)amino, (2-hydroxyethyl)(methyl)amino, and (1-hydroxypropan-2-yl)amino.

[000108] In some embodiments, the compound is represented by Formula I-NA:



Formula I-NA

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^5 and X^6 are each independently CH, CF, or N;

L^1 is selected from a direct bond and a C_1 - C_6 alkyl optionally substituted with $(E^{11})_m$, or when taken together with R^3 and the N atom to which L^1 and R^3 are attached form an optionally substituted heterocycle having from 4 to 8 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^1 is selected from the group consisting of hydroxy, alkoxy, cyano, haloalkoxy, halogen,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, amine, alkylamine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of aryl, alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, heterocyclyl, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano and heterocyclyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, alkoxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E¹¹, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E¹¹ taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is L⁷-E⁷ wherein:

L⁷ is a direct bond;

E⁷ is optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, urea, amine, amidine, acyl, carbamoyl, formyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

each occurrence of m is independently 0, 1, 2, 3, or 4;

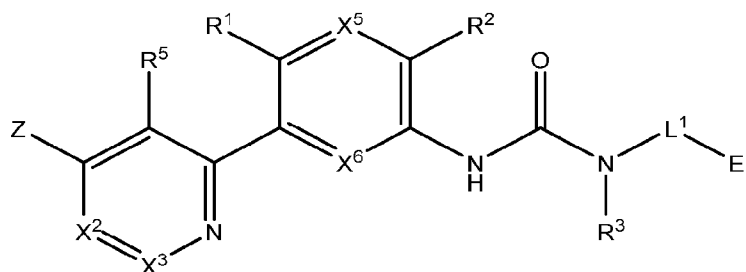
R¹ is selected from the group consisting of H, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, and halogen;

R² is selected from the group consisting of H and F;

R³ is selected from the group consisting of H, C₁-C₅ alkyl, and C₃-C₅ cycloalkyl; and

R⁵, at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen.

[000109] In some embodiments, the compound is represented by Formula I-O:



Formula I-O

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^2 is C-O-L²-E², C-L²-E², C-N(R⁴)-L²-E², CH, or N;

X^3 is CH, C-O-L³-E³, C-L³-E³, C-N(R⁴)-L³-E³, or N;

provided that not more than one of X^2 and X^3 are N;

X^5 and X^6 are each independently CH, CF, or N;

L¹ is selected from a direct bond and a C₁-C₆alkyl optionally substituted with (E¹¹)_m, or when taken together with R³ and the N atom to which L¹ and R³ are attached form an optionally substituted heterocycle having from 4 to 8 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

L² is a direct bond or a C₁-C₆ alkyl optionally substituted with (E²¹)_p;

L³ is a direct bond or a C₁-C₆ alkyl optionally substituted with (E³¹)_p;

E¹ is selected from the group consisting of H, hydroxy, alkoxy, cyano, haloalkoxy, halogen,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, amine, alkylamine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of aryl, alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, heterocyclyl, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano and heterocyclyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide,

amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, alkoxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E¹¹, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E¹¹ taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

E² is selected from the group consisting of H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, sulfone, hydroxy, alkoxy, alkoxyalkyl, cyano, sulfonyl, and

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl,

E²¹, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E²¹ taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

E³ is selected from the group consisting of haloalkoxy, H, alkyl, acyl, amine, aminoalkyl, amide, haloalkyl, cyano, sulfone, hydroxy, alkoxy, alkoxyalkyl, cyano, sulfonyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, or cyano, cyanoalkyl, heterocyclyl, and

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E^{31} , at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; or wherein two occurrences of E^{31} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is L^7-E^7 wherein:

L^7 is a direct bond;

E^7 is selected from the group consisting of:

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, cycloalkyl, alkoxy, alkoxyalkyl, amine, acyl, carbamoyl, formyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, urea, amine, amidine, acyl, carbamoyl, formyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

each occurrence of m is independently 0, 1, 2, 3, or 4;

each occurrence of p is independently 0, 1, or 2;

R^1 is selected from the group consisting of H, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, and halogen;

R^2 is selected from the group consisting of H and F;

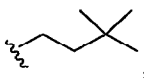
R^3 is selected from the group consisting of H, C_1-C_5 alkyl, and C_3-C_5 cycloalkyl;

R^4 , at each occurrence, is independently H or alkyl; and

R^5 , at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen;

with the proviso that:

when E^7 is morpholinyl, X^2 is N, X^3 is $C-L^3-E^3$, and L^3 is a direct bond, then E^3 is not heteroaryl;

when L^1-E^1 is , R^1 is methyl, R^2 is H, R^3 is H, R^5 is H, X^5 is N or CH, X^6 is CH, E^7 is a substituent selected from the group consisting of oxetanyl, tetrahydrofuranyl, and tetrahydropyranyl, and

X^2 is selected from the group consisting of:

(i) $C-L^2-E^2$, wherein L^2-E^2 is selected from H;

(ii) C-O-L²-E², wherein O-L²-E² is selected from the group consisting of methoxy, ethoxy, isopropoxy, 2-methoxyethoxy, 2-hydroxyethoxy, (tetrahydro-2*H*-pyran-4-yl)oxy, and (1-ethylpiperidin-4-yl)oxy;

(iii) C-N(R⁴)-L²-E², wherein N(R⁴)-L²-E² is selected from the group consisting of (2-methoxyethyl)amino, (2-hydroxyethyl)(methyl)amino, and (1-hydroxypropan-2-yl)amino; and

(iv) N,

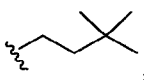
then X³ is not selected from the group consisting of:

(i) C-L³-E³, wherein L³-E³ is selected from the group consisting of H, methyl, 3-hydroxyoxetan-3-yl, 4-hydroxy-piperidin-1-yl, 4-amino-4-methylpiperidin-1-yl, and 2-oxooxazolidin-3-yl;

(ii) C-O-L³-E³, wherein O-L³-E³ is selected from the group consisting of methoxy, 2-hydroxyethoxy, and 2,3-dihydroxypropoxy;

(iii) C-N(R⁴)-L³-E³, wherein N(R⁴)-L³-E³ is selected from the group consisting of bis(2-hydroxyethyl)amino and (2-hydroxyethyl)amino; and

(iv) N; and

when L¹-E¹ is , R¹ is methyl, R² is H, R³ is H, R⁵ is H, X⁵ is N or CH, X⁶ is CH, X³ is C-L³-E³, L³ is a direct bond, E³ is selected from the group consisting of oxetanyl, tetrahydrofuranyl, and tetrahydropyranyl, and

X² is selected from the group consisting of:

(i) C-L²-E², wherein L²-E² is selected from H;

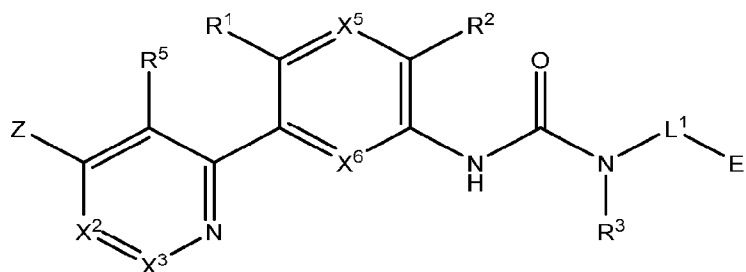
(ii) C-O-L²-E², wherein O-L²-E² is selected from the group consisting of methoxy, ethoxy, isopropoxy, 2-methoxyethoxy, 2-hydroxyethoxy, (tetrahydro-2*H*-pyran-4-yl)oxy, and (1-ethylpiperidin-4-yl)oxy;

(iii) C-N(R⁴)-L²-E², wherein N(R⁴)-L²-E² is selected from the group consisting of (2-methoxyethyl)amino, (2-hydroxyethyl)(methyl)amino, and (1-hydroxypropan-2-yl)amino; and

(iv) N,

then E⁷ is not selected from the group consisting of: 3-hydroxyoxetan-3-yl, 4-hydroxy-piperidin-1-yl, 4-amino-4-methylpiperidin-1-yl, and 2-oxooxazolidin-3-yl.

[000110] In some embodiments, the compound is represented by Formula I-OA:



Formula I-OA

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^2 is C-O-L²-E², C-L²-E², C-N(R⁴)-L²-E², CH, or N;

X^3 is CH, C-O-L³-E³, C-L³-E³, C-N(R⁴)-L³-E³, or N;

provided that not more than one of X^2 and X^3 are N;

X^5 and X^6 are each independently CH, CF, or N;

L¹ is selected from a direct bond and a C₁-C₆alkyl optionally substituted with (E¹¹)_m, or when taken together with R³ and the N atom to which L¹ and R³ are attached form an optionally substituted heterocycle having from 4 to 8 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

L² is a direct bond or a C₁-C₆ alkyl optionally substituted with (E²¹)_p;

L³ is a direct bond or a C₁-C₆ alkyl optionally substituted with (E³¹)_p;

E¹ is selected from the group consisting of hydroxy, alkoxy, cyano, haloalkoxy, halogen,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, amine, alkylamine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of aryl, alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, heterocyclyl, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano and heterocyclyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide,

amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, alkoxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E¹¹, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E¹¹ taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

E² is selected from the group consisting of H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, sulfone, hydroxy, alkoxy, alkoxyalkyl, cyano, sulfonyl, and

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl,

E²¹, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E²¹ taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

E³ is selected from the group consisting of haloalkoxy, H, alkyl, acyl, amine, aminoalkyl, amide, haloalkyl, cyano, sulfone, hydroxy, alkoxy, alkoxyalkyl, cyano, sulfonyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, or cyano, cyanoalkyl, heterocyclyl, and

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E^{31} , at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{31} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is L^7-E^7 wherein:

L^7 is a direct bond;

E^7 is optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, urea, amine, amidine, acyl, carbamoyl, formyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

each occurrence of m is independently 0, 1, 2, 3, or 4;

each occurrence of p is independently 0, 1, or 2;

R^1 is selected from the group consisting of H, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, and halogen;

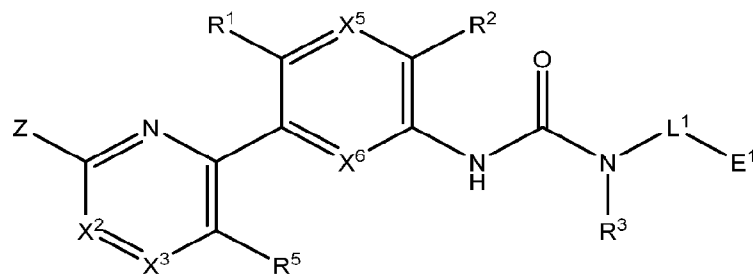
R^2 is selected from the group consisting of H and F;

R^3 is selected from the group consisting of H, C_1 - C_5 alkyl, and C_3 - C_5 cycloalkyl;

R^4 , at each occurrence, is independently H or alkyl; and

R^5 , at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen.

[000111] In some embodiments, the compound is represented by Formula I-P:



Formula I-P

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^2 is $C-O-L^2-E^2$, $C-L^2-E^2$, $C-N(R^4)-L^2-E^2$, CH, or N;

X^3 is CH, $C-O-L^3-E^3$, $C-L^3-E^3$, $C-N(R^4)-L^3-E^3$, or N;

provide that not more than one of X^2 and X^3 are N;

X^5 and X^6 are each independently CH, CF, or N;

L¹ is selected from a direct bond and a C₁-C₆alkyl optionally substituted with (E¹¹)_m, or when taken together with R³ and the N atom to which L¹ and R³ are attached form an optionally substituted heterocycle having from 4 to 8 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

L² is a direct bond or a C₁-C₆ alkyl optionally substituted with (E²¹)_p;

L³ is a direct bond or a C₁-C₆ alkyl optionally substituted with (E³¹)_p;

E¹ is selected from the group consisting of H, hydroxy, alkoxy, cyano, haloalkoxy, halogen,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, amine, alkylamine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of aryl, alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, heterocyclyl, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano and heterocyclyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, alkoxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E¹¹, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E¹¹ taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

E² is selected from the group consisting of H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, sulfone, hydroxy, alkoxy, alkoxyalkyl, cyano, sulfonyl, and

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl,

E^{21} , at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{21} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

E^3 is selected from the group consisting of haloalkoxy, H, alkyl, acyl, amine, aminoalkyl, amide, haloalkyl, cyano, sulfone, hydroxy, alkoxy, alkoxyalkyl, cyano, sulfonyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, or cyano, cyanoalkyl, and heterocyclyl, and

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, hydroxy, or cyano;

E^{31} , at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{31} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is L^7-E^7 wherein:

L^7 is a direct bond;

E^7 is selected from the group consisting of:

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, cycloalkyl, alkoxy, alkoxyalkyl, amine, acyl, carbamoyl, formyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, urea, amine, amidine, acyl, carbamoyl, formyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

each occurrence of m is independently 0, 1, 2, 3, or 4;

each occurrence of p is independently 0, 1, or 2;

R^1 is selected from the group consisting of H, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, and halogen;

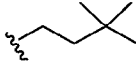
R^2 is selected from the group consisting of H and F;

R^3 is selected from the group consisting of H, C_1 - C_5 alkyl, and C_3 - C_5 cycloalkyl;

R^4 , at each occurrence, is independently H or alkyl; and

R^5 , at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen;

with the proviso that:

when L^1-E^1 is , R^1 is methyl, R^2 is H, R^3 is H, R^5 is H, X^5 is N or CH, X^6 is CH, E^7 is a substituent selected from the group consisting of oxetanyl, tetrahydrofuranyl, and tetrahydropyranyl, and

X^2 is selected from the group consisting of:

(i) $C-L^2-E^2$, wherein L^2-E^2 is selected from H;

(ii) $C-O-L^2-E^2$, wherein $O-L^2-E^2$ is selected from the group consisting of methoxy, ethoxy, isopropoxy, 2-methoxyethoxy, 2-hydroxyethoxy, (tetrahydro-2H-pyran-4-yl)oxy, and (1-ethylpiperidin-4-yl)oxy;

(iii) $C-N(R^4)-L^2-E^2$, wherein $N(R^4)-L^2-E^2$ is selected from the group consisting of (2-methoxyethyl)amino, (2-hydroxyethyl)(methyl)amino, and (1-hydroxypropan-2-yl)amino; and

(iv) N,

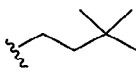
then X^3 is not selected from the group consisting of:

(i) $C-L^3-E^3$, wherein L^3-E^3 is selected from the group consisting of H, methyl, 3-hydroxyoxetan-3-yl, 4-hydroxy-piperidin-1-yl, 4-amino-4-methylpiperidin-1-yl, and 2-oxooxazolidin-3-yl;

(ii) $C-O-L^3-E^3$, wherein $O-L^3-E^3$ is selected from the group consisting of methoxy, 2-hydroxyethoxy, and 2,3-dihydroxypropoxy;

(iii) C-N(R⁴)-L³-E³, wherein N(R⁴)-L³-E³ is selected from the group consisting of bis(2-hydroxyethyl)amino and (2-hydroxyethyl)amino; and

(iv) N; and

when L¹-E¹ is , R¹ is methyl, R² is H, R³ is H, R⁵ is H, X⁵ is N or CH, X⁶ is CH, X³ is C-L³-E³, L³ is a direct bond, E³ is selected from the group consisting of oxetanyl, tetrahydrofuranyl, and tetrahydropyranyl, and

X² is selected from the group consisting of:

(i) C-L²-E², wherein L²-E² is selected from H;

(ii) C-O-L²-E², wherein O-L²-E² is selected from the group consisting of methoxy, ethoxy, isopropoxy, 2-methoxyethoxy, 2-hydroxyethoxy, (tetrahydro-2H-pyran-4-yl)oxy, and (1-ethylpiperidin-4-yl)oxy;

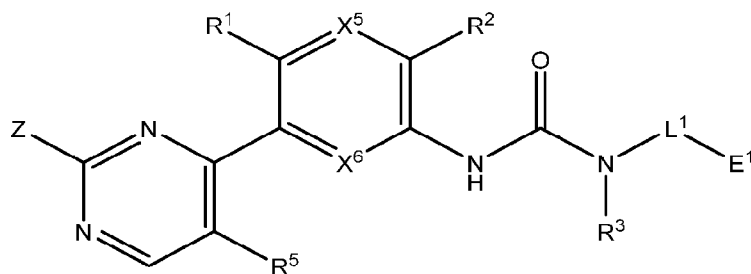
(iii) C-N(R⁴)-L²-E², wherein N(R⁴)-L²-E² is selected from the group consisting of (2-methoxyethyl)amino, (2-hydroxyethyl)(methyl)amino, and (1-hydroxypropan-2-yl)amino; and

(iv) N,

then E⁷ is not selected from the group consisting of: 3-hydroxyoxetan-3-yl, 4-hydroxy-piperidin-1-yl, 4-amino-4-methylpiperidin-1-yl, and 2-oxooxazolidin-3-yl; and

when E⁷ is 5- or 6- membered optionally substituted heteroaryl or 5- or 6-membered optionally substituted heterocyclyl, R⁵ is H or F, X⁵ is CH, X⁶ is CH, CD, or CF, X² is N, and X³ is C-O-L³-E³ or C-N(R⁴)-L³-E³, then L¹ is not taken together with R³ and the N atom to which L¹ and R³ are attached form an optionally substituted heterocycle having from 4 to 7 atoms in the ring structure.

[000112] In some embodiments, the compound is represented by Formula I-PA:



Formula I-PA

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^5 and X^6 are each independently CH, CF, or N;

L^1 is selected from a direct bond and a C_1 - C_6 alkyl optionally substituted with $(E^{11})_m$, or when taken together with R^3 and the N atom to which L^1 and R^3 are attached form an optionally substituted heterocycle having from 4 to 8 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^1 is selected from the group consisting of hydroxy, alkoxy, cyano, haloalkoxy, halogen,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, amine, alkylamine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of aryl, alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, heterocyclyl, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano and heterocyclyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, alkoxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E^{11} , at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{11} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is L^7 - E^7 wherein:

L^7 is a direct bond;

E⁷ is optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, urea, amine, amidine, acyl, carbamoyl, formyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

each occurrence of m is independently 0, 1, 2, 3, or 4;

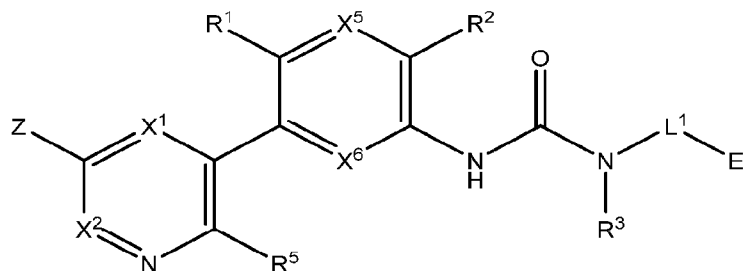
R¹ is selected from the group consisting of H, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, and halogen;

R² is selected from the group consisting of H and F;

R³ is selected from the group consisting of H, C₁-C₅ alkyl, and C₃-C₅ cycloalkyl; and

R⁵, at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen.

[000113] In some embodiments, the compound is represented by Formula I-Q:



Formula I-Q

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X¹ is each independently CR⁵, or N;

X² is C-O-L²-E², C-L²-E², C-N(R⁴)-L²-E², CH, or N;

provided that not more than one of X¹ and X² are N;

X⁵ and X⁶ are each independently CH, CF, or N;

L¹ is selected from a direct bond and a C₁-C₆alkyl optionally substituted with (E¹¹)_m, or when taken together with R³ and the N atom to which L¹ and R³ are attached form an optionally substituted heterocycle having from 4 to 8 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

L³ is a direct bond or a C₁-C₆ alkyl optionally substituted with (E³¹)_p;

E¹ is selected from the group consisting of H, hydroxy, alkoxy, cyano, haloalkoxy, halogen,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, amine, alkylamine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of aryl, alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, heterocyclyl, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano and heterocyclyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, alkoxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E¹¹, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E¹¹ taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

E² is selected from the group consisting of H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, sulfone, hydroxy, alkoxy, alkoxyalkyl, cyano, sulfonyl, and

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E²¹, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E²¹ taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is L⁷-E⁷ wherein:

L⁷ a direct bond;

E^7 is selected from the group consisting of:

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, cycloalkyl, alkoxy, alkoxyalkyl, amine, acyl, carbamoyl, formyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, urea, amine, amidine, acyl, carbamoyl, formyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

each occurrence of m is independently 0, 1, 2, 3, or 4;

each occurrence of p is independently 0, 1, or 2;

R^1 is selected from the group consisting of H, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, and halogen;

R^2 is selected from the group consisting of H and F;

R^3 is selected from the group consisting of H, C_1 - C_5 alkyl, and C_3 - C_5 cycloalkyl;

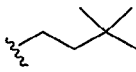
R^4 , at each occurrence, is independently H or alkyl; and

R^5 , at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen,

with the proviso that

when E^7 is morpholinyl, X^1 is CH, X^2 is C-O- L^2 - E^2 , R^5 is H, X^6 is CH, CD, or CF, and R^3 is H, then L^1 - E^1 is not optionally substituted alkyl, optionally substituted C_3 - C_6 cycloalkyl, optionally substituted C_3 - C_6 cycloalkylalkyl, optionally substituted C_4 - C_6 heterocyclyl, or optionally substituted heterocyclylalkyl;

when E^7 is morpholinyl, X^1 is CH, X^2 is C-O- L^2 - E^2 , R^5 is H, and X^6 is CH, CD, or CF, then L^1 is not taken together with R^3 and the N atom to which L^1 and R^3 are attached form an optionally substituted heterocycle having from 4 to 8 atoms in the ring structure;

when L^1 - E^1 is , R^1 is methyl, R^2 is H, R^3 is H, X^1 is N or CH, R^5 is H, X^5 is N or CH, X^6 is CH, and E^7 is a substituent selected from the group consisting of oxetanyl, tetrahydrofuranyl, and tetrahydropyranyl,

then X^2 is not selected from the group consisting of:

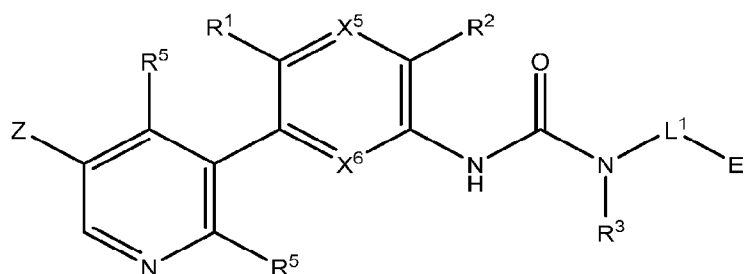
(i) C- L^2 - E^2 , wherein L^2 - E^2 is selected from H;

(ii) C-O-L²-E², wherein O-L²-E² is selected from the group consisting of methoxy, ethoxy, isopropoxy, 2-methoxyethoxy, 2-hydroxyethoxy, (tetrahydro-2H-pyran-4-yl)oxy, and (1-ethylpiperidin-4-yl)oxy;

(iii) C-N(R⁴)-L²-E², wherein N(R⁴)-L²-E² is selected from the group consisting of (2-methoxyethyl)amino, (2-hydroxyethyl)(methyl)amino, and (1-hydroxypropan-2-yl)amino; and

(iv) N.

[000114] In some embodiments, the compound is represented by Formula I-QA:



Formula I-QA

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X¹ is each independently CR⁵ or N;

X⁵ and X⁶ are each independently CH, CF, or N;

L¹ is selected from a direct bond and a C₁-C₆alkyl optionally substituted with (E¹¹)_m, or when taken together with R³ and the N atom to which L¹ and R³ are attached form an optionally substituted heterocycle having from 4 to 8 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E¹ is selected from the group consisting of hydroxy, alkoxy, cyano, haloalkoxy, halogen,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, amine, alkylamine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of aryl, alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, heterocyclyl, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano and heterocyclyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, alkoxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E¹¹, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E¹¹ taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is L⁷-E⁷ wherein:

L⁷ a direct bond;

E⁷ is optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, urea, amine, amidine, acyl, carbamoyl, formyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

each occurrence of m is independently 0, 1, 2, 3, or 4;

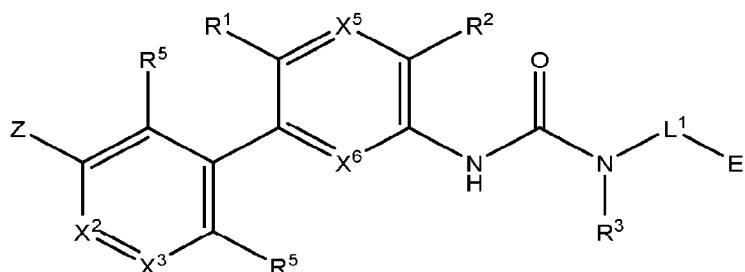
R¹ is selected from the group consisting of H, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, and halogen;

R² is selected from the group consisting of H and F;

R³ is selected from the group consisting of H, C₁-C₅ alkyl, and C₃-C₅ cycloalkyl; and

R⁵, at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen.

[000115] In some embodiments, the compound is represented by Formula I-R:



Formula I-R

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^2 is CH, C-O-L²-E², C-L²-E², or C-N(R⁴)-L²-E²;

X^3 is CH, C-O-L³-E³, C-L³-E³, or C-N(R⁴)-L³-E³;

X^5 and X^6 are each independently CH, CF, or N;

L¹ is selected from a direct bond and a C₁-C₆alkyl optionally substituted with (E¹¹)_m, or when taken together with R³ and the N atom to which L¹ and R³ are attached form an optionally substituted heterocycle having from 4 to 8 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

L² is a direct bond or a C₁-C₆ alkyl optionally substituted with (E²¹)_p;

L³ is a direct bond or a C₁-C₆ alkyl optionally substituted with (E³¹)_p;

E¹ is selected from the group consisting of H, hydroxy, alkoxy, cyano, haloalkoxy, halogen,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, amine, alkylamine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of aryl, alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, heterocyclyl, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano and heterocyclyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide,

amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, alkoxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E¹¹, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E¹¹ taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

E² is selected from the group consisting of H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, sulfone, hydroxy, alkoxy, alkoxyalkyl, cyano, sulfonyl, and

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E²¹, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E²¹ taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

E³ is selected from the group consisting of haloalkoxy, H, alkyl, acyl, amine, aminoalkyl, amide, haloalkyl, cyano, sulfone, hydroxy, alkoxy, alkoxyalkyl, cyano, sulfonyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, or cyano, cyanoalkyl, and heterocyclyl, and

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E^{31} , at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; or wherein two occurrences of E^{31} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is L^7-E^7 wherein:

L^7 a direct bond;

E^7 is selected from the group consisting of:

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, cycloalkyl, alkoxy, alkoxyalkyl, amine, acyl, carbamoyl, formyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, urea, amine, amidine, acyl, carbamoyl, formyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

each occurrence of m is independently 0, 1, 2, 3, or 4;

each occurrence of p is independently 0, 1, or 2;

R^1 is selected from the group consisting of H, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, and halogen;

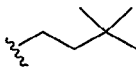
R^2 is selected from the group consisting of H and F;

R^3 is selected from the group consisting of H, C_1 - C_5 alkyl, and C_3 - C_5 cycloalkyl;

R^4 , at each occurrence, is independently H or alkyl; and

R^5 , at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen;

with the proviso that:

when L^1-E^1 is , R^1 is methyl, R^2 is H, R^3 is H, R^5 is H, X^5 is N or CH, X^6 is CH, E^7 is a substituent selected from the group consisting of oxetanyl, tetrahydrofuranyl, and tetrahydropyranyl, and

X^2 is selected from the group consisting of:

(i) $C-L^2-E^2$, wherein L^2-E^2 is selected from H;

(ii) C-O-L²-E², wherein O-L²-E² is selected from the group consisting of methoxy, ethoxy, isopropoxy, 2-methoxyethoxy, 2-hydroxyethoxy, (tetrahydro-2*H*-pyran-4-yl)oxy, and (1-ethylpiperidin-4-yl)oxy; and

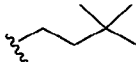
(iii) C-N(R⁴)-L²-E², wherein N(R⁴)-L²-E² is selected from the group consisting of (2-methoxyethyl)amino, (2-hydroxyethyl)(methyl)amino, and (1-hydroxypropan-2-yl)amino;

then X³ is not selected from the group consisting of:

(i) C-L³-E³, wherein L³-E³ is selected from the group consisting of H, methyl, 3-hydroxyoxetan-3-yl, 4-hydroxy-piperidin-1-yl, 4-amino-4-methylpiperidin-1-yl, and 2-oxooxazolidin-3-yl;

(ii) C-O-L³-E³, wherein O-L³-E³ is selected from the group consisting of methoxy, 2-hydroxyethoxy, and 2,3-dihydroxypropoxy; and

(iii) C-N(R⁴)-L³-E³, wherein N(R⁴)-L³-E³ is selected from the group consisting of bis(2-hydroxyethyl)amino and (2-hydroxyethyl)amino; and

when L¹-E¹ is , R¹ is methyl, R² is H, R³ is H, R⁵ is H, X⁵ is N or CH, X⁶ is CH, X³ is C-L³-E³, L³ is a direct bond, E³ is selected from the group consisting of oxetanyl, tetrahydrofuranyl, and tetrahydropyranyl, and

X² is selected from the group consisting of:

(i) C-L²-E², wherein L²-E² is selected from H;

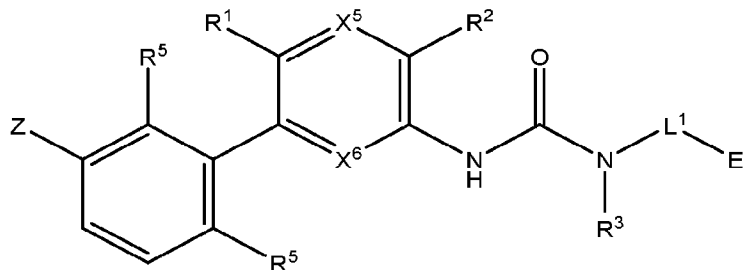
(ii) C-O-L²-E², wherein O-L²-E² is selected from the group consisting of methoxy, ethoxy, isopropoxy, 2-methoxyethoxy, 2-hydroxyethoxy, (tetrahydro-2*H*-pyran-4-yl)oxy, and (1-ethylpiperidin-4-yl)oxy; and

(iii) C-N(R⁴)-L²-E², wherein N(R⁴)-L²-E² is selected from the group consisting of (2-methoxyethyl)amino, (2-hydroxyethyl)(methyl)amino, and (1-hydroxypropan-2-yl)amino,

then E⁷ is not selected from the group consisting of: 3-hydroxyoxetan-3-yl, 4-hydroxy-piperidin-1-yl, 4-amino-4-methylpiperidin-1-yl, and 2-oxooxazolidin-3-yl; and

when E⁷ is 5- or 6- membered optionally substituted heteroaryl or 5- or 6-membered optionally substituted heterocyclyl, R⁵ is H or F, X⁵ is CH, X⁶ is CH, CD, or CF, X² is N, and X³ is C-O-L³-E³ or C-N(R⁴)-L³-E³, then L¹ is not taken together with R³ and the N atom to which L¹ and R³ are attached form an optionally substituted heterocycle having from 4 to 7 atoms in the ring structure.

[000116] In some embodiments, the compound is represented by Formula I-RA:



Formula I-RA

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^5 and X^6 are each independently CH, CF, or N;

L^1 is selected from a direct bond and a C_1 - C_6 alkyl optionally substituted with $(E^{11})_m$, or when taken together with R^3 and the N atom to which L^1 and R^3 are attached form an optionally substituted heterocycle having from 4 to 8 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^1 is selected from the group consisting of hydroxy, alkoxy, cyano, haloalkoxy, halogen,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, amine, alkylamine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of aryl, alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, heterocyclyl, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano and heterocyclyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, alkoxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E^{11} , at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{11} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is L^7-E^7 wherein:

L^7 a direct bond;

E^7 is optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, urea, amine, amidine, acyl, carbamoyl, formyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

each occurrence of m is independently 0, 1, 2, 3, or 4;

R^1 is selected from the group consisting of H, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, and halogen;

R^2 is selected from the group consisting of H and F;

R^3 is selected from the group consisting of H, C_1-C_5 alkyl, and C_3-C_5 cycloalkyl; and

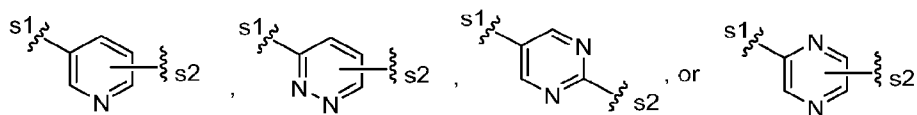
R^5 , at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen.

[000117] In some embodiments, E^1 is selected from the group consisting of H, hydroxy, alkoxy, cyano, haloalkoxy, halogen,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, amine, alkylamine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of aryl, alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, heterocyclyl, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, and heterocyclyl, and wherein the optionally substituted heteroaryl is not



wherein s1 is the site covalently linked to L¹; and s2 is the site covalently linked to H or the optionally substituted substituent,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, alkoxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

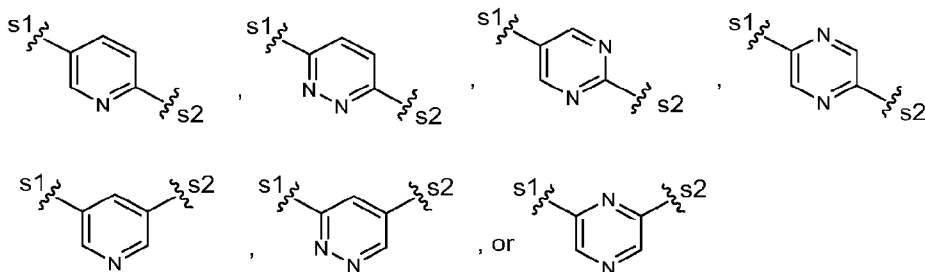
optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano.

[000118] In some embodiments, E¹ is selected from the group consisting of H, hydroxy, alkoxy, cyano, haloalkoxy, halogen,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, amine, alkylamine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of aryl, alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, heterocyclyl, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, and heterocyclyl, and wherein the optionally substituted heteroaryl is not

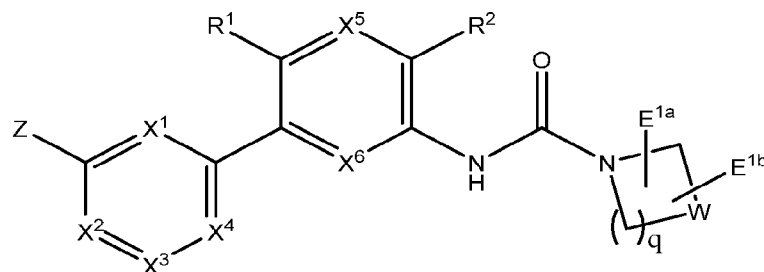


wherein s1 is the site covalently linked to L¹; and s2 is the site covalently linked to H or the optionally substituted substituent,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, alkoxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano.

[000119] In some embodiments, the compound is represented by Formula I-S:



Formula I-S

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^1 and X^4 are each independently CR^5 , or N;

X^5 and X^6 are each independently CH, CF, or N;

X^2 is N, CH, C=O, C-O- L^2 - E^2 , C- L^2 - E^2 , C-N(R^4)- L^2 - E^2 , or N- L^2 - E^2 ;

X^3 is C-O- L^3 - E^3 , C- L^3 - E^3 , C-N(R^4)- L^3 - E^3 , CH, C=O, N, or N- L^3 - E^3 ;

provided that not more than two of X^1 , X^2 , X^3 , and X^4 are N;

provided that when X^2 is N, X^3 is C-O- L^3 - E^3 , C- L^3 - E^3 , C-N(R^4)- L^3 - E^3 , N, or

CH;

provided that when X^3 is N, X^2 is N, CH, C-O- L^2 - E^2 , C- L^2 - E^2 , or C-N(R^4)- L^2 -

E^2 ;

provided that when X^2 is C=O, X^3 is N- L^3 - E^3 ;

provided that when X^3 is C=O, X^2 is N- L^2 - E^2 ;

L^2 is a direct bond or a C_1 - C_6 alkyl optionally substituted with $(E^{21})_p$;

L^3 is a direct bond or a C_1 - C_6 alkyl optionally substituted with $(E^{31})_p$;

each of E^{1a} and E^{1b} is independently selected from the group consisting of H, alkoxy, cyano, haloalkoxy, halogen,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano, and

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone;

or wherein E^{1a} and E^{1b} taken together with the carbon atom to which they are attached form an optionally substituted cycloalkyl ring or an optionally substituted heterocyclyl ring having from 3 to 6 atoms in the ring structure, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

or, when E^{1a} and E^{1b} are attached to the same carbon atom, E^{1a} and E^{1b} are taken together with the carbon atom to which they are attached to form oxo;

E² is selected from the group consisting of H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, sulfone, hydroxy, alkoxy, alkoxyalkyl, cyano, sulfonyl, and

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E²¹, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E²¹ taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

E³ is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, sulfonyl, haloalkoxy, H, alkyl, acyl, amine, aminoalkyl, amide, haloalkyl, cyano, sulfone,

optionally substituted heterocyclyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted heteroaryl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

optionally substituted cycloalkyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E³¹, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E³¹ taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

W is selected from the group consisting of CH₂, O, or N-R¹⁰,

Z is L⁷-E⁷ wherein:

L⁷ is a direct bond;

E⁷ is selected from the group consisting of:

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, cycloalkyl, alkoxy, alkoxyalkyl, amine, acyl, carbamoyl, formyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, urea, amine, amidine, acyl, carbamoyl, formyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

R¹ is selected from the group consisting of H, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, and halogen;

R² is selected from the group consisting of H and F;

R³ is selected from the group consisting of H, C₁-C₅ alkyl, and C₃-C₅ cycloalkyl;

R⁴, at each occurrence, is independently H or alkyl; and

R⁵, at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen;

R¹⁰, at each occurrence, is independently selected from the group consisting of H, C₁-C₆ alkyl, C₃-C₅ cycloalkyl, and C₁-C₆ acyl;

each occurrence of m is independently 0, 1, 2, 3, or 4;

each occurrence of p is independently 0, 1, or 2;

each occurrence of q is independently 1, 2, or 3;

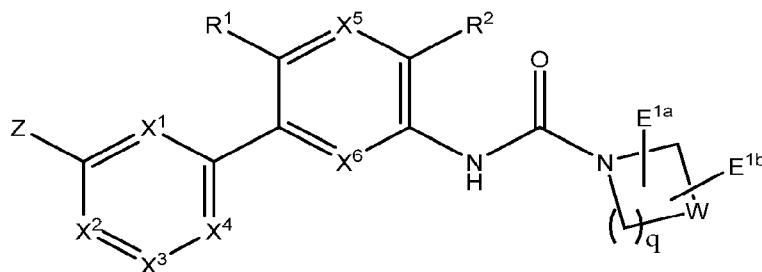
with the proviso that

E^7 is not morpholinyl,

when X^1 , X^4 , X^5 , and X^6 are CH, R^1 is $-\text{CH}_3$, X^2 is N, X^3 is $\text{C-L}^3\text{-E}^3$, L^3 is a direct bond, and E^3 is morpholinyl, then E^7 is not optionally substituted $\text{C}_3\text{-C}_6$ heterocyclyl or optionally substituted 5- or 6-membered heteroaryl; and

when X^1 and X^4 are each independently N, CH, or CF, X^5 is CH, and X^6 is CH, CD, or CF, then E^7 is not 5- or 6- membered optionally substituted heteroaryl or 5- or 6-membered optionally substituted heterocyclyl.

[000120] In some embodiments, the compound is represented by Formula I-SA:



Formula I-SA

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^1 and X^4 are each independently CR^5 , or N;

X^5 and X^6 are each independently CH, CF, or N;

X^2 is N, CH, C=O , $\text{C-O-L}^2\text{-E}^2$, $\text{C-L}^2\text{-E}^2$, $\text{C-N(R}^4\text{)-L}^2\text{-E}^2$, or $\text{N-L}^2\text{-E}^2$;

X^3 is $\text{C-O-L}^3\text{-E}^3$, $\text{C-L}^3\text{-E}^3$, $\text{C-N(R}^4\text{)-L}^3\text{-E}^3$, CH, C=O , N, or $\text{N-L}^3\text{-E}^3$,

provided that not more than two of X^1 , X^2 , X^3 , and X^4 are N;

provided that when X^2 is N, X^3 is $\text{C-O-L}^3\text{-E}^3$, $\text{C-L}^3\text{-E}^3$, $\text{C-N(R}^4\text{)-L}^3\text{-E}^3$, N, or CH;

provided that when X^3 is N, X^2 is N, CH, $\text{C-O-L}^2\text{-E}^2$, $\text{C-L}^2\text{-E}^2$, or $\text{C-N(R}^4\text{)-L}^2\text{-E}^2$;

provided that when X^2 is C=O , X^3 is $\text{N-L}^3\text{-E}^3$;

provided that when X^3 is C=O , X^2 is $\text{N-L}^2\text{-E}^2$;

L^2 is a direct bond or a $\text{C}_1\text{-C}_6$ alkyl optionally substituted with $(\text{E}^{21})_p$;

L³ is a direct bond or a C₁-C₆alkyl optionally substituted with (E³¹)_p;
each of E^{1a} and E^{1b} is independently selected from the group consisting of H, alkoxy, cyano, haloalkoxy, halogen,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano, and

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone;

or wherein E^{1a} and E^{1b} taken together with the carbon atom to which they are attached form an optionally substituted cycloalkyl ring or an optionally substituted heterocyclyl ring having from 3 to 6 atoms in the ring structure, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

or, when E^{1a} and E^{1b} are attached to the same carbon atom, E^{1a} and E^{1b} are taken together with the carbon atom to which they are attached to form oxo;

E² is selected from the group consisting of H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, sulfone, hydroxy, alkoxy, alkoxyalkyl, cyano, sulfonyl, and

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E²¹, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E²¹ taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

E³ is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, sulfonyl, haloalkoxy, H, alkyl, acyl, amine, aminoalkyl, amide, haloalkyl, cyano, sulfone,

optionally substituted heterocyclyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted heteroaryl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

optionally substituted cycloalkyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E^{31} , at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{31} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

W is selected from the group consisting of CH_2 , O, or $N-R^{10}$,

Z is L^7-E^7 wherein:

L^7 is a direct bond;

E^7 is optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, urea, amine, amidine, acyl, carbamoyl, formyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

R^1 is selected from the group consisting of H, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, and halogen;

R^2 is selected from the group consisting of H and F;

R^3 is selected from the group consisting of H, C_1-C_5 alkyl, and C_3-C_5 cycloalkyl;

R^4 , at each occurrence, is independently H or alkyl; and

R^5 , at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen;

R^{10} , at each occurrence, is independently selected from the group consisting of H, C_1-C_6 alkyl, C_3-C_5 cycloalkyl, and C_1-C_6 acyl;

each occurrence of m is independently 0, 1, 2, 3, or 4;

each occurrence of p is independently 0, 1, or 2;

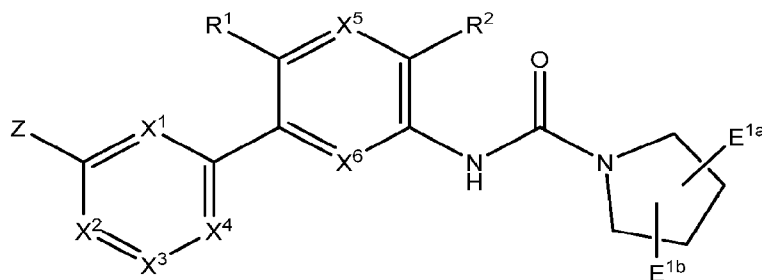
each occurrence of q is independently 1, 2, or 3;

with the proviso that

when X^1 , X^4 , X^5 , and X^6 are CH, R^1 is $-\text{CH}_3$, X^2 is N, X^3 is $\text{C}-\text{L}^3-\text{E}^3$, and L^3 is a direct bond, E^3 is not morpholinyl; and

when X^1 and X^4 are each independently N, CH, or CF, X^5 is CH, and X^6 is CH, CD, or CF, E^7 is not 5- or 6- membered optionally substituted heteroaryl.

[000121] In some embodiments, the compound is represented by Formula I-T:



Formula I-T

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^1 and X^4 are each independently CR^5 , or N;

X^5 and X^6 are each independently CH, CF, or N;

X^2 is N, CH, $\text{C}=\text{O}$, $\text{C}-\text{O}-\text{L}^2-\text{E}^2$, $\text{C}-\text{L}^2-\text{E}^2$, $\text{C}-\text{N}(\text{R}^4)-\text{L}^2-\text{E}^2$, or $\text{N}-\text{L}^2-\text{E}^2$;

X^3 is $\text{C}-\text{O}-\text{L}^3-\text{E}^3$, $\text{C}-\text{L}^3-\text{E}^3$, $\text{C}-\text{N}(\text{R}^4)-\text{L}^3-\text{E}^3$, CH, $\text{C}=\text{O}$, N, or $\text{N}-\text{L}^3-\text{E}^3$,

provided that not more than two of X^1 , X^2 , X^3 , and X^4 are N;

provided that when X^2 is N, X^3 is $\text{C}-\text{O}-\text{L}^3-\text{E}^3$, $\text{C}-\text{L}^3-\text{E}^3$, $\text{C}-\text{N}(\text{R}^4)-\text{L}^3-\text{E}^3$, N, or CH;

provided that when X^3 is N, X^2 is N, CH, $\text{C}-\text{O}-\text{L}^2-\text{E}^2$, $\text{C}-\text{L}^2-\text{E}^2$, or $\text{C}-\text{N}(\text{R}^4)-\text{L}^2-\text{E}^2$;

provided that when X^2 is $\text{C}=\text{O}$, X^3 is $\text{N}-\text{L}^3-\text{E}^3$;

provided that when X^3 is $\text{C}=\text{O}$, X^2 is $\text{N}-\text{L}^2-\text{E}^2$;

L^2 is a direct bond or a $\text{C}_1\text{-C}_6$ alkyl optionally substituted with $(\text{E}^{21})_p$;

L^3 is a direct bond or a $\text{C}_1\text{-C}_6$ alkyl optionally substituted with $(\text{E}^{31})_p$;

each of E^{1a} and E^{1b} is independently selected from the group consisting of H, alkoxy, cyano, haloalkoxy, halogen,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano, and

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone;

or wherein E^{1a} and E^{1b} taken together with the carbon atom to which they are attached form an optionally substituted cycloalkyl ring or an optionally substituted heterocyclyl ring having from 3 to 6 atoms in the ring structure, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

or, when E^{1a} and E^{1b} are attached to the same carbon atom, E^{1a} and E^{1b} are taken together with the carbon atom to which they are attached to form oxo;

E² is selected from the group consisting of H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, sulfone, hydroxy, alkoxy, alkoxyalkyl, cyano, sulfonyl, and

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E²¹, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E²¹ taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

E³ is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, sulfonyl, haloalkoxy, H, alkyl, acyl, amine, aminoalkyl, amide, haloalkyl, cyano, sulfone,

optionally substituted heterocyclyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, or sulfone,

optionally substituted heteroaryl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

optionally substituted cycloalkyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E^{31} , at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{31} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is L^7-E^7 wherein:

L^7 is a direct bond;

E^7 is selected from the group consisting of:

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, cycloalkyl, alkoxy, alkoxyalkyl, amine, acyl, carbamoyl, formyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, urea, amine, amidine, acyl, carbamoyl, formyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

each occurrence of m is independently 0, 1, 2, 3, or 4;

each occurrence of p is independently 0, 1, or 2;

R^1 is selected from the group consisting of H, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, and halogen;

R^2 is selected from the group consisting of H and F;

R^3 is selected from the group consisting of H, C_1 - C_5 alkyl, and C_3 - C_5 cycloalkyl;

R^4 , at each occurrence, is independently H or alkyl; and

R^5 , at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen;

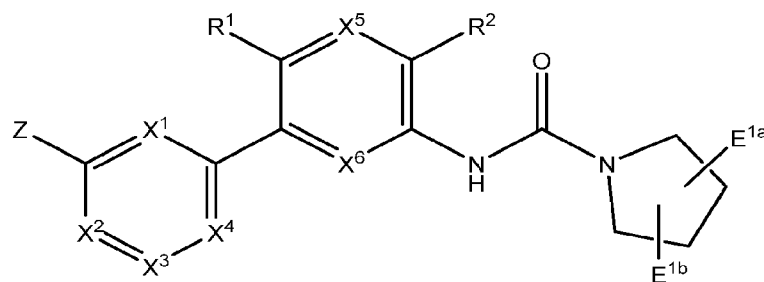
with the proviso that

E^7 is not morpholinyl;

when X^1 , X^4 , X^5 , and X^6 are CH, R^1 is $-\text{CH}_3$, X^2 is N, X^3 is $\text{C}-\text{L}^3-\text{E}^3$, L^3 is a direct bond, and E^3 is morpholinyl, then E^7 is not optionally substituted C_3 - C_6 heterocyclyl or optionally substituted 5- or 6-membered heteroaryl; and

when X^1 and X^4 are each independently N, CH, or CF, X^5 is CH, and X^6 is CH, CD, or CF, then E^7 is not 5- or 6-membered optionally substituted heteroaryl or 5- or 6-membered optionally substituted heterocyclyl.

[000122] In some embodiments, the compound is represented by Formula I-TA:



Formula I-TA

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^1 and X^4 are each independently CR^5 , or N;

X^5 and X^6 are each independently CH, CF, or N;

X^2 is N, CH, $\text{C}=\text{O}$, $\text{C}-\text{O}-\text{L}^2-\text{E}^2$, $\text{C}-\text{L}^2-\text{E}^2$, $\text{C}-\text{N}(\text{R}^4)-\text{L}^2-\text{E}^2$, or $\text{N}-\text{L}^2-\text{E}^2$;

X^3 is $\text{C}-\text{O}-\text{L}^3-\text{E}^3$, $\text{C}-\text{L}^3-\text{E}^3$, $\text{C}-\text{N}(\text{R}^4)-\text{L}^3-\text{E}^3$, CH, $\text{C}=\text{O}$, N, or $\text{N}-\text{L}^3-\text{E}^3$,

provided that not more than two of X^1 , X^2 , X^3 , and X^4 are N;

provided that when X^2 is N, X^3 is $\text{C}-\text{O}-\text{L}^3-\text{E}^3$, $\text{C}-\text{L}^3-\text{E}^3$, $\text{C}-\text{N}(\text{R}^4)-\text{L}^3-\text{E}^3$, N, or CH;

provided that when X^3 is N, X^2 is N, CH, $\text{C}-\text{O}-\text{L}^2-\text{E}^2$, $\text{C}-\text{L}^2-\text{E}^2$, or $\text{C}-\text{N}(\text{R}^4)-\text{L}^2-\text{E}^2$;

provided that when X^2 is $\text{C}=\text{O}$, X^3 is $\text{N}-\text{L}^3-\text{E}^3$;

provided that when X^3 is $\text{C}=\text{O}$, X^2 is $\text{N}-\text{L}^2-\text{E}^2$;

L^2 is a direct bond or a C_1 - C_6 alkyl optionally substituted with $(\text{E}^{21})_p$;

L^3 is a direct bond or a C_1 - C_6 alkyl optionally substituted with $(\text{E}^{31})_p$;

each of E^{1a} and E^{1b} is independently selected from the group consisting of H, alkoxy, cyano, haloalkoxy, halogen,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano, and

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone;

or wherein E^{1a} and E^{1b} taken together with the carbon atom to which they are attached form an optionally substituted cycloalkyl ring or an optionally substituted heterocyclyl ring having from 3 to 6 atoms in the ring structure, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

or, when E^{1a} and E^{1b} are attached to the same carbon atom, E^{1a} and E^{1b} are taken together with the carbon atom to which they are attached to form oxo;

E² is selected from the group consisting of H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, sulfone, hydroxy, alkoxy, alkoxyalkyl, cyano, sulfonyl, and

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E²¹, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E²¹ taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

E³ is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, sulfonyl, haloalkoxy, H, alkyl, acyl, amine, aminoalkyl, amide, haloalkyl, cyano, sulfone,

optionally substituted heterocyclyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, or sulfone,

optionally substituted heteroaryl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

optionally substituted cycloalkyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E^{31} , at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{31} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is L^7-E^7 wherein:

L^7 is a direct bond;

E^7 is optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, urea, amine, amidine, acyl, carbamoyl, formyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

each occurrence of m is independently 0, 1, 2, 3, or 4;

each occurrence of p is independently 0, 1, or 2;

R^1 is selected from the group consisting of H, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, and halogen;

R^2 is selected from the group consisting of H and F;

R^3 is selected from the group consisting of H, C_1 - C_5 alkyl, and C_3 - C_5 cycloalkyl;

R^4 , at each occurrence, is independently H or alkyl; and

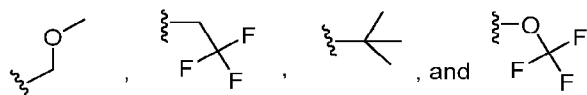
R^5 , at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen;

with the proviso that

when X^1 , X^4 , X^5 , and X^6 are CH, R^1 is $-CH_3$, X^2 is N, X^3 is $C-L^3-E^3$, and L^3 is a direct bond, E^3 is not morpholinyl; and

when X^1 and X^4 are each independently N, CH, or CF, X^5 is CH, and X^6 is CH, CD, or CF, then E^7 is not 5- or 6- membered optionally substituted heteroaryl.

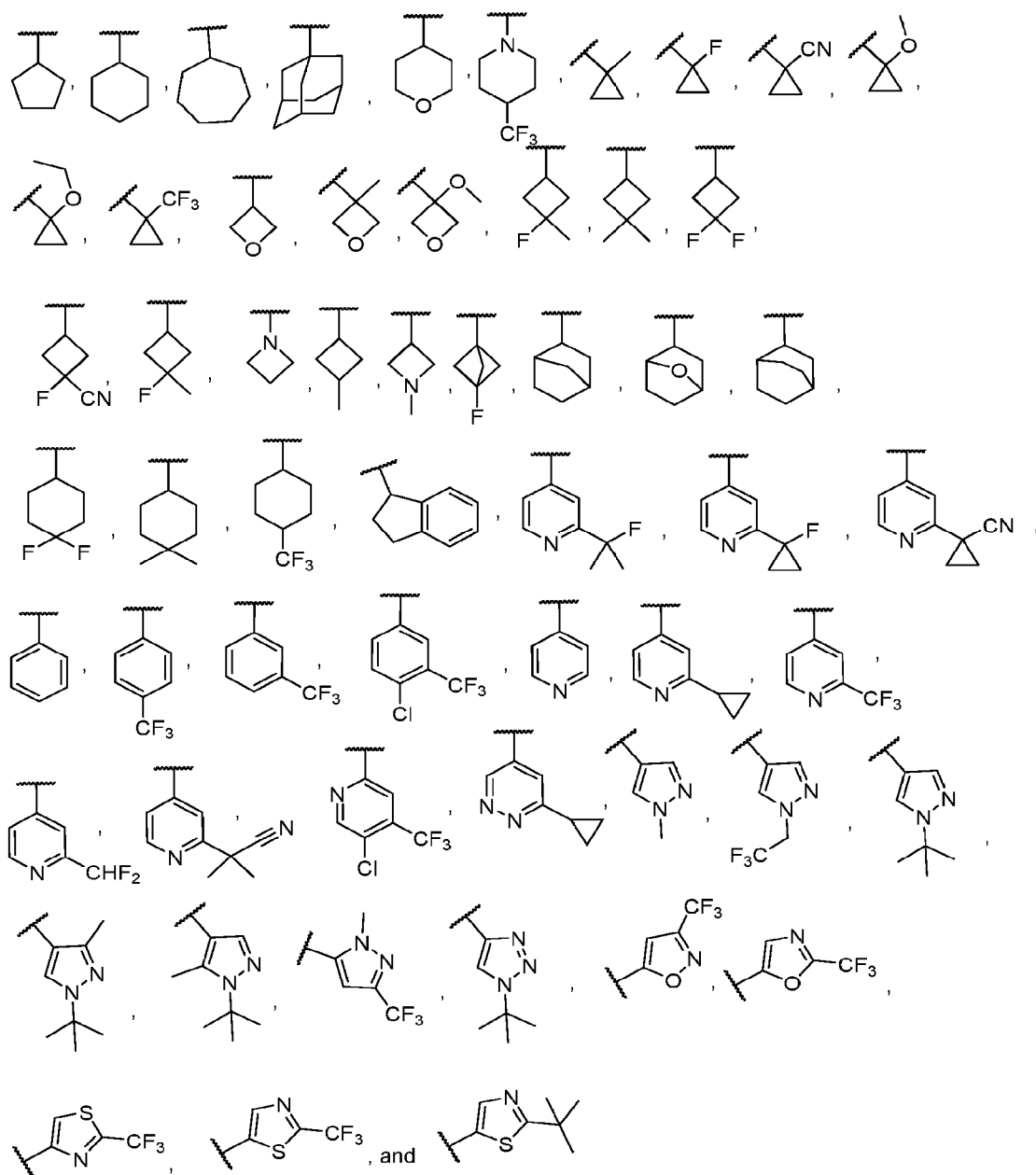
[000123] In some embodiments, E^{1a} is selected from the group consisting of H and OMe. In some embodiments, E^{1a} is selected from the group consisting of H, OMe,



. In some embodiments, E^{1b} is selected from the group consisting of H and OMe. In some embodiments, is selected from the group

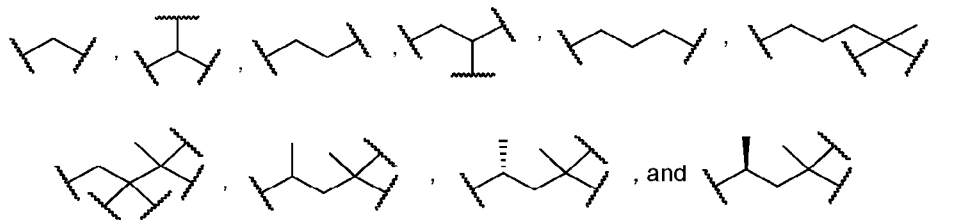
consisting of H, OMe, . In some embodiments, W is CH₂ or O. In some embodiments, W is CH₂.

[000124] In some embodiments, E¹ is selected from the group consisting of H, Me, CF₃, CH₂CF₃, OMe, OEt, OCF₃, F, CN,



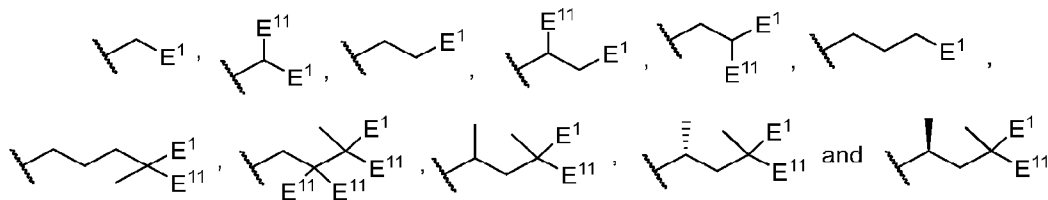
[000125] In some embodiments, E¹ is selected from the group consisting of H, Me, CF₃, CH₂CF₃, OMe, OEt, OCF₃, F, and CN.

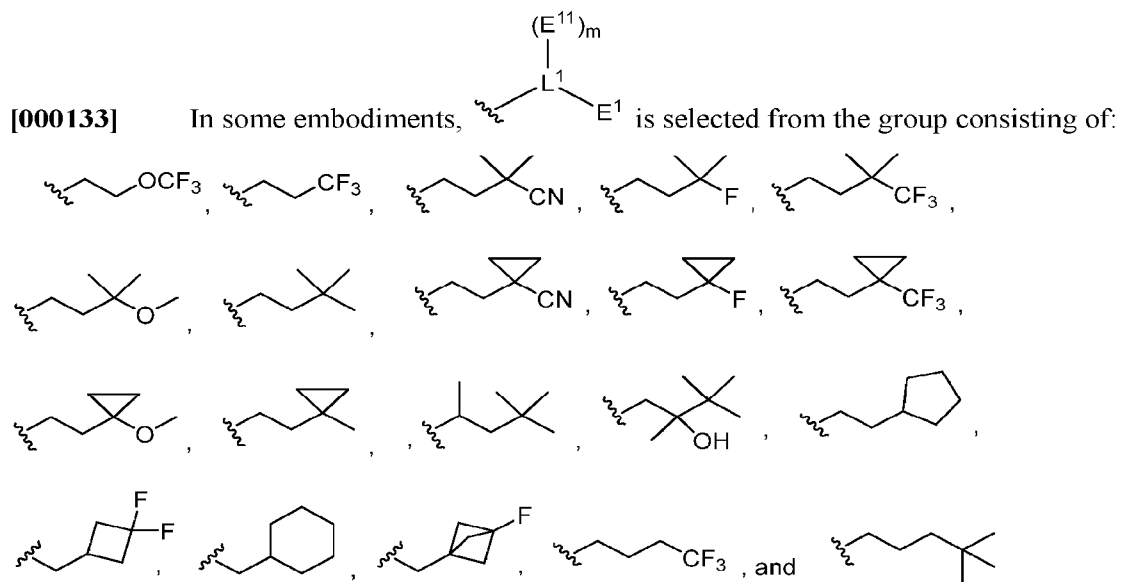
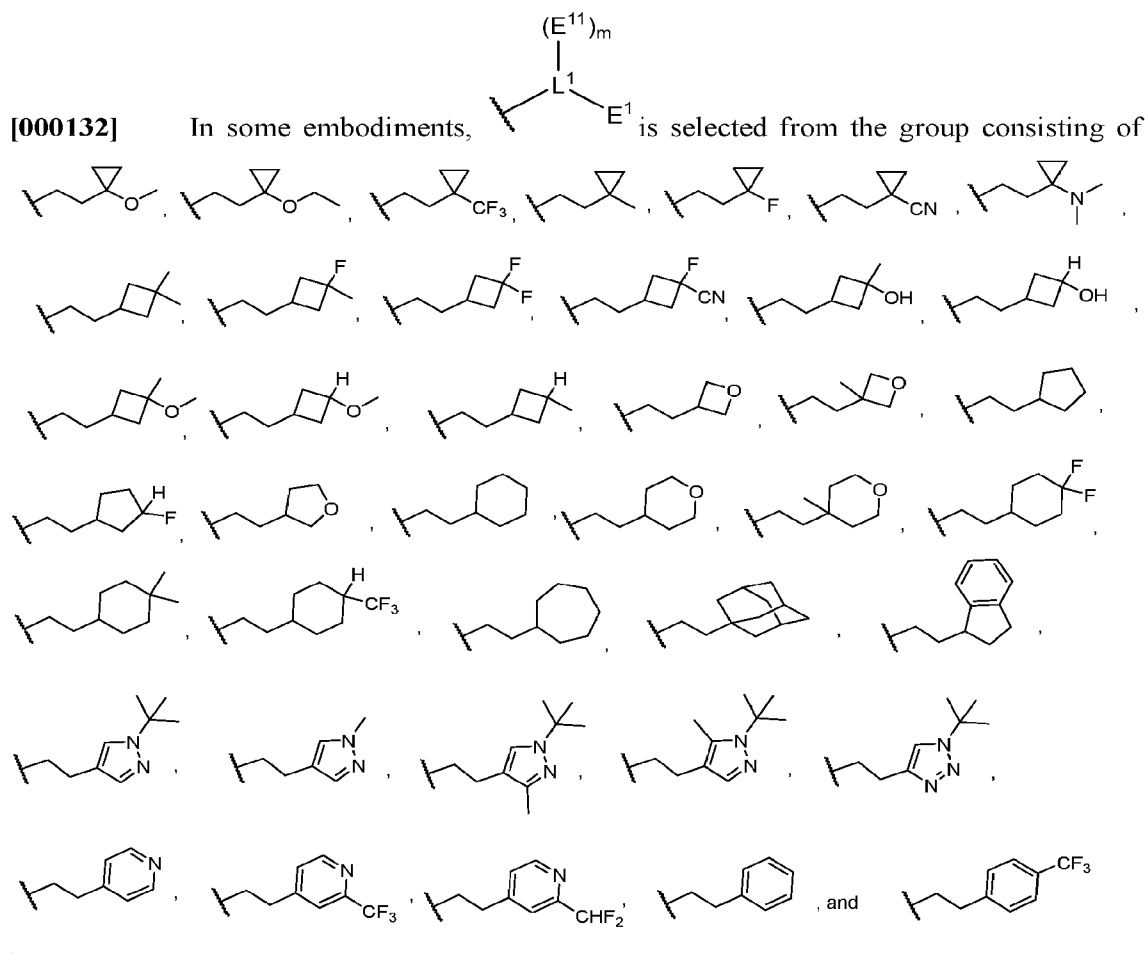
[000129] In some embodiments, L^1 is selected from the group consisting of direct bond,



[000130] In some embodiments, L^1 is a direct bond. In some embodiments, L^1 is a C₁-C₆ alkyl optionally substituted with $(E^{11})_m$. In some embodiments, L^1 is taken together with R^3 and the N atom to which L^1 and R^3 are attached to form a heterocycle having from 4 to 8 atoms in the ring structure.

[000131] In some embodiments, $\begin{array}{c} (E^{11})_m \\ | \\ L^1 \\ | \\ E^1 \end{array}$ is selected from the group consisting of:

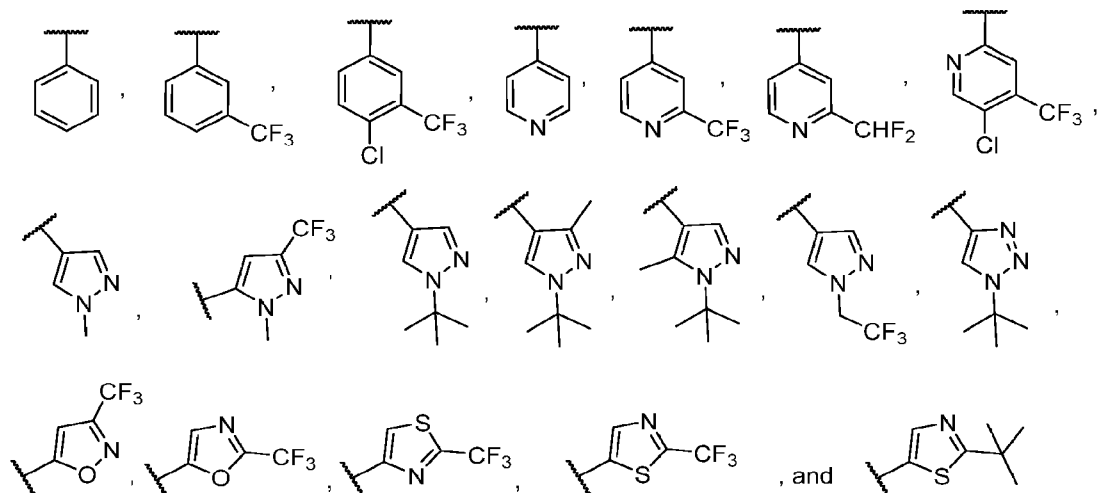




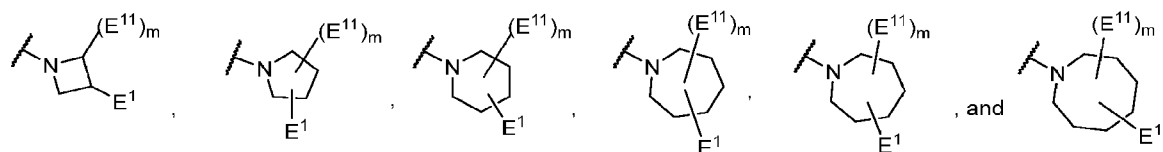
[000136] In some embodiments, when L^1 is a direct bond,



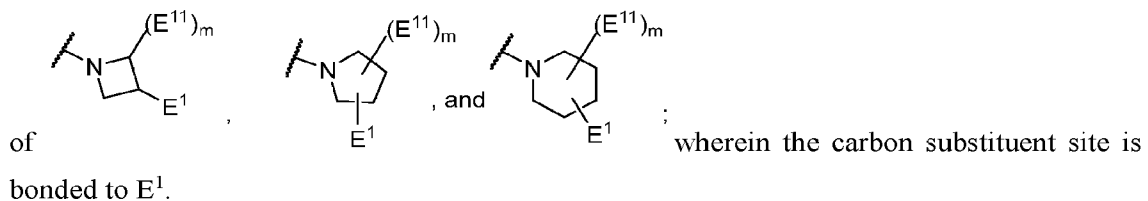
is selected from the group consisting of



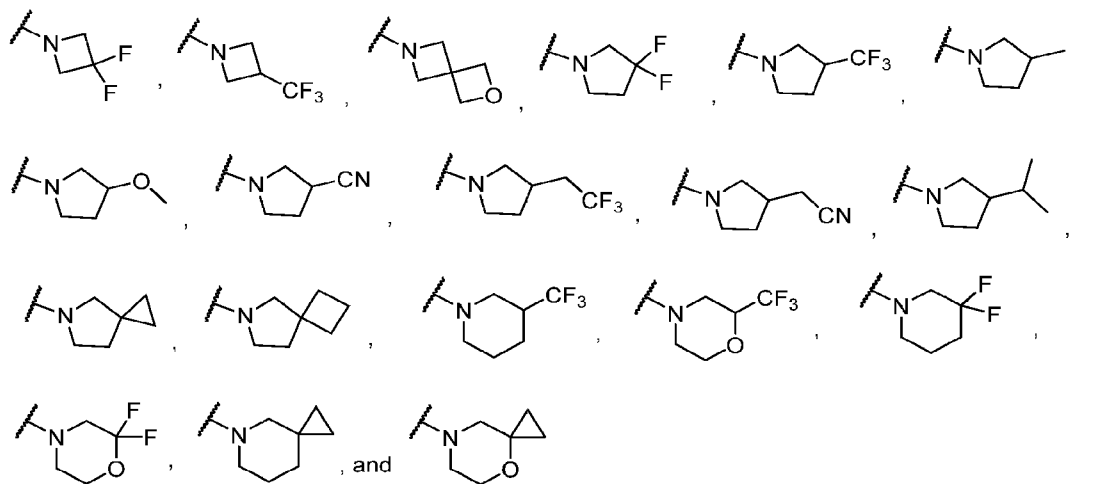
[000137] In some embodiments, L¹ and R³ taken together with the N atom to which they are attached form a heterocycle having from 4 to 8 atoms in the ring structure wherein the ring structure is selected from the group consisting of



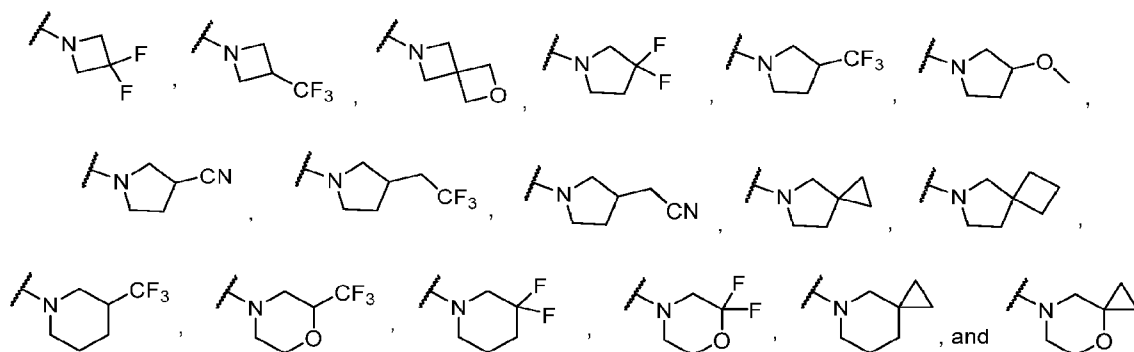
[000138] In some embodiments, the ring structure is selected from the group consisting



[000139] In some embodiments, the ring structure is selected from the group consisting of:

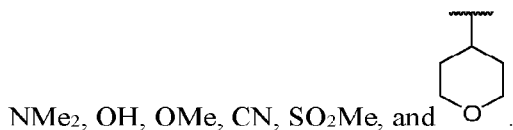


[000140] In some embodiments, the ring structure is selected from the group consisting of:

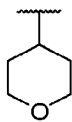


[000141] In some embodiments, E² is selected from the group consisting of hydroxy, C₁-C₆ alkoxy, C₁-C₆ alkoxyalkyl, cyano, sulfonyl, H, C₁-C₆ alkyl, amine, C₁-C₆ haloalkoxy, C₁-C₆ haloalkyl, sulfone, and an optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ alkoxy, amide, amine, C₁-C₆ acyl, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, halogen, hydroxy, C₁-C₆ hydroxyalkyl, oxo, cyano, and C₁-C₆ cyanoalkyl.

[000142] In some embodiments, E² is selected from the group consisting of H, Me,

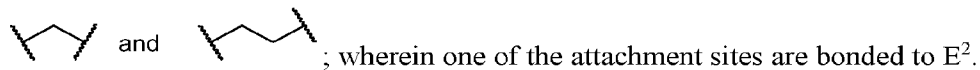


[000143] In some embodiments, E^2 is selected from the group consisting of: H, Me, NMe₂, OH, OMe, CN, and SO₂Me.

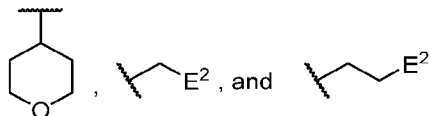


[000144] In some embodiments, E^2 is

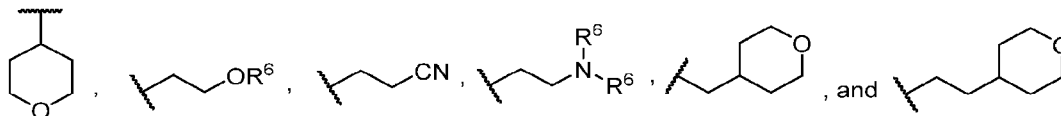
[000145] In some embodiments, L^2 is selected from the group consisting of direct bond,



[000146] In some embodiments, L^2-E^2 is selected from the group consisting of:

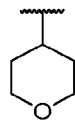
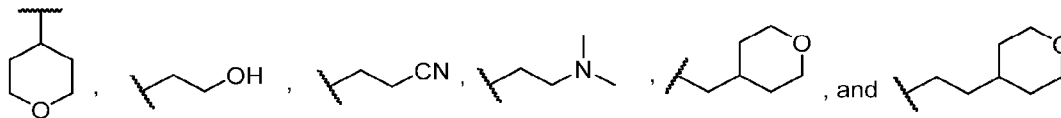


[000147] In some embodiments, L^2-E^2 is selected from the group consisting of



wherein R^6 , at each occurrence, is independently selected from the group consisting of H, C₁-C₆ alkyl, C₃-C₅ cycloalkyl, and C₁-C₆ acyl.

[000148] In some embodiments, L^2-E^2 is selected from the group consisting of



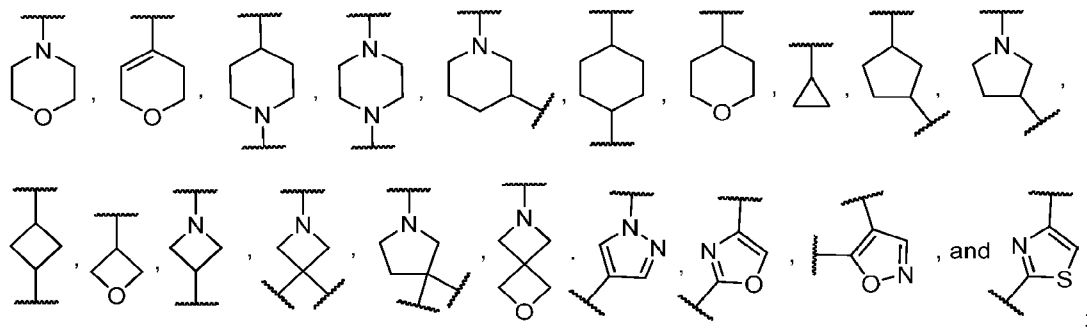
[000149] In some embodiments, L^2-E^2 is

[000150] In some embodiments, L^2-E^2 is H, alkyl or cycloalkyl.

[000151] In some embodiments, E^3 is selected from the group consisting of hydroxy, C₁-C₆ alkoxy, C₁-C₆ alkoxyalkyl, cyano, sulfonyl, C₁-C₆ haloalkoxy, H, C₁-C₆ alkyl, C₁-C₆ acyl, amine, C₁-C₆ aminoalkyl, amide, C₁-C₆ haloalkyl, optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkoxyalkyl, amide, amine, C₁-C₆ aminoalkyl, C₁-C₆ acyl, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, halogen, hydroxy, C₁-C₆ hydroxyalkyl, oxo, cyano, C₁-C₆ cyanoalkyl, and sulfone, optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected

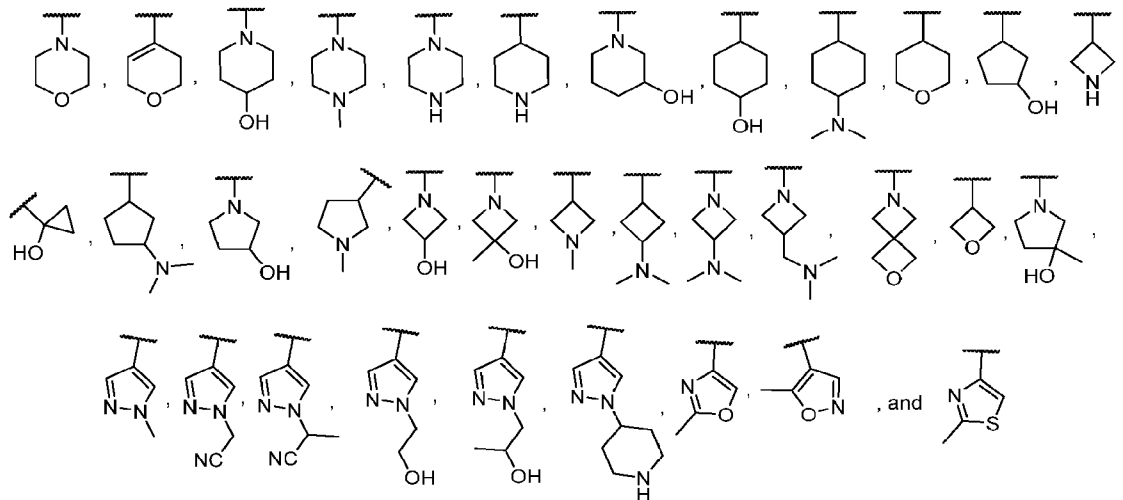
from the group consisting of C₁-C₆ alkyl, C₁-C₆ alkoxy, amide, amine, C₁-C₆ acyl, C₁-C₆ alkoxyalkyl, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, halogen, hydroxy, C₁-C₆ hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, halogen, hydroxy, and cyano.

[000152] In some embodiments, E³ is selected from the group consisting of H, Me, N(R⁶)₂, C(=O)Me, SO₂Me, OR⁶, CN,

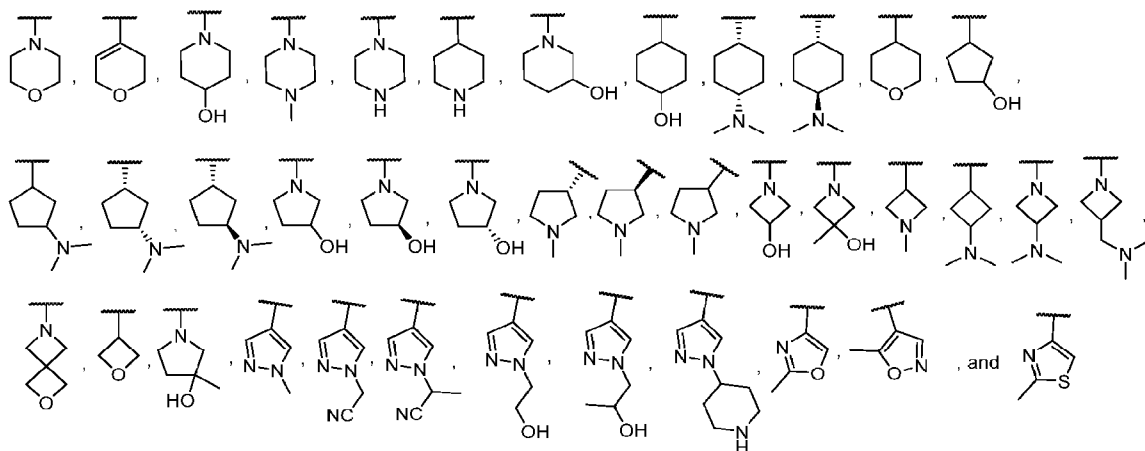


wherein R⁶, at each occurrence, is independently H, C₁-C₆ alkyl, C₃-C₅ cycloalkyl, or C₁-C₆ acyl; and wherein one of the attachment sites are bonded to E³.

[000153] In some embodiments, E³ is selected from the group consisting of H, Me, NMe₂, C(=O)Me, SO₂Me, OH, CN,

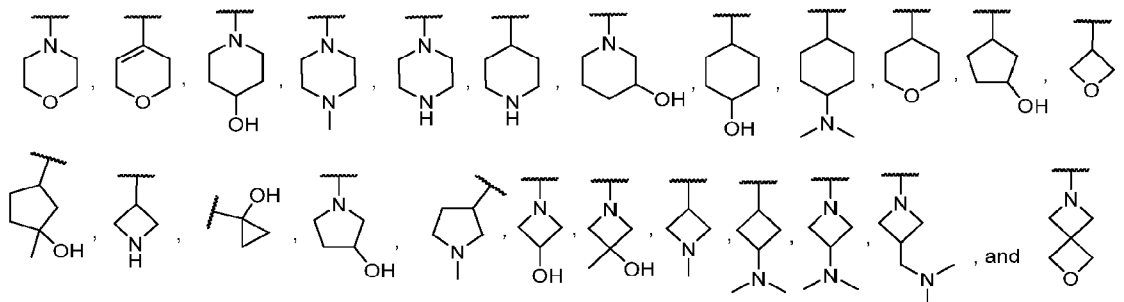


[000154] In some embodiments, E³ is selected from the group consisting of H, Me, NMe₂, C(=O)Me, SO₂Me, OH, CN,

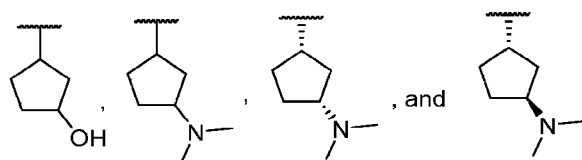


[000155] In some embodiments, E^3 is selected from the group consisting of H, Me, $N(R^6)_2$, $C(=O)Me$, SO_2Me , OR^6 , and CN.

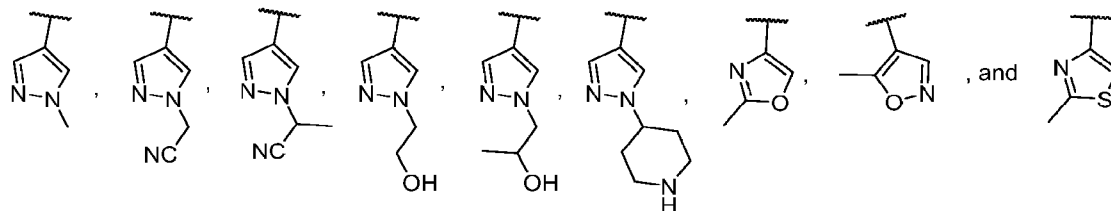
[000156] In some embodiments, E^3 is selected from the group consisting of



[000157] In some embodiments, E^3 is selected from the group consisting of:



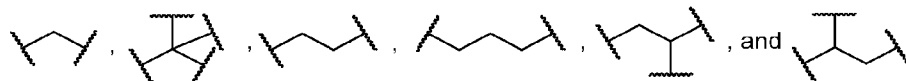
[000158] In some embodiments, E^3 is selected from the group consisting of:



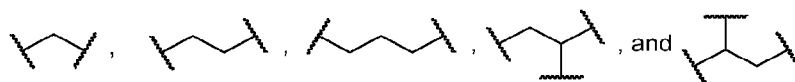
[000159] In some embodiments, E^{31} , at each occurrence is independently selected from the group consisting of H, C_1 - C_6 alkyl, C_3 - C_5 cycloalkyl, C_1 - C_6 alkoxy, oxetanyl, C_1 -

C6alkoxyalkyl, cyano, C1-C6cyanoalkyl, C1-C6haloalkoxy, C1-C6haloalkyl, hydroxy, C1-C6hydroxyalkyl, and halogen, or wherein two occurrences of E³¹ taken together with the carbon atom to which they are attached form a C3-C6 cycloalkyl ring. In some embodiments, E³¹ is, at each occurrence, independently selected from the group consisting of H, Me, CF₃, OH, OMe, OEt, oxetanyl, OCF₃, CH₂OH, F, and CN, or wherein two occurrences of E³¹ taken together with the carbon atom to which they are attached form cyclopropyl ring.

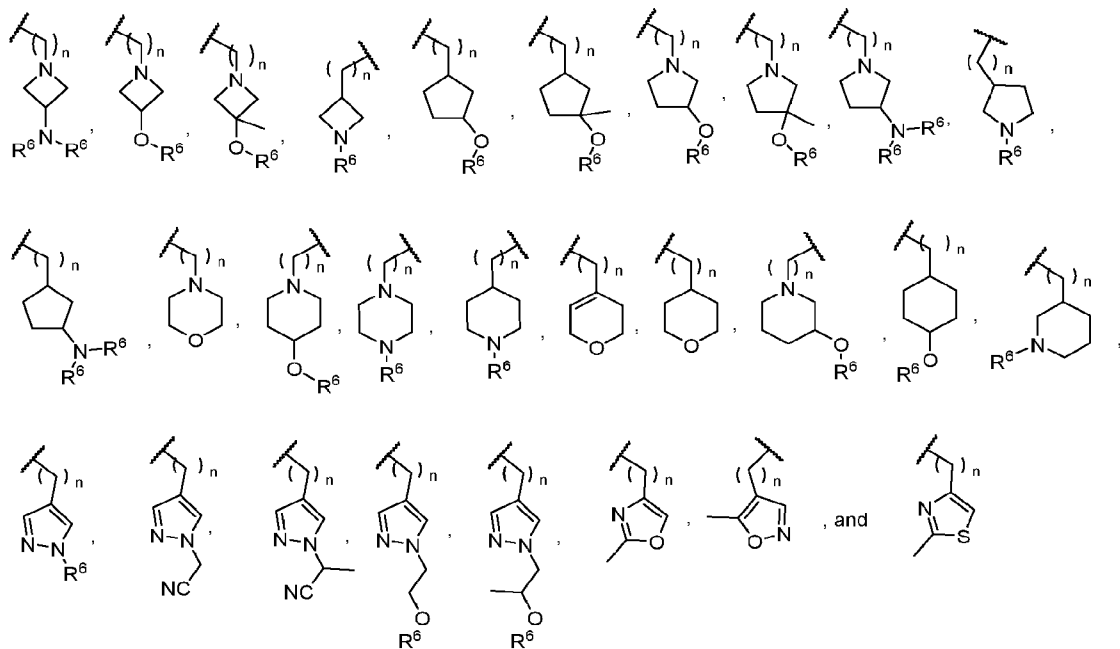
[000160] In some embodiments, L^3 is selected from the group consisting of direct bond,



[000161] In some embodiments, L^3 is selected from the group consisting of direct bond,

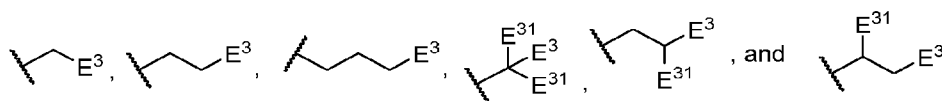


[000162] In some embodiments, $L^3(E^3)(E^{31})_p$ is selected from the group consisting of

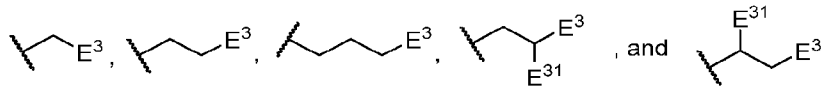


wherein R⁶, at each occurrence, is independently selected from the group consisting of H, C₁-C₆ alkyl, C₃-C₅ cycloalkyl, and C₁-C₆ acyl.

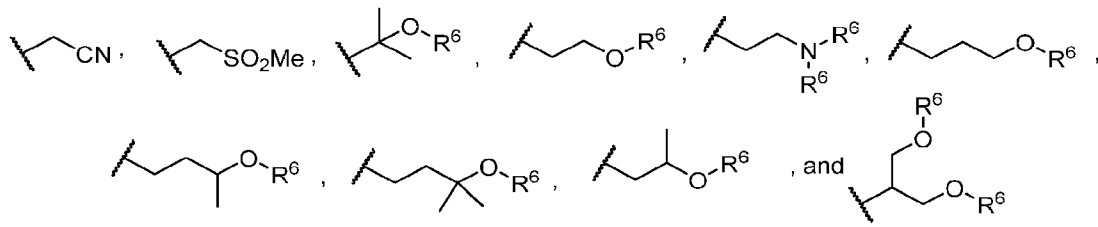
[000163] In some embodiments, $L^3(E^3)(E^{31})_p$ is selected from the group consisting of



[000164] In some embodiments, $L^3(E^3)(E^{31})_p$ is selected from the group consisting of:

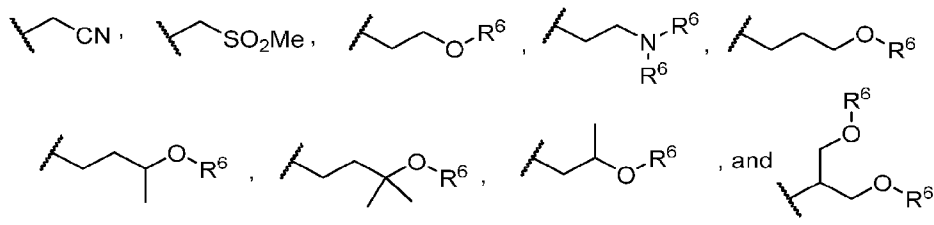


[000165] In some embodiments, $L^3(E^3)(E^{31})_p$ is selected from the group consisting of



wherein R^6 , at each occurrence, is independently selected from the group consisting of H, C₁-C₆ alkyl, C₃-C₅ cycloalkyl, and C₁-C₆ acyl.

[000166] In some embodiments, $L^3(E^3)(E^{31})_p$ is selected from the group consisting of



wherein R^6 , at each occurrence, is independently selected from the group consisting of H, C₁-C₆ alkyl, C₃-C₅ cycloalkyl, and C₁-C₆ acyl.

[000167] In some embodiments, E^7 is selected from the group consisting of:

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, cycloalkyl, alkoxy, alkoxyalkyl, amine, acyl, carbamoyl, formyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

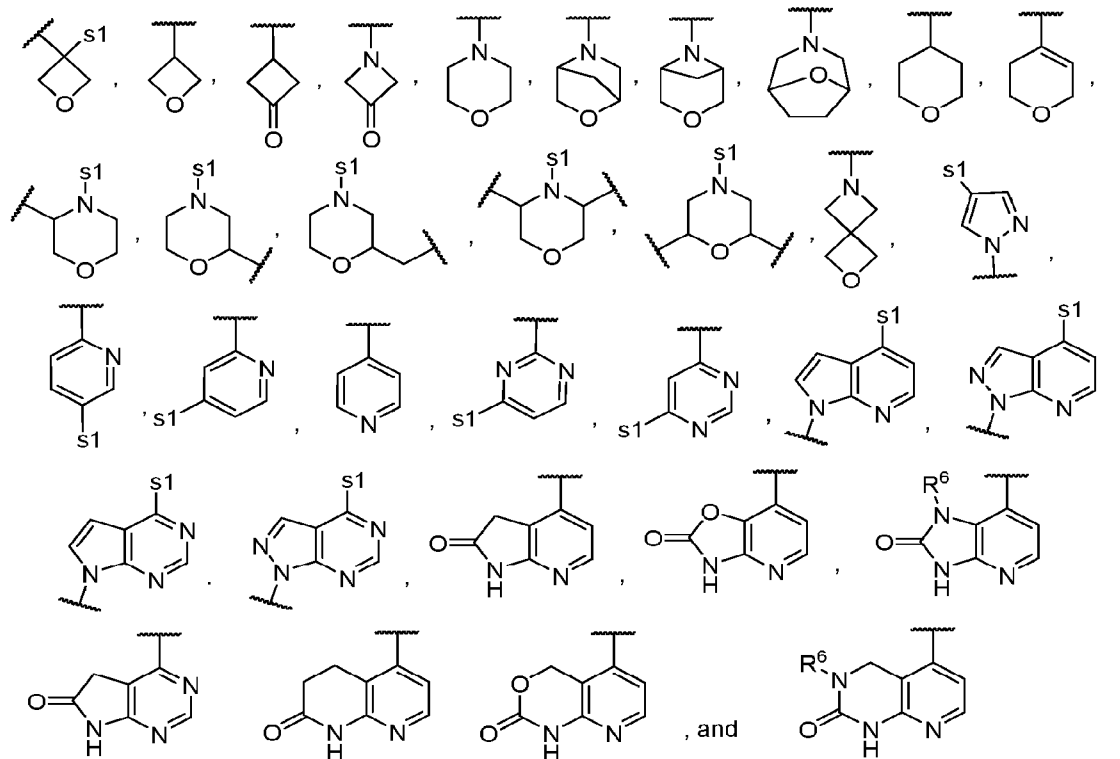
optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, urea, amine, acyl, carbamoyl, formyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano.

[000168] In some embodiments, E^7 is selected from the group consisting of: H,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, cycloalkyl, alkoxy, alkoxyalkyl, amine, acyl, carbamoyl, formyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

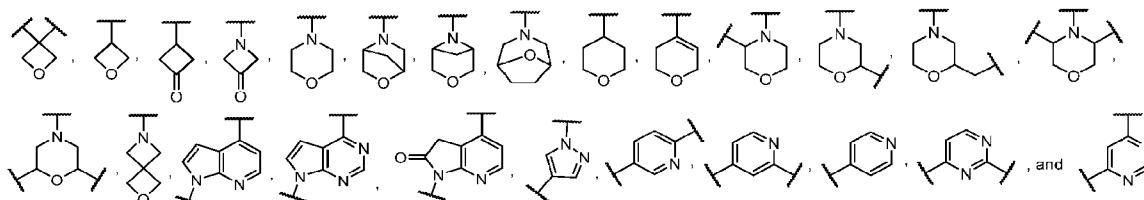
optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, carbamoyl, urea, amine, acyl, carbamoyl, formyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano.

[000169] In some embodiments, E⁷ is selected from the group consisting of:



; wherein R⁶, at each occurrence, is independently selected from the group consisting of H, C₁-C₆ alkyl, C₃-C₅ cycloalkyl, and C₁-C₆ acyl; and wherein s1 indicates the site of attachment to X¹-X⁴ ring and wherein  indicates site of optional substituent when s1 is present or  indicates site of attachment to ring when s1 is not present.

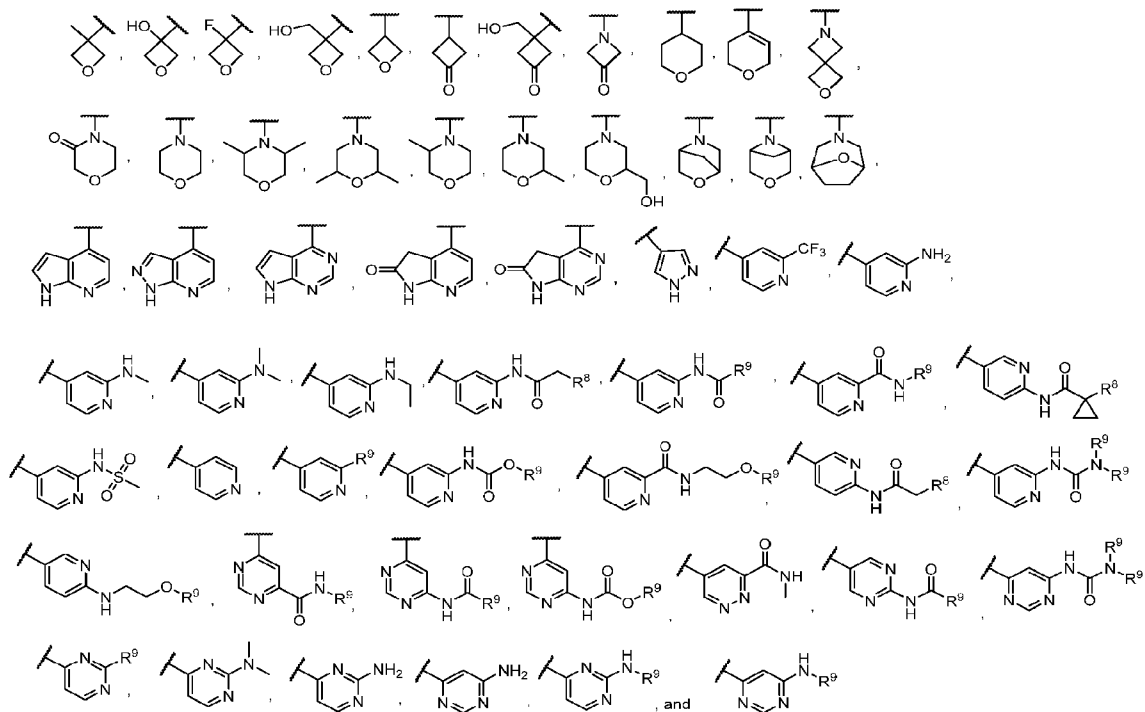
[000170] In some embodiments, E⁷ is selected from the group consisting of:



; wherein R⁶, at each occurrence, is independently selected from the group consisting of H, C₁-C₆ alkyl, C₃-C₅ cycloalkyl, and C₁-C₆ acyl; wherein one of the attachment sites are bonded

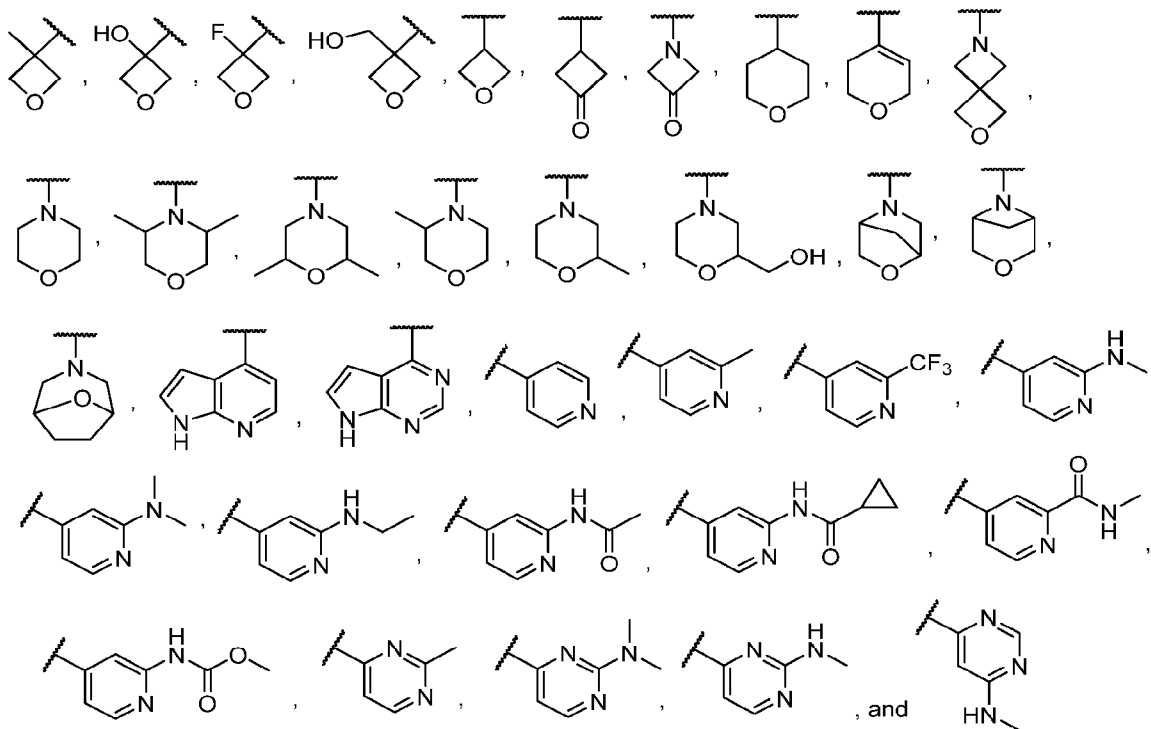
to ring and the other of the attachment sites is bonded to optional substituent(s) if more than one attachment sites are present.

[000171] In some embodiments, E⁷ is selected from the group consisting of:



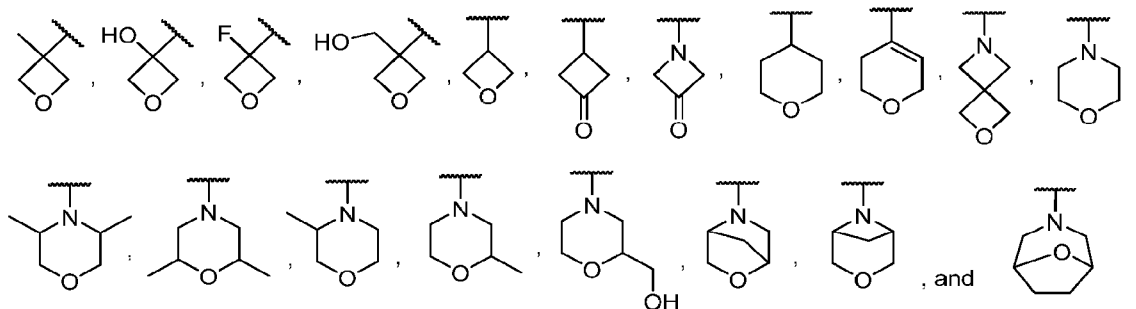
; wherein R⁶, at each occurrence, is independently selected from the group consisting of H, C₁-C₆ alkyl, C₃-C₅ cycloalkyl, and C₁-C₆ acyl; R⁸ is selected from the group consisting of H, OH, alkoxy, cyano, F, and amino; and R⁹, at each occurrence, is independently selected from the group consisting of H, C₁-C₆ alkyl, and C₃-C₅ cycloalkyl.

[000172] In some embodiments, E⁷ is selected from the group consisting of:

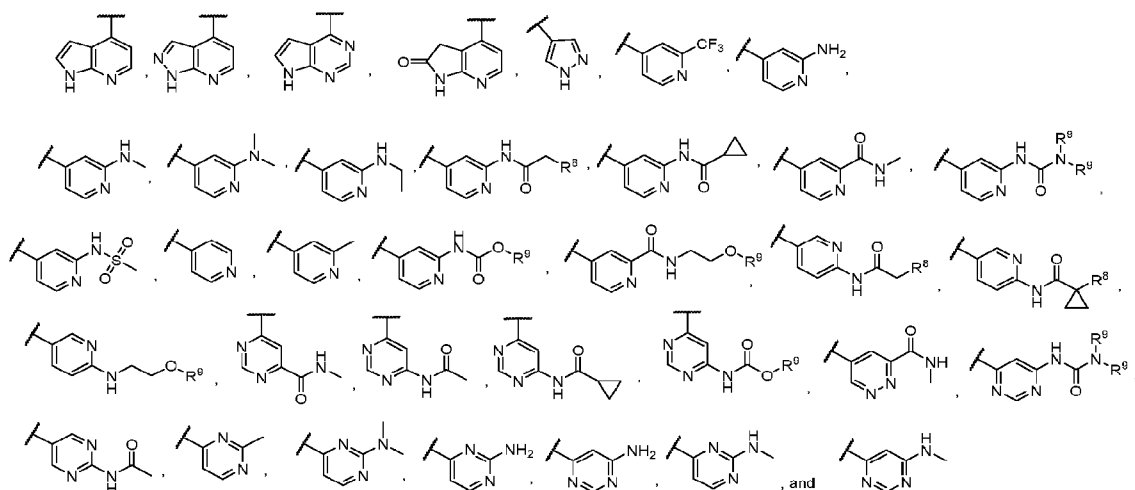


; wherein R⁶, at each occurrence, is independently selected from the group consisting of H, C₁-C₆ alkyl, C₃-C₅ cycloalkyl, and C₁-C₆ acyl.

[000173] In some embodiments, E⁷ is selected from the group consisting of

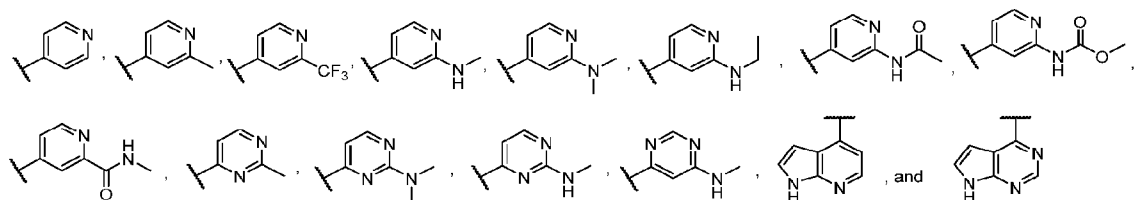


[000174] In some embodiments, E⁷ is selected from the group consisting of

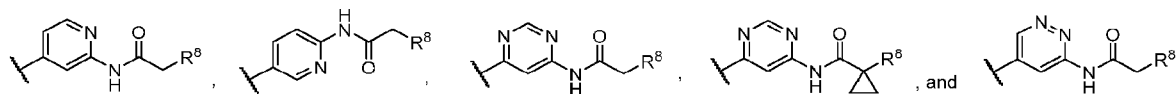


; wherein R⁸ is selected from the group consisting of H, OH, alkoxy, cyano, F, and amino; and R⁹, at each occurrence, is independently selected from the group consisting of H, C₁-C₆ alkyl, and C₃-C₅ cycloalkyl.

[000175] In some embodiments, E⁷ is selected from the group consisting of

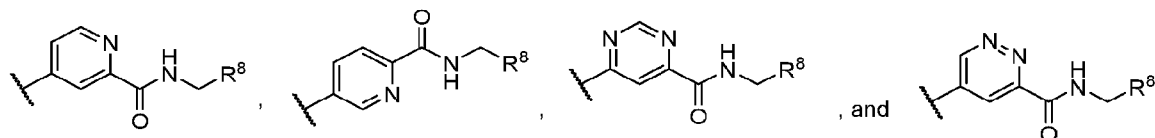


[000176] In some embodiments, E⁷ is selected from



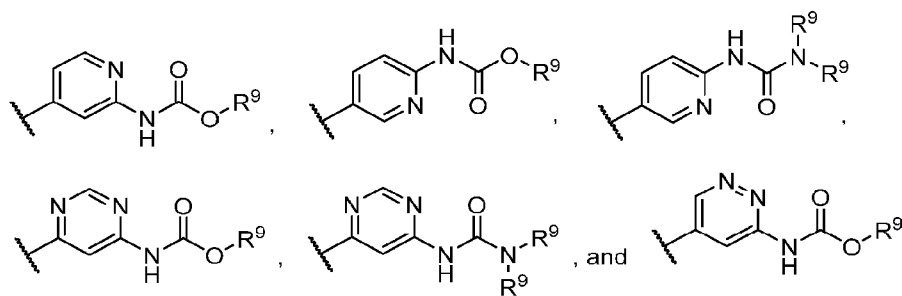
; wherein R⁸ is selected from the group consisting of H, OH, alkoxy, cyano, F, and amino.

[000177] In some embodiments, E⁷ is selected from



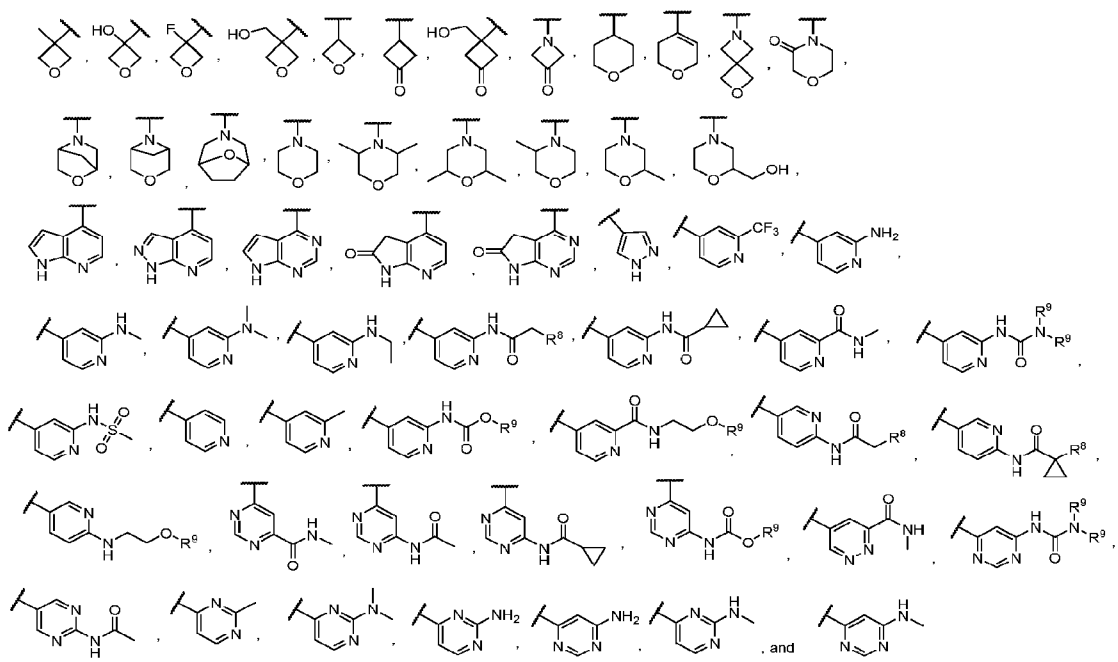
; wherein R⁸ is selected from the group consisting of H, OH, alkoxy, cyano, F, and amino.

[000178] In some embodiments, E⁷ is selected from



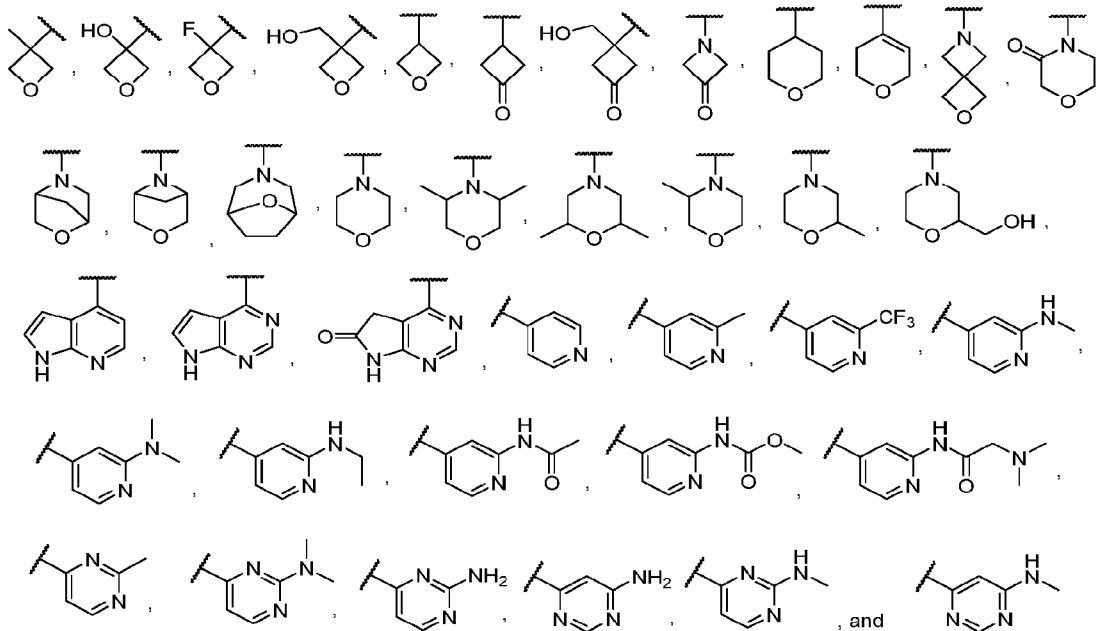
; wherein R^9 , at each occurrence, is independently selected from the group consisting of H, C₁-C₆ alkyl, and C₃-C₅ cycloalkyl.

[000179] In some embodiments, E^7 is selected from the group consisting of

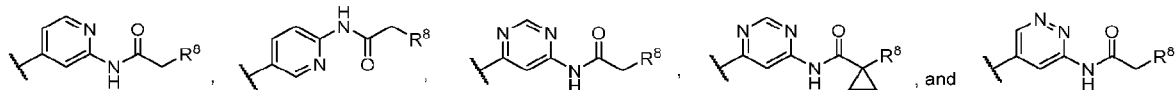


wherein R^8 is selected from the group consisting of H, OH, alkoxy, cyano, F, and amino.

[000180] In some embodiments, E⁷ is selected from the group consisting of

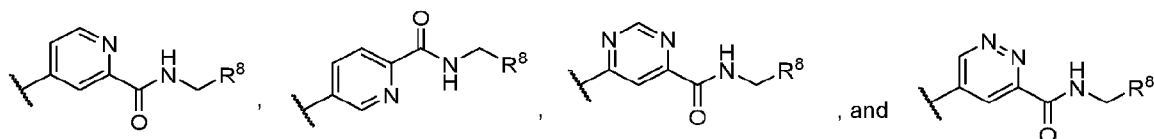


[000181] In some embodiments, E⁷ is selected from



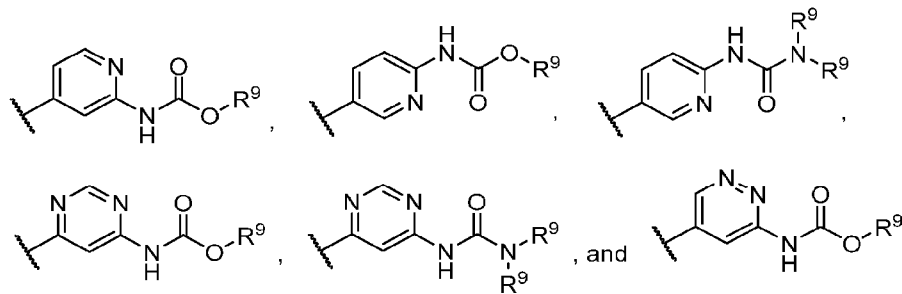
wherein R⁸ is selected from the group consisting of H, OH, alkoxy, cyano, F, and amino.

[000182] In some embodiments, E⁷ is selected from



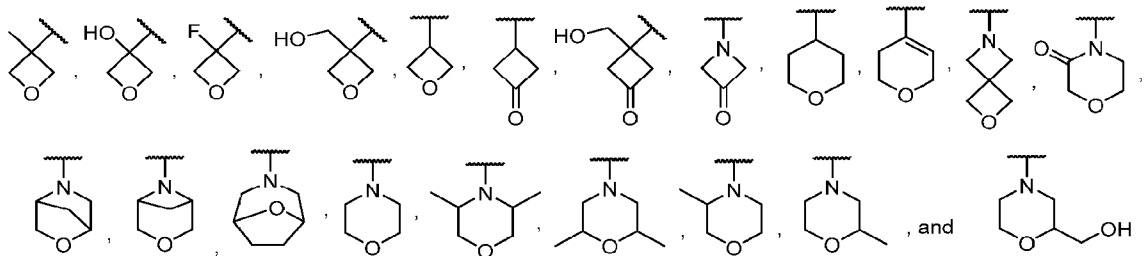
; wherein R⁸ is selected from the group consisting of H, OH, alkoxy, cyano, F, and amino.

[000183] In some embodiments, E⁷ is selected from

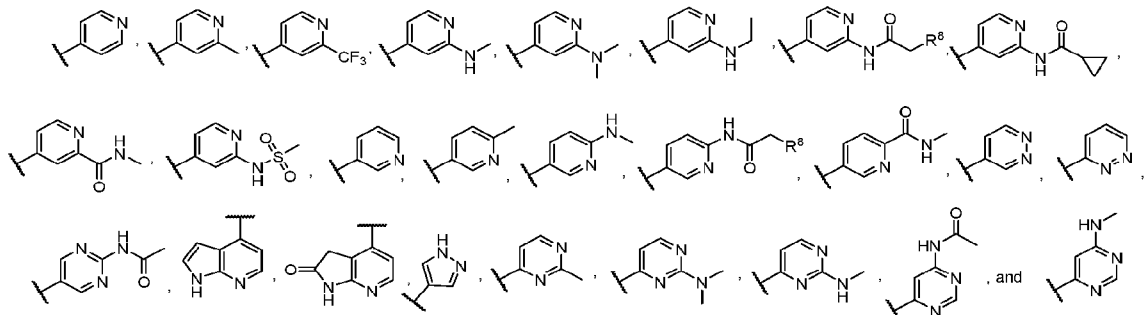


; wherein R⁹, at each occurrence, is independently selected from the group consisting of H, C₁-C₆ alkyl, and C₃-C₅ cycloalkyl.

[000184] In some embodiments, E⁷ is selected from the group consisting of

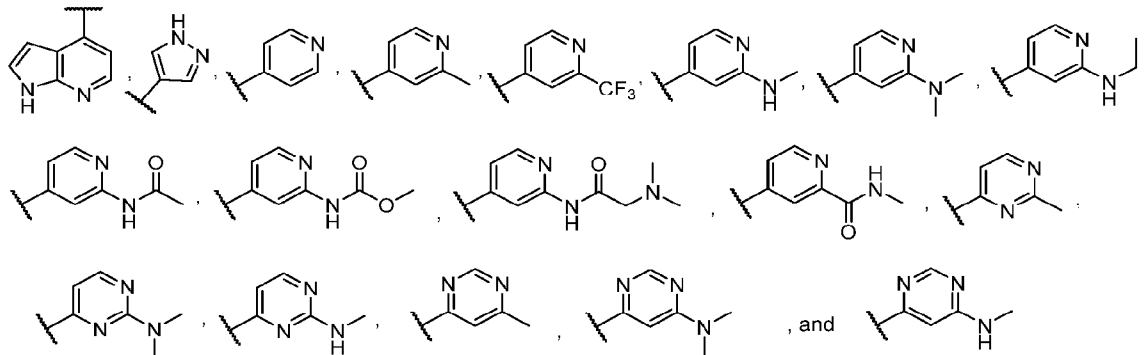


[000185] In some embodiments, E⁷ is selected from the group consisting of



; wherein R⁸ is selected from the group consisting of H, OH, alkoxy, cyano, F, and amino.

[000186] In some embodiments, E^7 is selected from the group consisting of:



[000187] In some embodiments, X^5 is N and X^6 is CH or CF. In some embodiments, X^5 is CH or CF and X^6 is N. In some embodiments, X^5 and X^6 are CH. In some embodiments, X^5 is N and X^6 is CH. In some embodiments, X^5 is N and X^6 is CF. In some embodiments, X^5 is CH and X^6 is N. In some embodiments, X^5 is CF and X^6 is N. In some embodiments, X^5 and X^6 are CH or CF. In some embodiments, X^5 is CH and X^6 is CH. In some embodiments, X^5 is CH and X^6 is CF. In some embodiments, X^5 is CF and X^6 is CH. In some embodiments, X^5 is CF and X^6 is CF.

[000188] In some embodiments, R^1 is selected from the group consisting of H, alkyl, haloalkyl, haloalkoxy, cyano, and halogen. In some embodiments, R^1 is selected from the group consisting of H, C_1 - C_6 alkyl, CN, and halogen. In some embodiments, R^1 is selected from the group consisting of H, Me, Et, F, Br, and Cl. In some embodiments, R^1 is selected from the group consisting of Me and F.

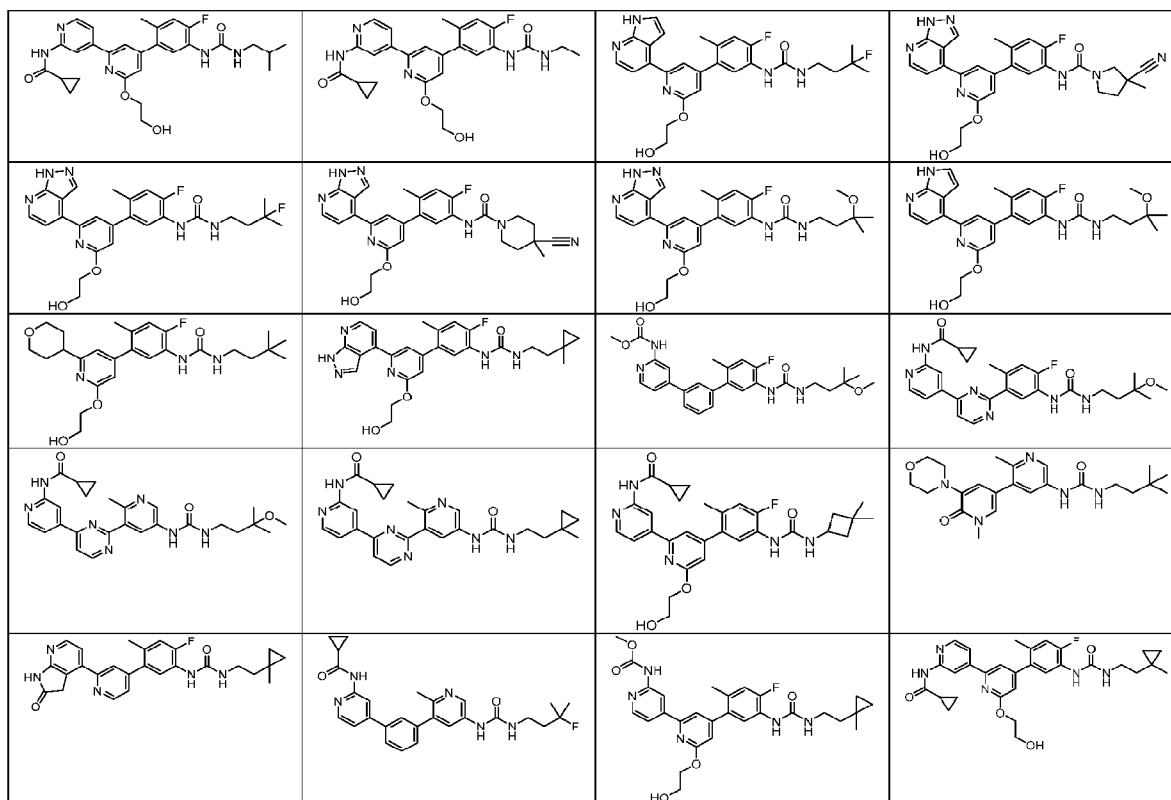
[000189] In some embodiments, R^2 is H or F. In some embodiments, R^2 is H. In some embodiments, R^2 is F.

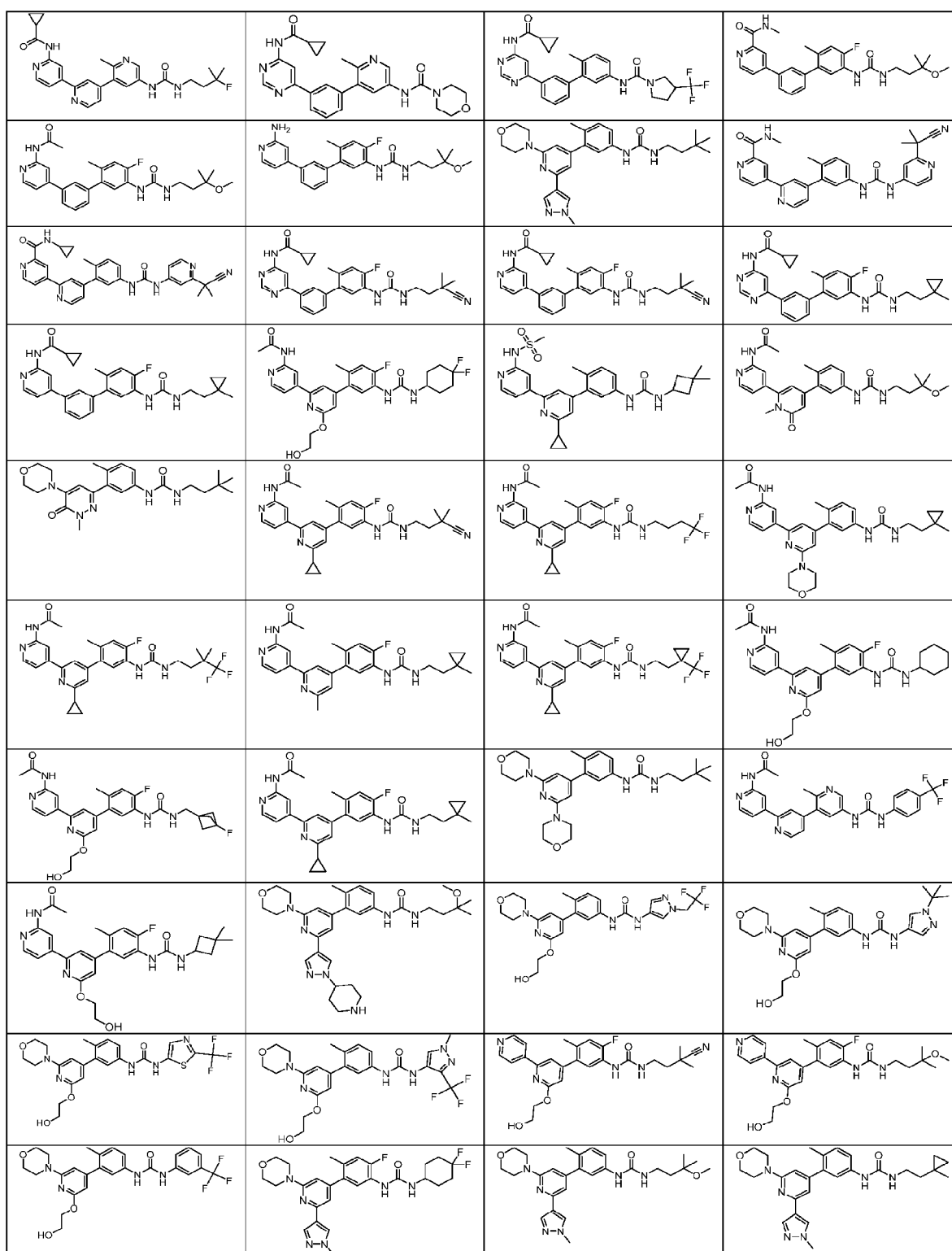
[000190] In some embodiments, R^3 is H or Me. In some embodiments, R^3 is H.

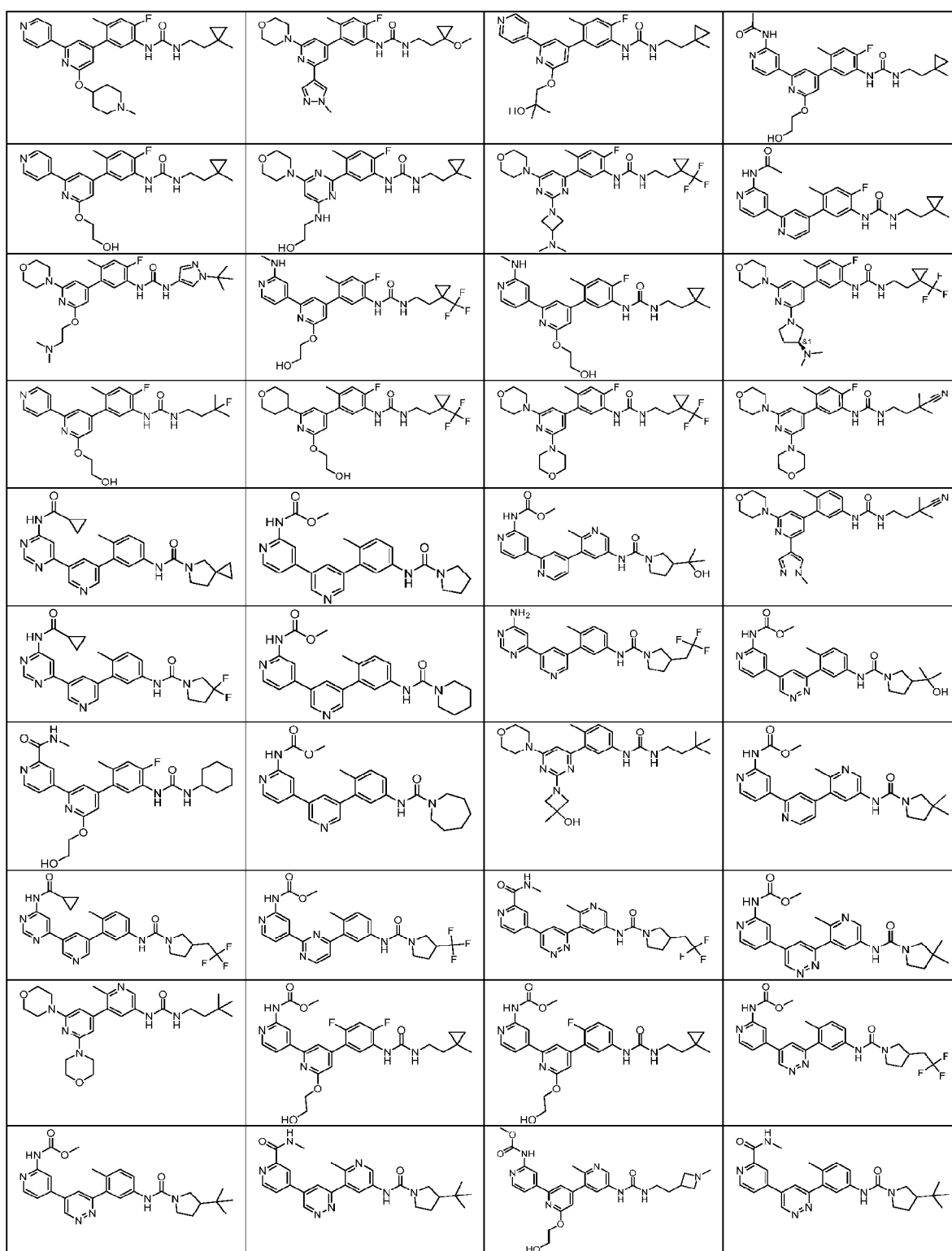
[000191] In some embodiments, R^4 is H or C_1 - C_6 alkyl. In some embodiments, R^4 is H or Me.

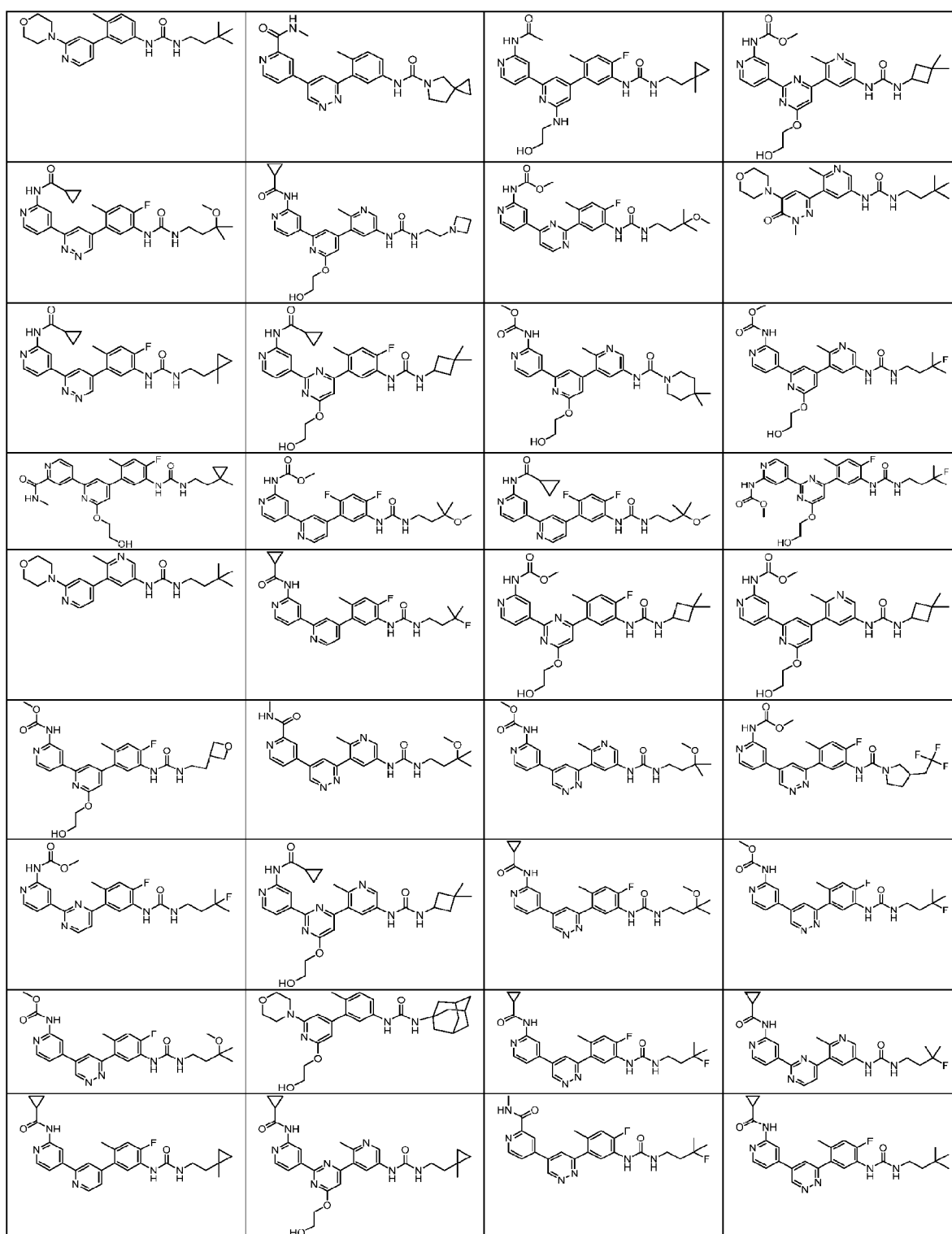
[000192] In some embodiments, R^5 is selected from the group consisting of H, C_1 - C_6 alkyl, and halogen. In some embodiments, R^5 is selected from the group consisting of H, Me, Et, F, and Cl. In some embodiments, R^5 is H.

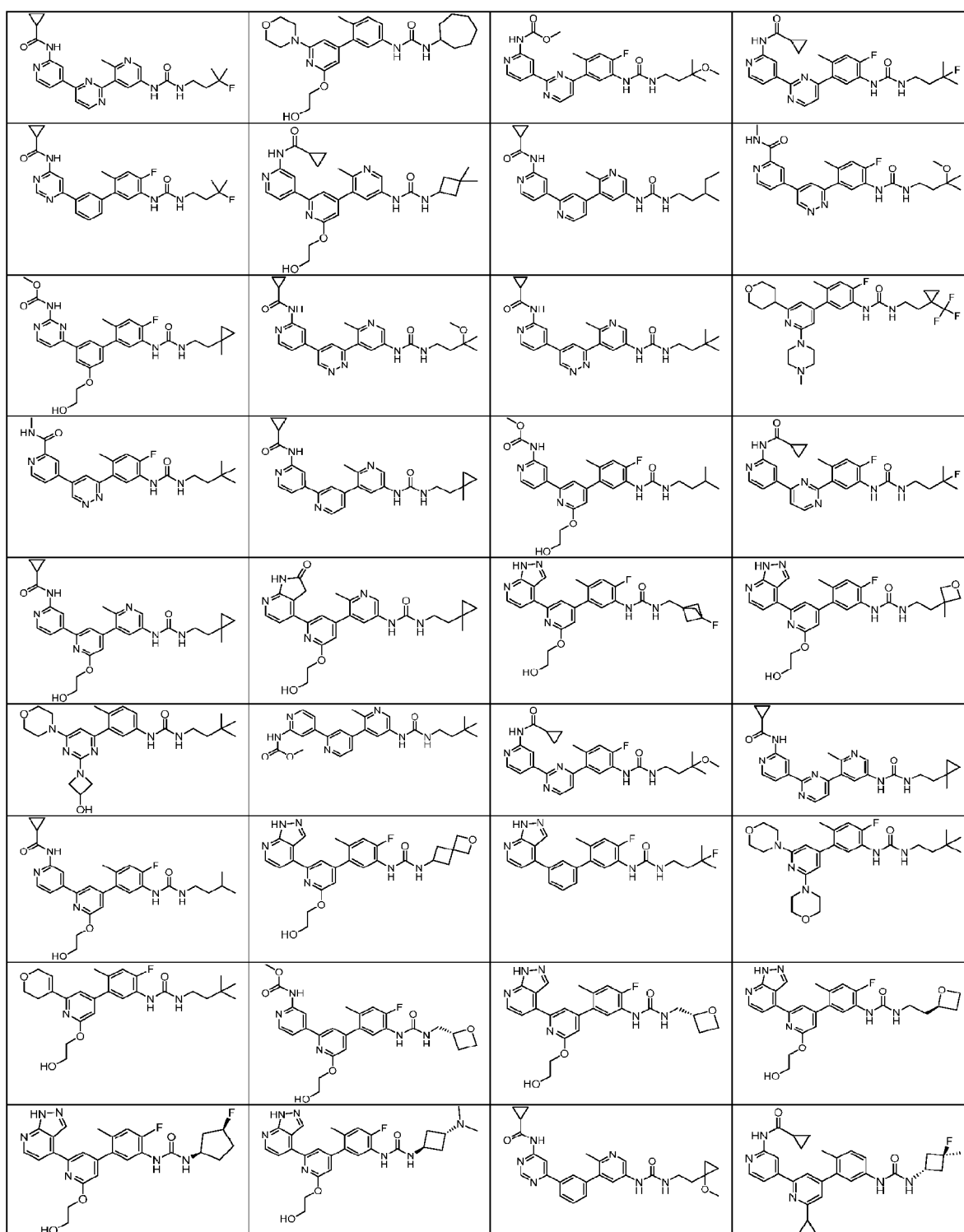
[000193] In an embodiment, described herein is a compound selected from the group consisting of:

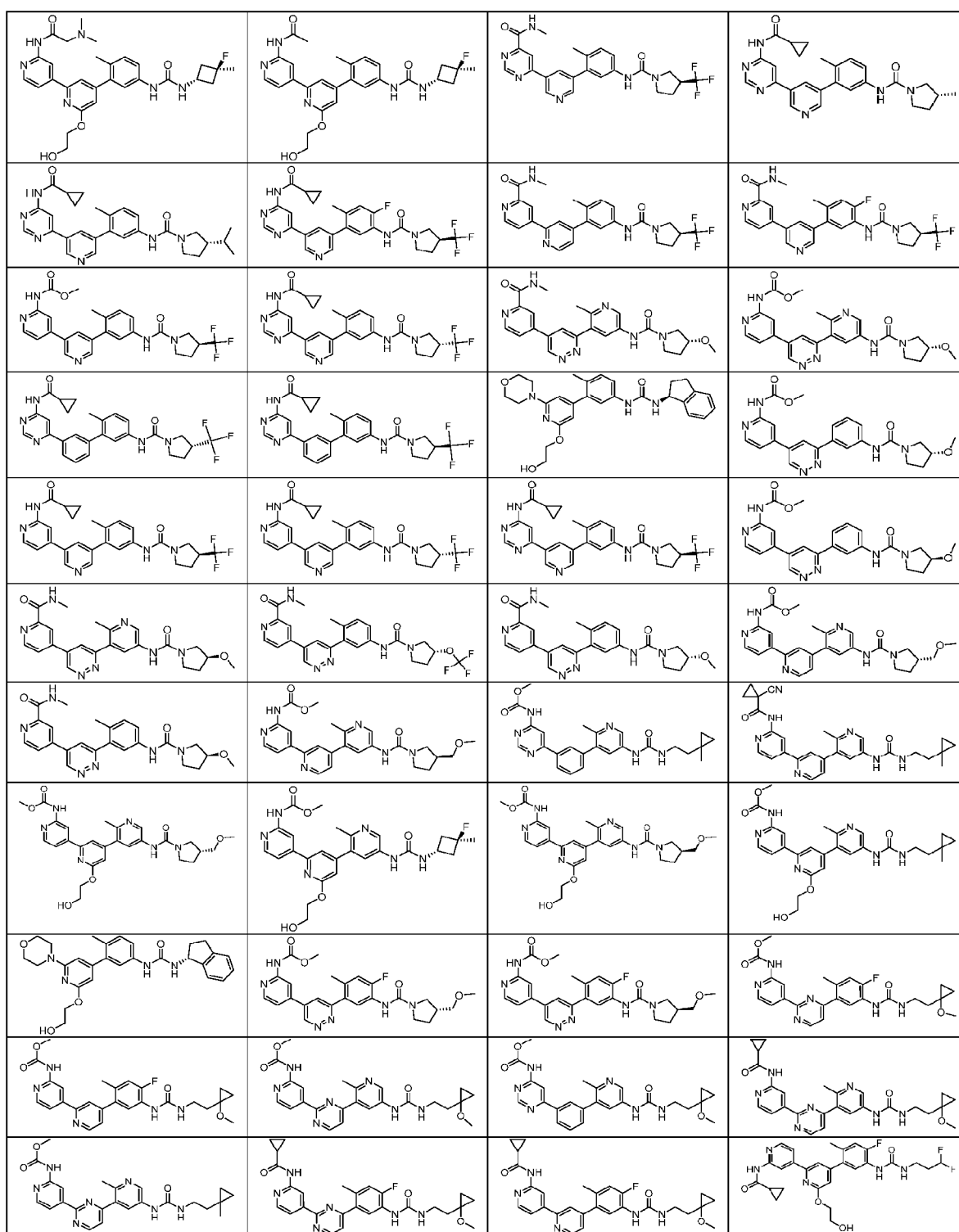


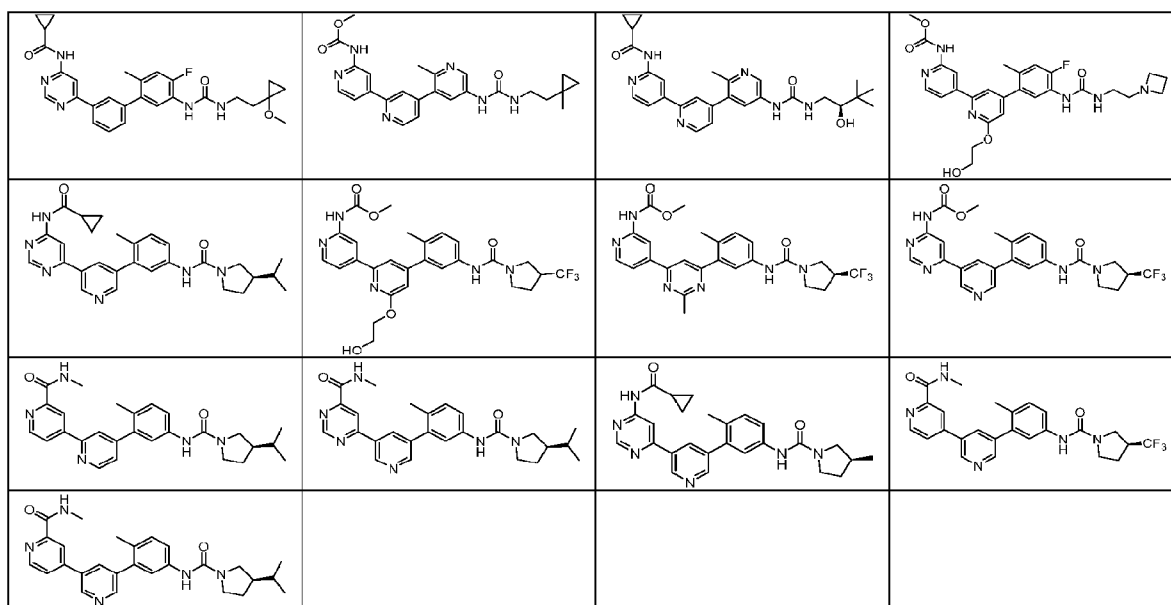












or pharmaceutically acceptable salts, enantiomers, stereoisomers, or tautomers thereof.

Methods of Treatment

[000194] Compounds described herein can act as RAF inhibitors, *e.g.*, BRAF inhibitors or CRAF inhibitors, and are therefore useful in the treatment of diseases and disorders in patients in need thereof, such as cancer. Exemplary cancers include, but are not limited to, melanoma, multiple myeloma, thyroid cancer, ovarian cancer, colorectal cancer, colon cancer, pancreatic cancer, lung cancer, bladder cancer, gastrointestinal stromal tumors, solid tumors, blood-borne cancers, hairy cell leukemia, acute myelogenous leukemia (AML), or other cancers caused by activation of the RAS → RAF → MEK → ERK signaling pathway. In some embodiments, a cancer described herein is a BRAF V600X driven cancer, an atypical BRAF mutated cancer, a BRAF fusion cancer, a CRAF fusion cancer, or a RAS mutant cancer. In some embodiments, the cancer has a BRAF oncogenic mutation. In some embodiments, the cancer has a RAS oncogenic mutation. In some embodiments, the RAS oncogenic mutation is RAS Q61R or Q61K mutation. In some embodiments, the cancer has a NF1 oncogenic mutation. In some embodiments, the lung cancer is non-small lung cancer (NSCL). In some embodiments, the colorectal cancer is colon cancer. In some embodiments, the colorectal cancer is rectal cancer.

[000195] The compounds provided herein may be administered to patients (animals and humans) in need of such treatment in dosages that will provide optimal pharmaceutical

efficacy. It will be appreciated that the dose required for use in any particular application will vary from patient to patient, not only with the particular compound or composition selected, but also with the route of administration, the nature of the condition being treated, the age and condition of the patient, concurrent medication or special diets then being followed by the patient, and other factors which those skilled in the art will recognize, with the appropriate dosage ultimately being at the discretion of the attendant physician. For treating clinical conditions and diseases noted above, a compound provided herein may be administered orally, subcutaneously, topically, parenterally, by inhalation spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants, and vehicles. Parenteral administration may include subcutaneous injections, intravenous or intramuscular injections or infusion techniques.

[000196] Treatment can be continued for as long or as short a period as desired. The compositions may be administered on a regimen of, for example, one to four or more times per day. A suitable treatment period can be, for example, at least about one week, at least about two weeks, at least about one month, at least about six months, at least about 1 year, or indefinitely. A treatment period can terminate when a desired result is achieved.

Combination Therapy

[000197] Compounds described herein, *e.g.*, a compound of the disclosure as described herein, can be administered in combination with one or more additional therapeutic agents to treat a disorder described herein, such as a cancer described herein. For example, provided in the present disclosure is a pharmaceutical composition comprising a compound described herein, *e.g.*, a compound of the disclosure as described herein, one or more additional therapeutic agents, and a pharmaceutically acceptable excipient. In some embodiments, a compound of the disclosure as described herein and one additional therapeutic agent is administered. In some embodiments, a compound of the disclosure as described herein and two additional therapeutic agents are administered. In some embodiments, a compound of the disclosure as described herein and three additional therapeutic agents are administered. Combination therapy can be achieved by administering two or more therapeutic agents, each of which is formulated and administered separately. For example, a compound of the disclosure as described herein and an additional therapeutic agent can be formulated and administered separately. Combination therapy can also be achieved by administering two or more therapeutic agents in a single formulation, for example a pharmaceutical composition comprising a compound of the disclosure as described herein as one therapeutic agent and

one or more additional therapeutic agents such as a MAPK pathway inhibitor or chemotherapeutic agent. For example, a compound of the disclosure as described herein and an additional therapeutic agent can be administered in a single formulation. Other combinations are also encompassed by combination therapy. While the two or more agents in the combination therapy can be administered simultaneously, they need not be. For example, administration of a first agent (or combination of agents) can precede administration of a second agent (or combination of agents) by minutes, hours, days, or weeks. Thus, the two or more agents can be administered within minutes of each other or within 1, 2, 3, 6, 9, 12, 15, 18, or 24 hours of each other or within 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14 days of each other or within 2, 3, 4, 5, 6, 7, 8, 9, or weeks of each other. In some cases, even longer intervals are possible. While in many cases it is desirable that the two or more agents used in a combination therapy be present in within the patient's body at the same time, this need not be so.

[000198] Combination therapy can also include two or more administrations of one or more of the agents used in the combination using different sequencing of the component agents. For example, if agent X and agent Y are used in a combination, one could administer them sequentially in any combination one or more times, *e.g.*, in the order X-Y-X, X-X-Y, Y-X-Y, Y-Y-X, X-X-Y-Y, etc.

[000199] In some embodiments, compounds described herein are combined with other agents including MAPK pathway inhibitors. In some embodiments, the other agent is an inhibitor of RAS. In some embodiments, the other agent is an inhibitor of KRAS G12C. In some embodiments, the other agent is a MEK inhibitor. In some embodiments the other agent is an ERK inhibitor.

[000200] In some embodiments, compounds described herein are combined with an immunomodulatory agent. In some embodiments, the immunomodulatory enhances the adaptive immune response. In some embodiments, the immunomodulatory enhances the activity of antigen-presenting cells. In some embodiments, the immunomodulatory agent enhances the anti-tumor activity of myeloid cells including macrophages. In some embodiments, the immunomodulatory enhances the anti-tumor activity of Natural Killer cells. In some embodiments, the immunomodulatory agent enhances the activity of effector T Cells, including cytotoxic T Cells.

[000201] In some embodiments, the one or more additional therapeutic agents that may be administered in combination with a compound provided herein can be a MAPK pathway

inhibitor. Such MAPK pathway inhibitors include, for example, MEK inhibitors, ERK inhibitors, and Ras inhibitors.

[000202] Exemplary MEK inhibitors include, but are not limited to, trametinib, selumetinib, cobimetinib, binimetinib, mirdametinib, and pharmaceutically acceptable salts thereof. Exemplary ERK inhibitors include, but are not limited to, include, but are not limited to, ulixertinib, SCH772984, LY3214996, ravoxertinib, VX-11e, ASN-007, GDC-0994, MK-8353, ASTX-029, LTT462, KO-947, and pharmaceutically acceptable salts thereof. Exemplary Ras inhibitors include, but are not limited to, AMG-510, MRTX849, ARS-1620, ARS-3248, LY3499446, and pharmaceutically acceptable salts thereof.

[000203] In some embodiments, the additional therapeutic agents can be immunomodulatory agents including but not limited to anti-PD-1 or anti-PDL-1 therapeutics including pembrolizumab, nivolumab, pidilizumab, cemiplimab, atezolizumab, durvalumab, BMS-936559, or avelumab. In some embodiments, the additional therapeutic agents can be anti-TIM3 (anti-HAVcr2) therapeutics including but not limited to TSR-022 or MBG453, anti-LAG3 therapeutics including but not limited to relatlimab, LAG525, or TSR-033, anti-4-1BB (anti-CD37, anti-TNFRSF9), CD40 agonist therapeutics including but not limited to SGN-40, CP-870,893 or RO7009789, anti-CD47 therapeutics including but not limited to Hu5F9-G4, anti-CD20 therapeutics, anti-CD38 therapeutics, STING agonists including but not limited to ADU-S100, MK-1454, ASA404, or amidobenzimidazoles. In some embodiments, the additional therapeutic agents can be anti-CTLA4 agents including ipilimumab, tremelimumab. In some embodiments, the additional therapeutic agents can be hypomethylating agents including but not limited to azacytidine or decitabine, other immunomodulatory therapeutics including but not limited to epidermal growth factor inhibitors, statins, metformin, angiotensin receptor blockers, thalidomide, lenalidomide, pomalidomide, prednisone, or dexamethasone. In some embodiments, the additional therapeutic agents can be immunotherapeutic agents including targeted therapeutic agents, cancer vaccines, and CAR-T cell therapy.

[000204] The compounds described herein may be administered in combination with other therapeutic agents known to treat cancers. Such other therapeutic agents include radiation therapy, anti-tubulin agents, DNA alkylating agents, DNA synthesis-inhibiting agents, DNA intercalating agents, anti-estrogen agents, anti-androgens, steroids, anti-EGFR agents, kinase inhibitors, mTOR inhibitors, PI3 kinase inhibitors, cyclin-dependent kinase inhibitors, CD4/CD6 kinase inhibitors, topoisomerase inhibitors, Histone Deacetylase (HDAC) inhibitors, DNA methylation inhibitors, anti-HER2 agents, anti-angiogenic agents,

proteasome inhibitors, PARP (poly ADP ribose polymerase) inhibitors, cell cycle regulating kinase inhibitors, thalidomide, lenalidomide, antibody-drug-conjugates (ADCs).

[000205] In an embodiment, the additional therapeutic agents can be chemotherapeutic agents including but not limited to an anti-tubulin agents (for example, paclitaxel, paclitaxel protein-bound particles for injectable suspension including but not limited to nab-paclitaxel, eribulin, docetaxel, ixabepilone, vincristine, auristatins, or maytansinoids), vinorelbine, DNA-alkylating agents (including but not limited to cisplatin, carboplatin, oxaliplatin, cyclophosphamide, ifosfamide, temozolomide), DNA intercalating agents or DNA topoisomerase inhibitors (including but not limited to anthracyclines such as doxorubicin, pegylated liposomal doxorubicin, daunorubicin, idarubicin, mitoxantrone, or epirubicin, camptothecins such as topotecan, irinotecan, or exatecan), 5-fluorouracil, capecitabine, cytarabine, decitabine, 5-aza cytidine, gemcitabine, and methotrexate.

[000206] In some embodiments, the additional therapeutic agents can be kinase inhibitors including but not limited to erlotinib, gefitinib, neratinib, afatinib, osimertinib, lapatanib, crizotinib, brigatinib, ceritinib, alectinib, lorlatinib, everolimus, temsirolimus, abemaciclib, LEE011, palbociclib, cabozantinib, ripretinib, sunitinib, pazopanib, sorafenib, regorafenib, sunitinib, axitinib, dasatinib, imatinib, nilotinib, idelalisib, ibrutinib, BLU-667, Loxo 292, larotrectinib, and quizartinib,

[000207] In some embodiments, the additional therapeutic agents can be anti-estrogen agents including but not limited to tamoxifen, fulvestrant, anastrozole, letrozole, and exemestane, anti-androgen agents including but not limited to abiraterone acetate, enzalutamide, nilutamide, bicalutamide, flutamide, cyproterone acetate, steroid agents including but not limited to prednisone and dexamethasone, PARP inhibitors including but not limited to neraparib, olaparib, talazoparib, and rucaparib, topoisomerase I inhibitors including but not limited to irinotecan, camptothecin, exatecan, and topotecan, topoisomerase II inhibitors including but not limited to anthracyclines, etoposide, etoposide phosphate, and mitoxantrone, Histone Deacetylase (HDAC) inhibitors including but not limited to vorinostat, romidepsin, panobinostat, valproic acid, and belinostat, DNA methylation inhibitors including but not limited to DZNep and 5-aza-2'-deoxycytidine, proteasome inhibitors including but not limited to bortezomib and carfilzomib, biological agents including but not limited to trastuzumab, ado-trastuzumab, pertuzumab, cetuximab, and panitumumab.

[000208] In some embodiments, the additional therapeutic agents can be anti-angiogenic agents including but not limited to bevacizumab, aflibercept, and AMG386.

[000209] In some embodiments, the additional therapeutic agents can be antibody-drug-conjugates (ADCs) including but not limited to ADCs containing DM1, DM4, MMAE, MMAF, or camptothecin payloads, brentuximab vedotin and trastuzumab emtansine, radiotherapy, therapeutic vaccines including but not limited to sipuleucel-T.

[000210] In some embodiments, the additional therapeutic agent can be an autophagy inhibitor, an inhibitor of vesicular trafficking, including but not limited to ULK inhibitors such as ULK1 inhibitors, ULK2 inhibitors, ULK1/ULK2 inhibitors, VPS34 inhibitors, PPT1 inhibitors, or lysosomal blocking agents. In some embodiments, the additional therapeutic agent can be DCC-3116, SAR405, SB02024, hydroxychloroquine, chloroquine, and LYS05.

[000211] In some embodiments, the additional therapeutic agent can be EGFR inhibitors. Exemplary EGFR inhibitors include, but are not limited, cetuximab, osimertinib, and afatinib, and pharmaceutically acceptable salts thereof. In some embodiments, the additional therapeutic agent is selected from a luteinizing hormone-releasing hormone (LHRH) analog, including goserelin and leuprolide.

[000212] In some embodiments, the additional therapeutic agent is selected from the group consisting of selected from the group consisting of everolimus, trabectedin, abraxane, TLK 286, AV-299, DN-101, pazopanib, GSK690693, RTA 744, ON 0910.Na, AZD 6244 (ARRY-142886), AMN-107, TKI-258, GSK461364, AZD 1152, enzastaurin, vandetanib, ARQ-197, MK-0457, MLN8054, PHA-739358, R-763, AT-9263, pemetrexed, erlotinib, dasatinib, nilotinib, decatanib, panitumumab, amrubicin, oregovomab, Lep-etu, nolatrexed, AZD 2171, batabulin, ofatumumab, zanolimumab, edotecarin, tetrandrine, rubitecan, tesmilifene, oblimersen, ticilimumab, ipilimumab, gossypol, Bio 111, 131-I-TM-601, ALT-110, BIO 140, CC 8490, cilengitide, gimatecan, IL13-PE38QQR, INO 1001, IPdR₁ KRX-0402, lucanthone, LY 317615, neuradiab, vitespan, Rta 744, Sdx 102, talampanel, atrasentan, Xr 311, romidepsin, ADS-100380, sunitinib, 5-fluorouracil, vorinostat, etoposide, gemcitabine, doxorubicin, irinotecan, liposomal doxorubicin, 5'-deoxy-5-fluorouridine, vincristine, temozolomide, ZK-304709, seliciclib, PD0325901, AZD-6244, capecitabine, L-Glutamic acid, N-[4-[2-(2-amino-4,7-dihydro-4-oxo-1H-pyrrolo[2,3-d]pyrimidin-5-yl)-ethyl]benzoyl]-, disodium salt, heptahydrate, camptothecin, PEG-labeled irinotecan, tamoxifen, toremifene citrate, anastrozole, exemestane, letrozole, DES(diethylstilbestrol), estradiol, estrogen, conjugated estrogen, bevacizumab, IMC-1C11, CHIR-258, 3-[5-(methylsulfonylpiperadinemethyl)-indolyl]-quinolone, vatalanib, AG-013736, AVE-0005, the acetate salt of [D-Ser(tBu) 6, Azgly 10] (pyro-Glu-His-Trp-Ser-Tyr-D-Ser(tBu)-Leu-Arg-

Pro-Azgly-NH₂ acetate [C₅₉H₈₄N₁₈O₁₄-(C₂H₄O₂)_x where x=1 to 2.4], goserelin acetate, leuprolide acetate, triptorelin pamoate, medroxyprogesterone acetate, hydroxyprogesterone caproate, megestrol acetate, raloxifene, bicalutamide, flutamide, nilutamide, megestrol acetate, CP-724714, TAK-165, HKI-272, erlotinib, lapatanib, canertinib, ABX-EGF antibody, erbitux, EKB-569, PKI-166, GW-572016, Imafarnib, BMS-214662, tipifarnib, amifostine, NVP-LAQ824, suberoyl analog hydroxamic acid, valproic acid, trichostatin A, FK-228, SU11248, sorafenib, KRN951, aminoglutethimide, arnsacrine, anagrelide, L-asparaginase, Bacillus Calmette-Guerin (BCG) vaccine, bleomycin, buserelin, busulfan, carboplatin, carmustine, chlorambucil, cisplatin, cladribine, clodronate, cyproterone, cytarabine, dacarbazine, dactinomycin, daunorubicin, diethylstilbestrol, epirubicin, fludarabine, fludrocortisone, fluoxymesterone, flutamide, gemcitabine, gleevec, hydroxyurea, idarubicin, ifosfamide, imatinib, leuprolide, levamisole, lomustine, mechlorethamine, melphalan, 6-mercaptopurine, mesna, methotrexate, mitomycin, mitotane, mitoxantrone, nilutamide, octreotide, oxaliplatin, pamidronate, pentostatin, plicamycin, porfimer, procarbazine, raltitrexed, rituximab, streptozocin, teniposide, testosterone, thalidomide, thioguanine, thiotepa, tretinoin, vindesine, 13-cis-retinoic acid, phenylalanine mustard, uracil mustard, estramustine, altretamine, floxuridine, 5-deoxyuridine, cytosine arabinoside, 6-mercaptopurine, deoxycytosine, calcitriol, valrubicin, mithramycin, vinblastine, vinorelbine, topotecan, razoxin, marimastat, COL-3, neovastat, BMS-275291, squalamine, endostatin, SU5416, SU6668, EMD121974, interleukin-12, IM862, angiostatin, vitaxin, droloxifene, idoxifene, spironolactone, finasteride, cimitidine, trastuzumab, denileukin diftitox, gefitinib, bortezomib, irinotecan, topotecan, doxorubicin, docetaxel, vinorelbine, bevacizumab (monoclonal antibody) and erbitux, cremophor-free paclitaxel, epithilone B, BMS-247550, BMS-310705, droloxifene, 4-hydroxytamoxifen, pipendoxifene, ERA-923, arzoxifene, fulvestrant, acolbifene, lasofoxifene, idoxifene, TSE-424, HMR-3339, ZK186619, PTK787/ZK 222584, VX-745, PD 184352, rapamycin, 40-O-(2-hydroxyethyl)-rapamycin, temsirolimus, AP-23573, RAD001, ABT-578, BC-210, LY294002, LY292223, LY292696, LY293684, LY293646, wortmannin, ZM336372, L-779,450, PEG-filgrastim, darbepoetin, erythropoietin, granulocyte colony-stimulating factor, zoledronate, prednisone, cetuximab, granulocyte macrophage colony-stimulating factor, histrelin, pegylated interferon alfa-2a, interferon alfa-2a, pegylated interferon alfa-2b, interferon alfa-2b, azacitidine, PEG-L-asparaginase, lenalidomide, gemtuzumab, hydrocortisone, interleukin-11, dexrazoxane, alemtuzumab, all-transretinoic acid, ketoconazole, interleukin-2, megestrol, immune globulin, nitrogen mustard, methylprednisolone, ibritumomab tiuxetan, androgens,

decitabine, hexamethylmelamine, bexarotene, tositumomab, arsenic trioxide, cortisone, editronate, mitotane, cyclosporine, liposomal daunorubicin, Edwina-asparaginase, strontium 89, casopitant, netupitant, an NK-1 receptor antagonist, palonosetron, aprepitant, diphenhydramine, hydroxyzine, metoclopramide, lorazepam, alprazolam, haloperidol, droperidol, dronabinol, dexamethasone, methylprednisolone, prochlorperazine, granisetron, ondansetron, dolasetron, tropisetron, pegfilgrastim, erythropoietin, epoetin alfa and darbepoetin alfa, ipilimumab, and mixtures thereof.

Pharmaceutical Compositions and Kits

[000213] Another aspect of this disclosure provides pharmaceutical compositions comprising compounds as disclosed herein formulated together with a pharmaceutically acceptable carrier. In particular, the present disclosure provides pharmaceutical compositions comprising compounds as disclosed herein formulated together with one or more pharmaceutically acceptable carriers. These formulations include those suitable for oral, rectal, topical, buccal, parenteral (*e.g.*, subcutaneous, intramuscular, intradermal, or intravenous) rectal, vaginal, or aerosol administration, although the most suitable form of administration in any given case will depend on the degree and severity of the condition being treated and on the nature of the particular compound being used. For example, disclosed compositions may be formulated as a unit dose, and/or may be formulated for oral or subcutaneous administration.

[000214] Exemplary pharmaceutical compositions may be used in the form of a pharmaceutical preparation, for example, in solid, semisolid, or liquid form, which contains one or more of the compounds described herein, as an active ingredient, in admixture with an organic or inorganic carrier or excipient suitable for external, enteral, or parenteral applications. The active ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, solutions, emulsions, suspensions, and any other form suitable for use. The active object compound is included in the pharmaceutical composition in an amount sufficient to produce the desired effect upon the process or condition of the disease.

[000215] For preparing solid compositions such as tablets, the principal active ingredient may be mixed with a pharmaceutical carrier, *e.g.*, conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, *e.g.*, water, to form

a solid preformulation composition containing a homogeneous mixture of a compound provided herein, or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills, and capsules.

[000216] In solid dosage forms for oral administration (capsules, tablets, pills, dragees, powders, granules and the like), the subject composition is mixed with one or more pharmaceutically acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such as, for example, acetyl alcohol and glycerol monostearate; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; and (10) coloring agents. In the case of capsules, tablets and pills, the compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

[000217] A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the subject composition moistened with an inert liquid diluent. Tablets, and other solid dosage forms, such as dragees, capsules, pills, and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art.

[000218] Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous, or organic solvents, or mixtures thereof, and powders. Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups, and elixirs. In addition to the

subject composition, the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, cyclodextrins and mixtures thereof.

[000219] Suspensions, in addition to the subject composition, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

[000220] Formulations for rectal or vaginal administration may be presented as a suppository, which may be prepared by mixing a subject composition with one or more suitable non-irritating excipients or carriers comprising, for example, cocoa butter, polyethylene glycol, a suppository wax, or a salicylate, and which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the body cavity and release the active agent.

[000221] Dosage forms for transdermal administration of a subject composition include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches, and inhalants. The active component may be mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants which may be required.

[000222] The ointments, pastes, creams, and gels may contain, in addition to a subject composition, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

[000223] Powders and sprays may contain, in addition to a subject composition, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays may additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

[000224] Compositions and compounds of the present disclosure may alternatively be administered by aerosol. This is accomplished by preparing an aqueous aerosol, liposomal preparation or solid particles containing the compound. A non-aqueous (*e.g.*, fluorocarbon propellant) suspension could be used. Sonic nebulizers may be used because they minimize exposing the agent to shear, which may result in degradation of the compounds contained in

the subject compositions. Ordinarily, an aqueous aerosol is made by formulating an aqueous solution or suspension of a subject composition together with conventional pharmaceutically acceptable carriers and stabilizers. The carriers and stabilizers vary with the requirements of the particular subject composition, but typically include non-ionic surfactants (Tweens, Pluronics, or polyethylene glycol), innocuous proteins like serum albumin, sorbitan esters, oleic acid, lecithin, amino acids such as glycine, buffers, salts, sugars or sugar alcohols. Aerosols generally are prepared from isotonic solutions.

[000225] Pharmaceutical compositions of the present disclosure suitable for parenteral administration comprise a subject composition in combination with one or more pharmaceutically-acceptable sterile isotonic aqueous or non-aqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

[000226] Examples of suitable aqueous and non-aqueous carriers which may be employed in the pharmaceutical compositions provided herein include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate and cyclodextrins. Proper fluidity may be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

[000227] In another embodiment, provided are enteral pharmaceutical formulations including a disclosed compound, an enteric material, and a pharmaceutically acceptable carrier or excipient thereof. Enteric materials refer to polymers that are substantially insoluble in the acidic environment of the stomach, and that are predominantly soluble in intestinal fluids at specific pHs. The small intestine is the part of the gastrointestinal tract (gut) between the stomach and the large intestine, and includes the duodenum, jejunum, and ileum. The pH of the duodenum is about 5.5, the pH of the jejunum is about 6.5 and the pH of the distal ileum is about 7.5.

[000228] Accordingly, enteric materials are not soluble, for example, until a pH of about 5.0, of about 5.2, of about 5.4, of about 5.6, of about 5.8, of about 6.0, of about 6.2, of about 6.4, of about 6.6, of about 6.8, of about 7.0, of about 7.2, of about 7.4, of about 7.6, of about 7.8, of about 8.0, of about 8.2, of about 8.4, of about 8.6, of about 8.8, of about 9.0, of about 9.2, of about 9.4, of about 9.6, of about 9.8, or of about 10.0. Exemplary enteric

materials include cellulose acetate phthalate (CAP), hydroxypropyl methylcellulose phthalate (HPMCP), polyvinyl acetate phthalate (PVAP), hydroxypropyl methylcellulose acetate succinate (HPMCAS), cellulose acetate trimellitate, hydroxypropyl methylcellulose succinate, cellulose acetate succinate, cellulose acetate hexahydrophthalate, cellulose propionate phthalate, cellulose acetate maleate, cellulose acetate butyrate, cellulose acetate propionate, copolymer of methylmethacrylic acid and methyl methacrylate, copolymer of methyl acrylate, methylmethacrylate and methacrylic acid, copolymer of methylvinyl ether and maleic anhydride (Gantrez ES series), ethyl methacrylate-methylmethacrylate-chlorotrimethylammonium ethyl acrylate copolymer, natural resins such as zein, shellac and copal colophonium, and several commercially available enteric dispersion systems (*e.g.*, Eudragit L30D55, Eudragit FS30D, Eudragit L100, Eudragit S100, Kollicoat EMM30D, Estacryl 30D, Coateric, and Aquateric). The solubility of each of the above materials is either known or is readily determinable *in vitro*. The foregoing is a list of possible materials, but one of skill in the art with the benefit of the disclosure would recognize that it is not comprehensive and that there are other enteric materials that would meet the objectives described herein.

[000229] Advantageously, provided herein are kits for use by a *e.g.*, a consumer in need of treatment of cancer. Such kits include a suitable dosage form such as those described above and instructions describing the method of using such dosage form to mediate, reduce or prevent inflammation. The instructions would direct the consumer or medical personnel to administer the dosage form according to administration modes known to those skilled in the art. Such kits could advantageously be packaged and sold in single or multiple kit units. An example of such a kit is a so-called blister pack. Blister packs are well known in the packaging industry and are being widely used for the packaging of pharmaceutical unit dosage forms (tablets, capsules, and the like). Blister packs generally consist of a sheet of relatively stiff material covered with a foil of a preferably transparent plastic material. During the packaging process recesses are formed in the plastic foil. The recesses have the size and shape of the tablets or capsules to be packed. Next, the tablets or capsules are placed in the recesses and the sheet of relatively stiff material is sealed against the plastic foil at the face of the foil which is opposite from the direction in which the recesses were formed. As a result, the tablets or capsules are sealed in the recesses between the plastic foil and the sheet. Preferably the strength of the sheet is such that the tablets or capsules can be removed from the blister pack by manually applying pressure on the recesses whereby an opening is formed

in the sheet at the place of the recess. The tablet or capsule can then be removed via said opening.

[000230] It may be desirable to provide a memory aid on the kit, *e.g.*, in the form of numbers next to the tablets or capsules whereby the numbers correspond with the days of the regimen which the tablets or capsules so specified should be ingested. Another example of such a memory aid is a calendar printed on the card, *e.g.*, as follows "First Week, Monday, Tuesday, . . . etc. . . . Second Week, Monday, Tuesday, . . . " etc. Other variations of memory aids will be readily apparent. A "daily dose" can be a single tablet or capsule or several pills or capsules to be taken on a given day. Also, a daily dose of a first compound can consist of one tablet or capsule while a daily dose of the second compound can consist of several tablets or capsules and vice versa. The memory aid should reflect this.

EXAMPLES

[000231] The compounds described herein can be prepared in a number of ways based on the teachings contained herein and synthetic procedures known in the art. In the description of the synthetic methods described below; it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment and workup procedures, can be chosen to be the conditions standard for that reaction, unless otherwise indicated. It is understood by one skilled in the art of organic synthesis that the functionality present on various portions of the molecule should be compatible with the reagents and reactions proposed. Substituents not compatible with the reaction conditions will be apparent to one skilled in the art, and alternate methods are therefore indicated. The starting materials for the examples are either commercially available or are readily prepared by standard methods from known materials.

[000232] The following abbreviations are used in this disclosure and have the following definitions: "ADP" is adenosine diphosphate, "ATP" is adenosine triphosphate, "Ar" is argon gas, "Boc" is t-butylcarbonate, "BSA" is bovine serum albumin, "conc." is concentrated, "Cs₂CO₃" is cesium carbonate, "CuI" is copper (I) iodide, "CVs" is column volumes, "DBU" is 1,8-diazabicyclo[5.4.0]undec-7-ene, "DCE" is dichloroethane, "DCM" is dichloromethane, "DIEA" is *N,N*-diisopropylethylamine, "DMA" is *N,N*-dimethylacetamide, "DMAP" is 4-(dimethylamino)pyridine, "DMF" is *N,N*-dimethylformamide, "dppf" is 1,1'-bis(diphenylphosphino)ferrocene, "DMEM" is Dulbecco's Modified Eagle Media, "DMSO" is dimethylsulfoxide, "DPPA" is diphenylphosphoryl azide, "EDC" is 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide, "ESI" is electrospray ionization, "Et₂O" is diethylether,

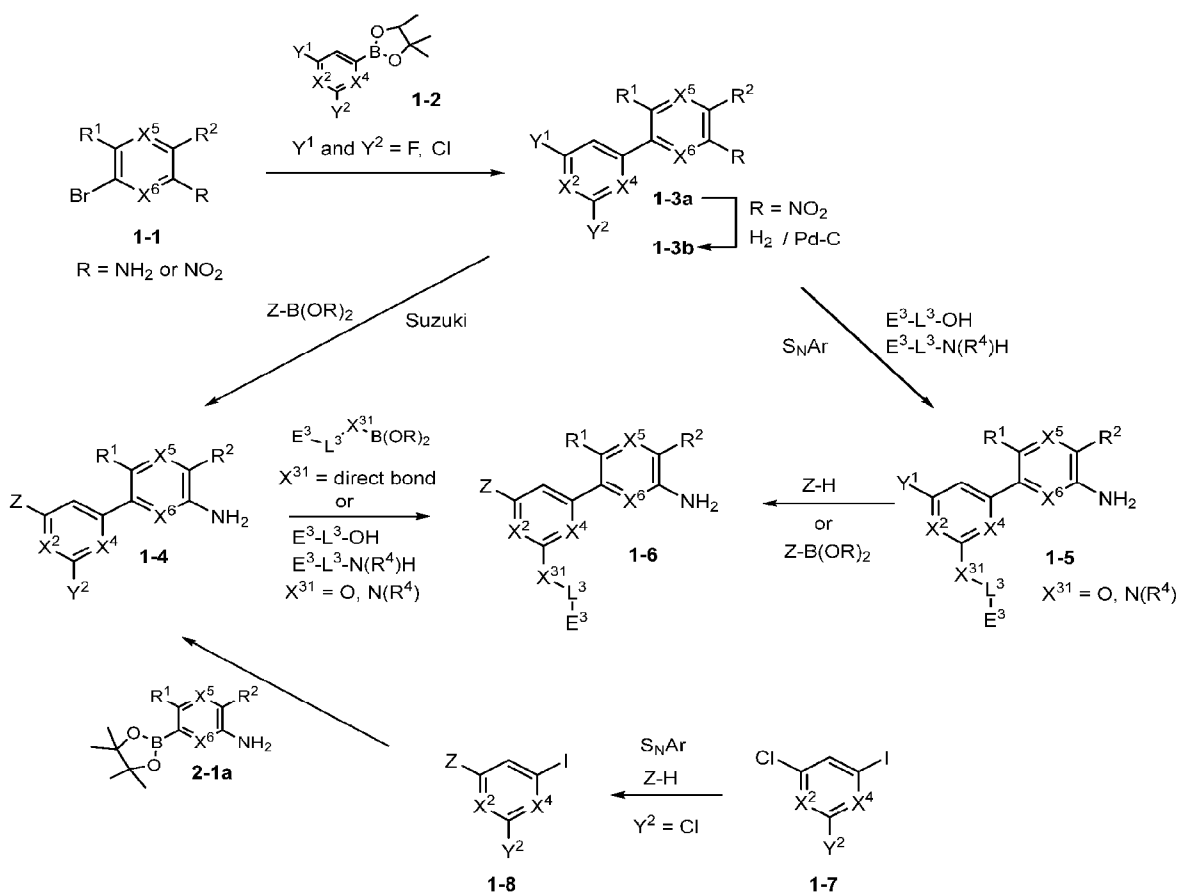
“EtOAc” is ethyl acetate, “EtOH” is ethanol, “GST” is glutathione S-transferase, “h” is hour or hours, “HATU” is hexafluorophosphate azabenzotriazole tetramethyl uronium, “H₂” is hydrogen gas, “HCl” is hydrochloric acid, “Hex” is hexane, “H₂O” is water, “HOBT” is hydroxybenzotriazole, “IC₅₀” is half maximal inhibitory concentration, “K₂CO₃” is potassium carbonate, “K₃PO₄” is potassium phosphate, “LAH” is lithium aluminum hydride, “LiMHDS” is lithium bis(trimethylsilyl)amide, “mCPBA” is *meta*-Chloroperoxybenzoic acid, MeCN” is acetonitrile, “MeOH” is methanol, “MgSO₄” is magnesium sulfate, “MHz” is megahertz, “min” is minute or minutes, “MS” is mass spectrometry, “NADH” is nicotinamide adenine dinucleotide, “NaH” is sodium hydride, “NaHCO₃” is sodium bicarbonate, “Na₂SO₄” is sodium sulfate, “NaBH₄” is sodium borohydride, “Na₂S₂O₃” is Sodium thiosulfate “NaSMe” is sodium thiomethoxide, “NH₄Cl” is ammonium chloride, “NH₄OH” is ammonium hydroxide, “NBS” is N-bromosuccinimide, “NMR” is nuclear magnetic resonance, “OMs” is O-mesylate, “PBS” is phosphate buffered saline, “Pd” is palladium, “Pd/C” is palladium on carbon, “Pd₂(dba)₃” is tris(dibenzylideneacetone)dipalladium(0), “Pd(OAc)₂” is palladium (II) acetate, “Pd(PPh₃)₄” is tetrakis(triphenylphosphine)palladium(0), “prep-HPLC” is preparative high performance liquid chromatography, “rt” is room temperature which is also known as “ambient temp,” which will be understood to consist of a range of normal laboratory temperatures ranging from 15-25 °C, “sat’d.” is saturated, “SFC” is supercritical fluid chromatography, “SM” is starting material, “S_NAr” is “nucleophilic aromatic substitution, “T₃P” is n-propanephosphonic acid anhydride, “TBAF” is tertabutyl ammonium fluoride, “TEA” is triethylamine, “TFA” is trifluoroacetic acid, “THF” is tetrahydrofuran, “TMS” is trimethylsilyl, “TBDMS” is tert-butyldimethylsilyl, “Tris” is tris(hydroxymethyl)aminomethane, “Xantphos” is 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene, “X-Phos” is 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl and “ZnCl₂” is zinc chloride.

General Chemistry

[000233] Exemplary compounds described herein are available by the general synthetic methods illustrated in the Schemes below, Intermediate preparations, and the accompanying Examples.

Synthetic Schemes

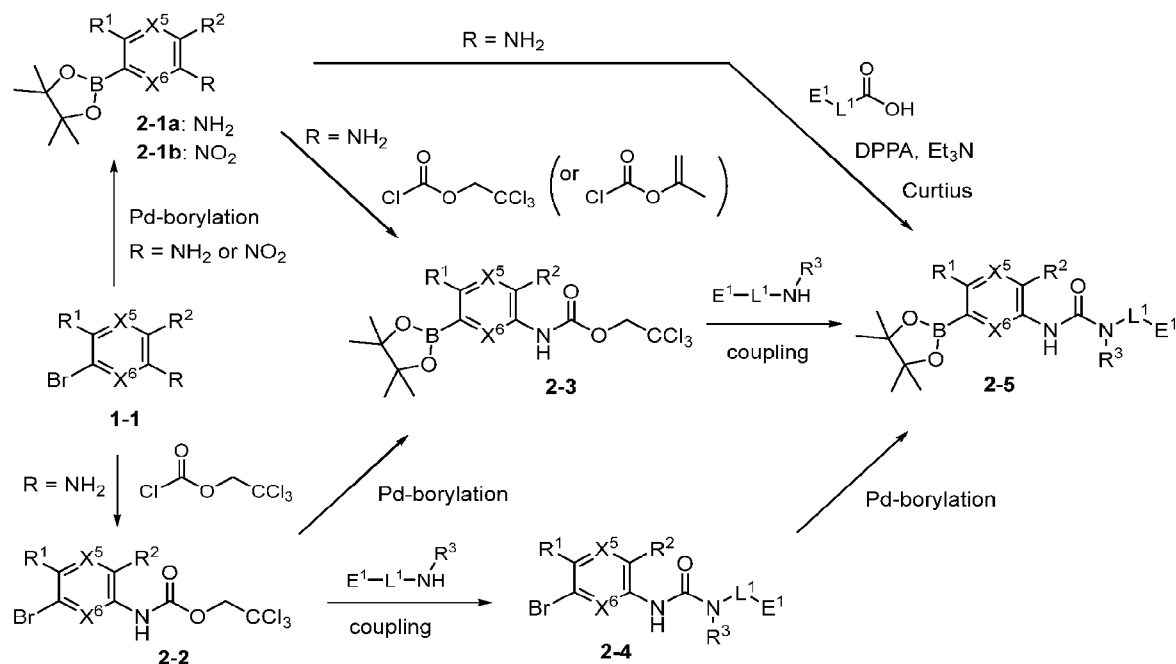
Scheme 1



[000234] Scheme 1 illustrates an exemplary preparation of intermediates **1-6**. Treatment of bromides **1-1** (R = NH₂) with commercially available boronates **1-2** (2,6-dichloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine, 4-chloro-2-fluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine, 2-chloro-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine or 2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine) in the presence of a palladium catalyst (Suzuki coupling) affords **1-3b**. Alternatively, treatment of bromides **1-1** (R = NO₂) with commercially available boronates **1-2** under Suzuki conditions to afford **1-3a**. Compounds **1-3a** can be reduced by Pd catalyzed hydrogenation (palladium on carbon 10 %, 50 % wet) or mild reducing conditions for example, zinc or iron metal with ammonium chloride to afford **1-3b**. Compounds **1-3b** (Y¹ = Cl, R = NH₂) reacts with Z-B(OR)₂ under Pd (0) catalyzed coupling conditions to provide **1-4**. Compounds **1-3b** (Y² = F or Cl) react with alcohols E³-L³-OH or amines E³-L³-N(R⁴)H by S_NAr reaction in the presence of base to afford **1-5**. Z-substituted intermediates **1-4** are converted to **1-6** by S_NAr with alcohols E³-L³-OH or amines E³-L³-N(R⁴)H. Z-substituted

intermediates **1-4** are converted to **1-6** by Suzuki reaction with $E^3-L^3-B(OR)_2$ using well known established literature conditions to those skilled in the art. Compounds **1-5** react with alcohols or amines Z-H by S_NAr reaction in the presence of base to afford **1-6**. Alternatively, **1-6** can be obtained by Suzuki reaction of **1-5** ($Y^1 = Cl$) with boronates or boronic acids Z-B(OR)₂. Commercially available starting materials **1-7** react with alcohols or amines Z-H by S_NAr reaction in the presence of base to obtain Z-substituted intermediates **1-8** ($Y^2 = Cl$) which can be converted to **1-4** by Suzuki reaction with boronates **1-9**. Boronates **2-1a** are commercially available or can be readily prepared from corresponding halides by known methods to those skilled in the art (see scheme 2).

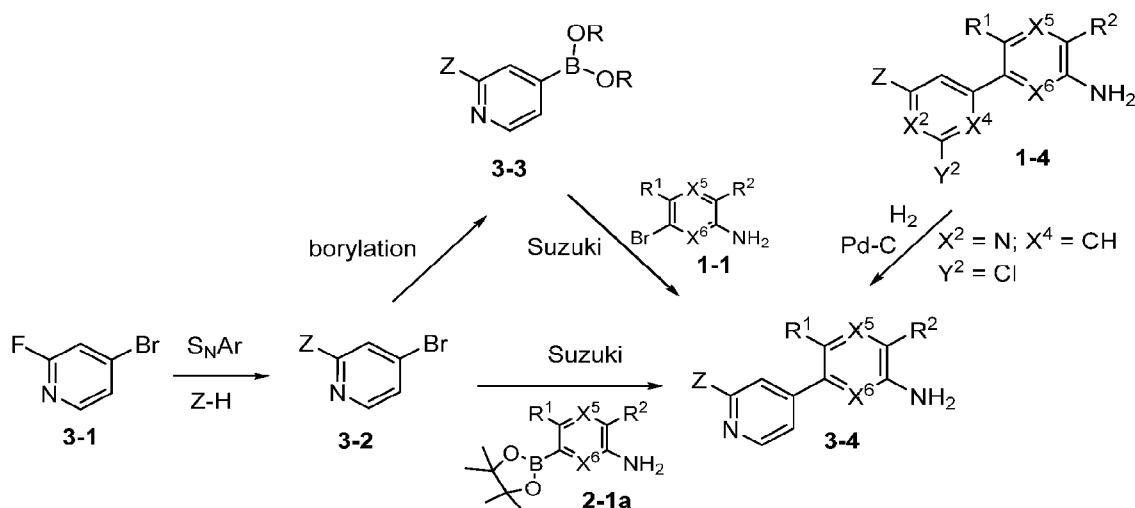
Scheme 2



[000235] Scheme 2 illustrates an exemplary preparation of intermediates **2-5**. Pd-borylation of **1-1** ($R = NH_2$ or NO_2) with bis(pinacolato)diboron in the presence of a palladium catalyst (example, $Pd(dppf)Cl_2$) affords boronates **2-1a** ($R = NH_2$) or **2-1b** ($R = NO_2$). Activation of **1-1** ($R = NH_2$) with 2,2,2-trichloroethyl chloroformate (or isopropenyl chloroformate) under Schotten-Baumann conditions (for example in a mixture of saturated aqueous $NaHCO_3$ and $EtOAc$) affords **2-2** which is further reacted with amines $E^1-L^1-N(R^3)H$

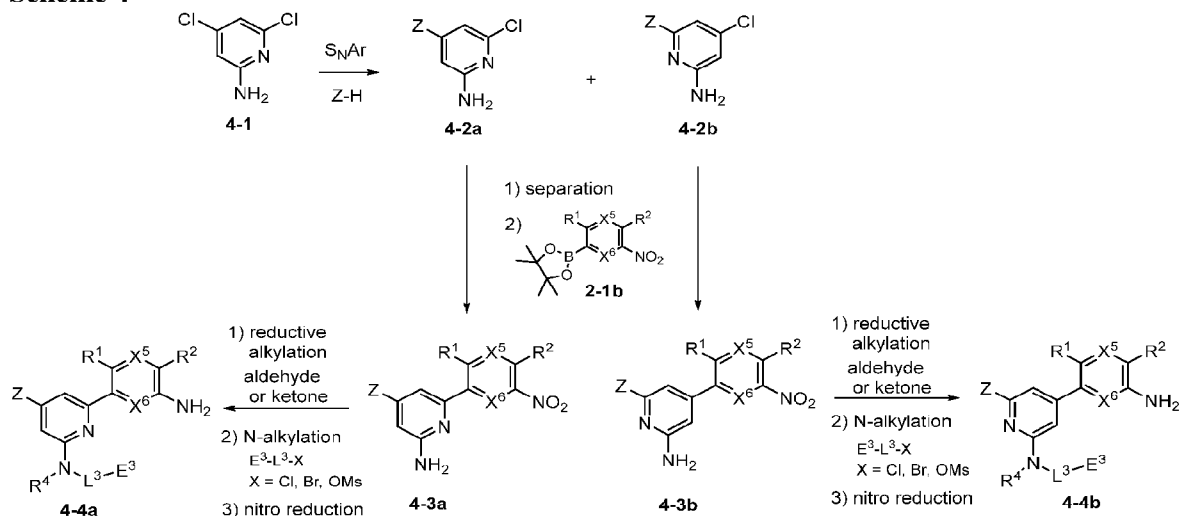
(commercially available or synthesized as described in WO2013134252) to furnish urea **2-4**. Compounds **2-3** can be obtained by activation of **2-1a** with 2,2,2-trichloroethyl chloroformate (or isopropenyl chloroformate) under Schotten-Baumann conditions or by Pd-borylation of **2-2** with bis(pinacolato)diboron. Intermediates **2-5** can be prepared by reaction of **2-1a** with carboxylic acids E^1-L^1-COOH (commercially available or synthesized as described in US20080019978A1, Organic Letters, 2020, 22, 1091-1095 and Tetrahedron, 1986, 42, 2931-2935) under Curtius rearrangement (*in situ* generation of isocyanate) conditions (DPPA and a base (Et_3N) in a suitable solvent such as 1,4-dioxane at elevated temperature), by coupling reaction of **2-3** with amines $E^1-L^1-N(R^3)H$ or by Pd-borylation of **2-4** with bis(pinacolato)diboron.

Scheme 3



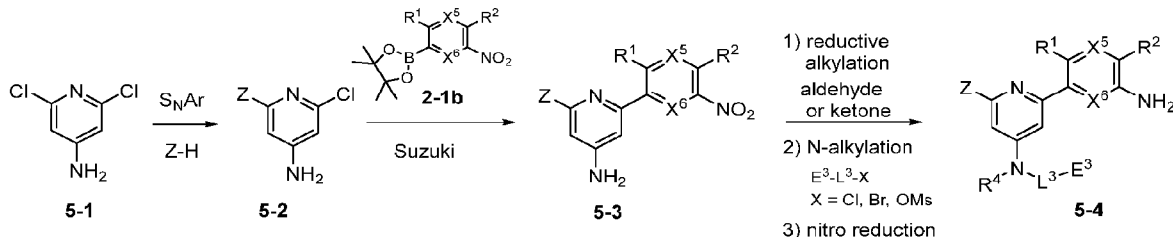
[000236] Scheme 3 illustrates an exemplary preparation of intermediates **3-4**. Commercially available 4-bromo-2-fluoropyridine **3-1** reacts with various alcohols or amines $Z-H$ by S_NAr reaction in the presence of base to obtain **3-2**. Amines **3-4** can be prepared in different approaches as shown in scheme 3. Bromides **3-2** upon borylation provide **3-3**. Borylation is a well-documented reaction to those skilled in the art. This transformation can be performed under different conditions such as trialkylborates in presence of $n-BuLi$ or Pd (0) catalyzed reaction with bis(pinacolato)diboron. Boronates or boronic acids **3-3** react with bromides **1-1** ($R = NH_2$) to produce **3-4**. In another approach, **3-4** can be prepared from **3-2** with boronates **2-1a** under Suzuki reaction conditions. De-chlorination of **1-4** (Scheme 1, where $X^2 = N$, $X^4 = CH$ and $Y^2 = Cl$) by palladium catalyzed hydrogenation affords **3-4**.

Scheme 4



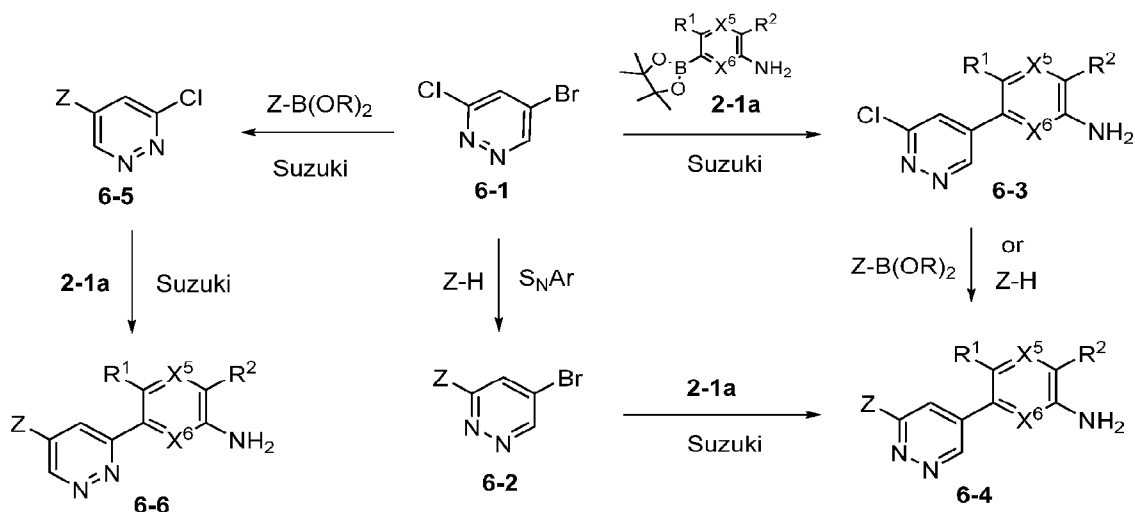
[000237] Scheme 4 describes an exemplary preparation of intermediates **4-4a** and **4-4b**. Commercially available 4,6-dichloropyridin-2-amine **4-1** reacts with alcohols or amines $Z-H$ by S_NAr reaction to provide **4-2a** and **4-2b** in the presence of a suitable base such as DIEA, K_2CO_3 , or NaH . When produced as a mixture, it is understood by those skilled in the art that **4-2a** and **4-2b** can be separated by a suitable purification method for example by SFC purification, crystallization, or chromatography. After separation of a mixture **4-2a** and **4-2b**, each isomer reacts with boronates **2-1b** under Suzuki conditions to obtain **4-3a** and **4-3b** respectively. Treatment of **4-3a** with aldehyde or ketone to introduce R^4 by reductive alkylation conditions known to those skilled in the art gives the R^4 substituted secondary amine. N-alkylation of the secondary amine with different alkylating agents (E^3-L^3-X ; $X = Cl, Br, OMs$) in the presence of base, followed by nitro reduction by palladium catalyzed hydrogenation or mild reducing conditions (zinc or iron metal with ammonium chloride) furnishes **4-4a**. In a similar manner, **4-3b** can be converted to **4-4b**.

Scheme 5



[000238] Scheme 5 illustrates an exemplary preparation of intermediates **5-4**. Commercially available 2,6-dichloropyridin-4-amine **5-1** reacts with alcohols or amines Z-H by $\text{S}_{\text{N}}\text{Ar}$ reaction in the presence of base such as DIEA, NaH, or K_2CO_3 to provide **5-2**. Suzuki reaction of **5-2** with boronates **2-1b** provides **5-3**. Intermediates **5-4** can be prepared from **5-3** in a similar manner as described in Scheme 4.

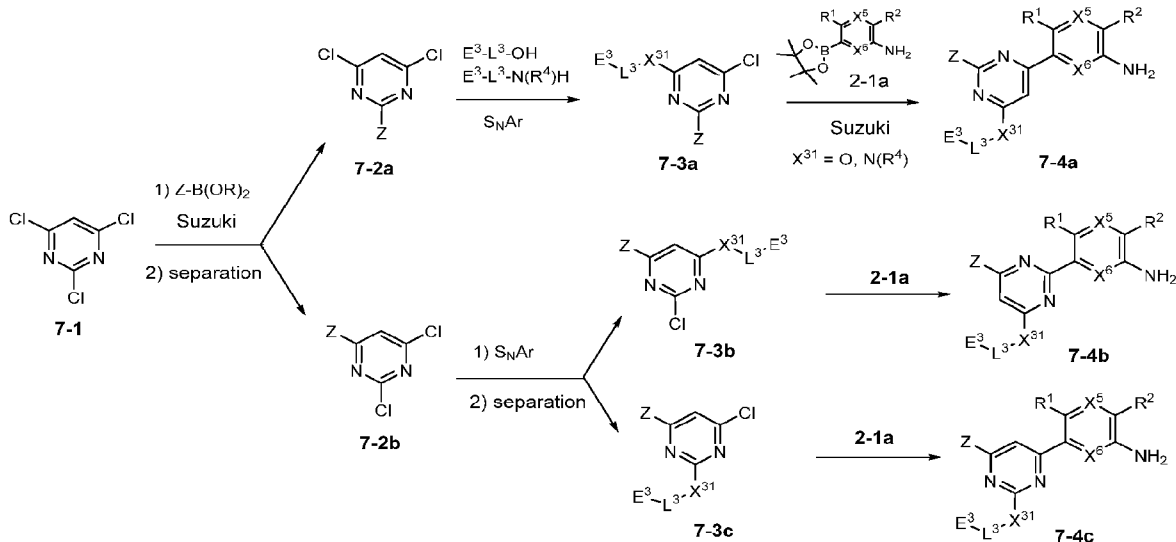
Scheme 6



[000239] Scheme 6 illustrates an exemplary preparation of pyridazine intermediates **6-4** and **6-6**. 5-Bromo-3-chloropyridazine **6-1** reacts with alcohols or amines Z-H to afford **6-2** by $\text{S}_{\text{N}}\text{Ar}$ reaction. Z-substituted bromides **6-2** react with boronates **2-1a** to afford **6-4** by Pd catalyzed Suzuki reactions. Alternatively, the treatment of 5-bromo-3-chloropyridazine **6-1** with boronates **2-1a** under Suzuki reaction conditions affords **6-3**. Finally, chlorides **6-3** react with boronates or boronic acids Z-B(OR)₂ to provide **6-4** by Pd (0) catalyzed Suzuki reaction. The treatment of 5-bromo-3-chloropyridazine **6-1** with boronates or boronic acids Z-B(OR)₂

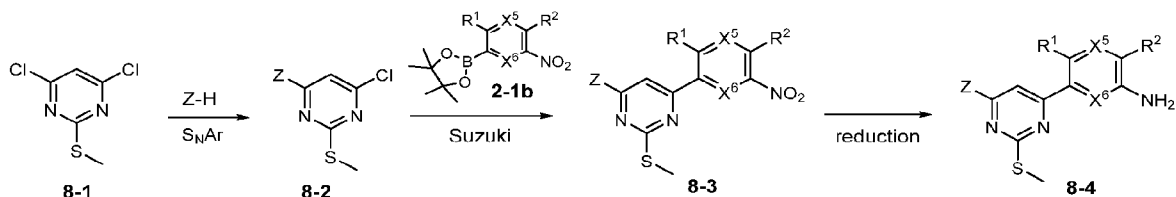
under Suzuki reaction conditions affords **6-5**. Z-substituted chlorides **6-5** react with boronates **2-1a** to provide **6-6** by Pd (0) catalyzed Suzuki reaction.

Scheme 7



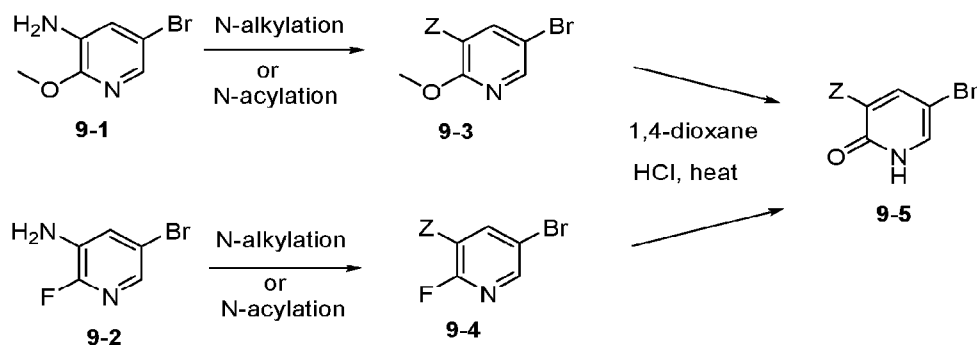
[000240] Scheme 7 illustrates an exemplary preparation of pyrimidine intermediates **7-4a**, **7-4b** and **7-4c**. 2,4,6-Trichloropyrimidine **7-1** reacts with boronates or boronic acids Z-B(OR)₂ in the presence of a palladium catalyst (Suzuki reaction) to afford a mixture of intermediates **7-2a** and **7-2b**, which can be separated by SFC purification, crystallization, or chromatography. **7-2a** reacts with alcohols (E³-L³-OH) or amines (E³-L³-N(R⁴)H) by S_NAr reaction to obtain **7-3a**. In a similar manner, reaction of **7-2b** with alcohols (E³-L³-OH) or amines (E³-L³-N(R⁴)H) by S_NAr reaction affords a mixture of **7-3b** and **7-3c** which can be separated by a suitable method (for example: SFC purification, column chromatography or recrystallization). Each intermediate **7-3a**, **7-3b** and **7-3c** reacts with boronates **2-1a** in the presence of a palladium catalyst (Suzuki reaction) to afford **7-4a**, **7-4b** and **7-4c** respectively.

Scheme 8



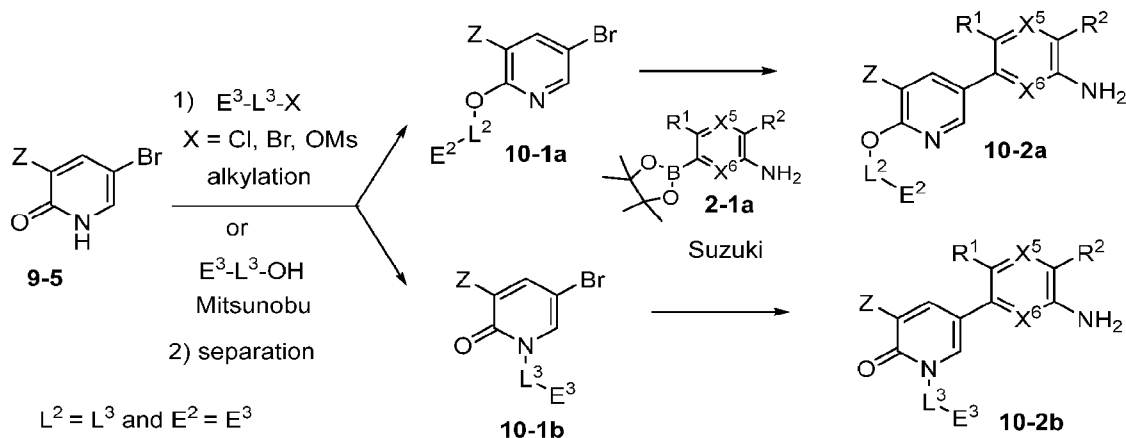
[000241] Scheme 8 illustrates an exemplary preparation of intermediates **8-4**. 4,6-Dichloro-2-(methylthio)pyrimidine **8-1** reacts with alcohols or amines Z-H in the presence of base to produce **8-2**. Treatment of **8-2** with boronates **2-1b** in the presence of a palladium catalyst (Suzuki reaction) affords **8-3**. Nitro reduction of **8-3** by palladium catalyzed hydrogenation or mild reducing conditions such as zinc or iron metal with ammonium chloride affords **8-4**.

Scheme 9



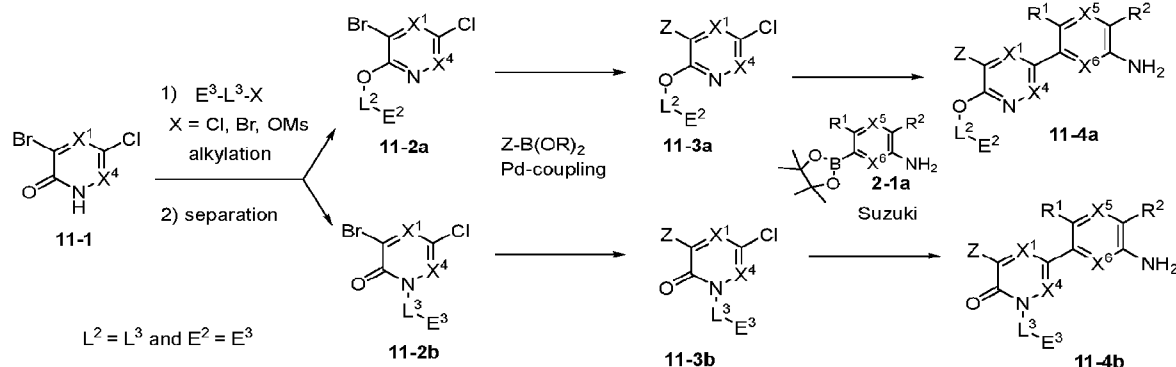
[000242] Scheme 9 describes an exemplary preparation of Z-substituted bromopyridones **9-5**. Either N-alkylation or N-acylation of 5-bromo-2-methoxypyridin-3-amine **9-1** and 5-bromo-2-fluoropyridin-3-amine **9-2** affords **9-3** and **9-4** respectively, wherein Z is attached to the pyridyl ring via nitrogen atom. Both **9-3** and **9-4** afford Z-substituted bromopyridones **9-5** under acidic conditions such as conc. HCl in 1,4-dioxane at elevated temperature or BBr₃ in halogenated solvents.

Scheme 10



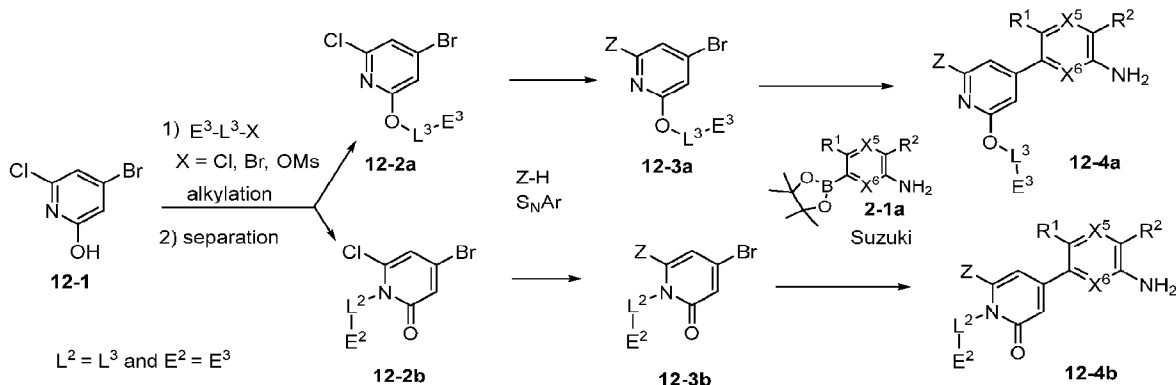
[000243] Scheme 10 illustrates an exemplary preparation of intermediates **10-2a** and **10-2b**. Compounds **9-5** (scheme 9) react with alkylating reagents (E^3-L^3-X , $X = Cl, Br, OMs$) in the presence of base such as silver carbonate in an aprotic solvent like toluene to produce the mixture of O-alkylated and N-alkylated **10-1a** and **10-1b** which can be separated by a suitable method, such as SFC purification, crystallization, or chromatography. Alternatively, **10-1a** can be prepared from **9-5** with alcohols (E^3-L^3-OH) by standard Mitsunobu reaction known to those skilled in the art. O-alkylated **10-1a** and N-alkylated **10-1b** can be reacted with boronates **2-1a** in the presence of a palladium catalyst (Suzuki reaction) to afford **10-2a** and **10-2b** respectively.

Scheme 11



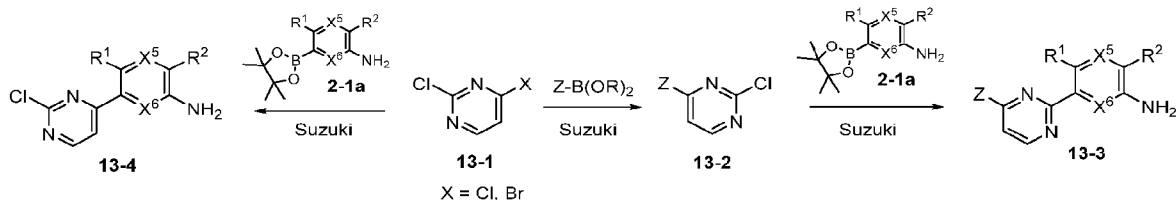
[000244] Scheme 11 illustrates an exemplary preparation of intermediates **11-4a** and **11-4b** compounds **11-1** (3-bromo-5-chloropyridin-2(1H)-one, 4-bromo-6-chloropyridazin-3(2H)-one, 3-bromo-5-chloropyrazin-2(1H)-one) reacts with alkylating reagents E^3-L^3-X ($X = Cl, Br, OMs$) in the presence of base such as silver carbonate in an aprotic solvent like toluene to produce a mixture of O-alkylated and N-alkylated **11-2a** and **11-2b** which can be separated by a suitable method such as SFC purification, crystallization or chromatography. Each **11-2a** and **11-2b** reacts with boronates or boronic acids $Z-B(OR)_2$ under Pd-catalyzed coupling reaction (for example, $Pd(OAc)_2$, (R)-(+)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl) in the presence of base like Cs_2CO_3 or K_2CO_3 in aprotic solvents like toluene or 1,4-dioxane to afford **11-3a** and **11-3b** respectively. Treatment of **11-3a** and **11-3b** with boronates **2-1a** in the presence of a palladium catalyst (Suzuki reaction) affords **11-4a** and **11-4b** respectively.

Scheme 12



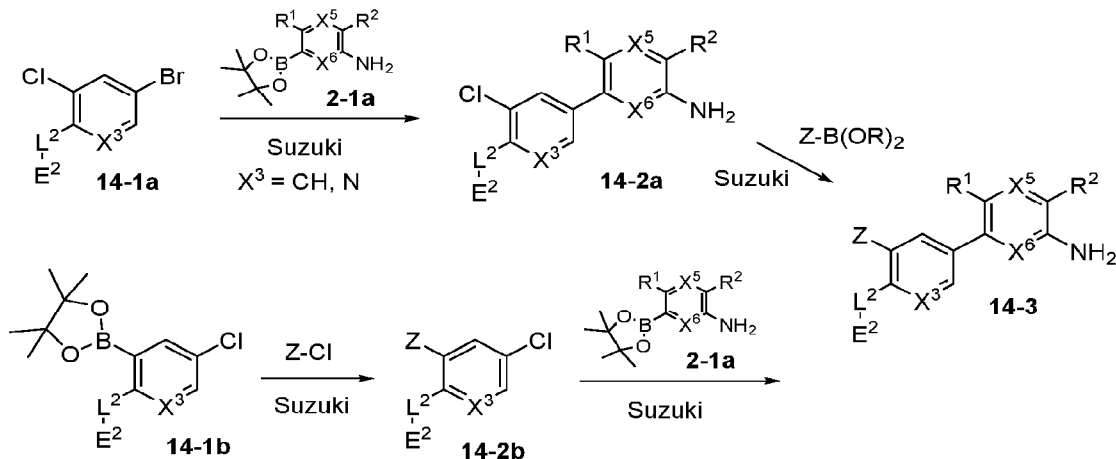
[000245] Scheme 12 illustrates an exemplary preparation of intermediates **12-4a** and **12-4b**. In a similar manner as described in scheme 11, 4-bromo-6-chloropyridin-2-ol **12-1** reacts with E^3-L^3-X ($X = Cl, Br, OMs$) to produce the mixture of O-alkylated and N-alkylated **12-2a** and **12-2b** which can be separated by a suitable method well known to those skilled in the art. Each **12-2a** and **12-2b** reacts with alcohols or amines $Z-H$ by S_NAr reaction to afford **12-3a** and **12-3b** respectively. Finally, **12-3a** and **12-3b** upon treatment with boronates **2-1a** in the presence of a palladium catalyst (Suzuki reaction) afford **12-4a** and **12-4b** respectively.

Scheme 13



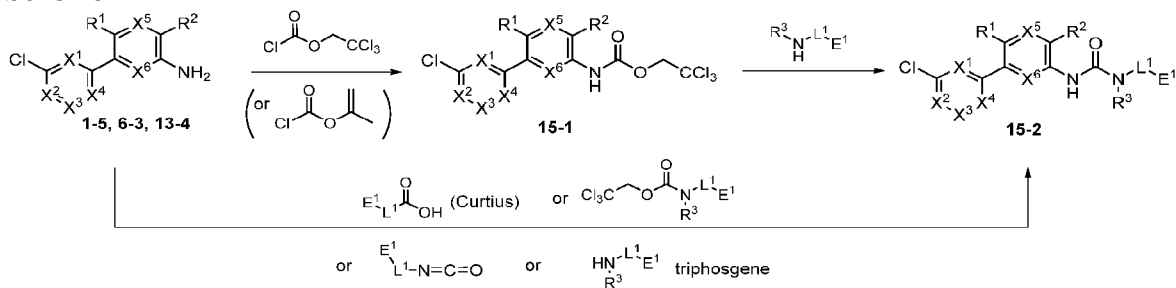
[000246] Scheme 13 illustrates an exemplary preparation of intermediates **13-3** and **13-4**. Compound **13-1** reacts with boronates or boronic acids $Z-B(OR)_2$ in the presence of a palladium catalyst (Suzuki reaction) to afford **13-2**. Z -substituted chlorides **13-2** react with boronates **2-1a** under Suzuki conditions to afford intermediates **13-3**. In a similar manner, compound **13-1** reacts with boronates **2-1a** in the presence of a palladium catalyst (Suzuki reaction) to afford **13-4**.

Scheme 14



[000247] Scheme 14 illustrates an exemplary preparation of intermediates **14-3**. Bromides **14-1a** (commercially available or synthesized by suitable method well known to those skilled in the art) react with boronates **2-1a** under Suzuki reaction conditions to furnish **14-2a**. Chlorides **14-2a** react with boronates or boronic acid $Z-B(OR)_2$ under Suzuki conditions to afford **14-3**. In a similar manner, intermediates **14-3** can be prepared from boronates **14-1b** (commercially available or synthesized by suitable method well known to those skilled in the art). Boronates **14-1b** react with Chlorides $Z-Cl$ in the presence of a palladium catalyst (Suzuki reaction) to afford **14-2b**. Finally, **14-2b** reacts with boronates **2-1a** under Suzuki conditions to obtain **14-3**.

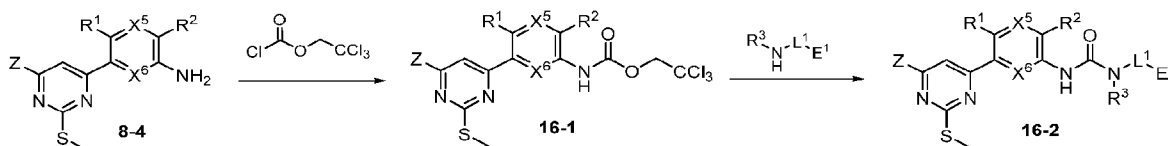
Scheme 15



[000248] Scheme 15 illustrates an exemplary preparation of intermediates **15-2**. Activation of **1-5**, **6-3** and **13-4** with 2,2,2-trichloroethyl chloroformate (or isopropenyl chloroformate) under Schotten-Baumann conditions give intermediates **15-1**. Compounds **15-1**

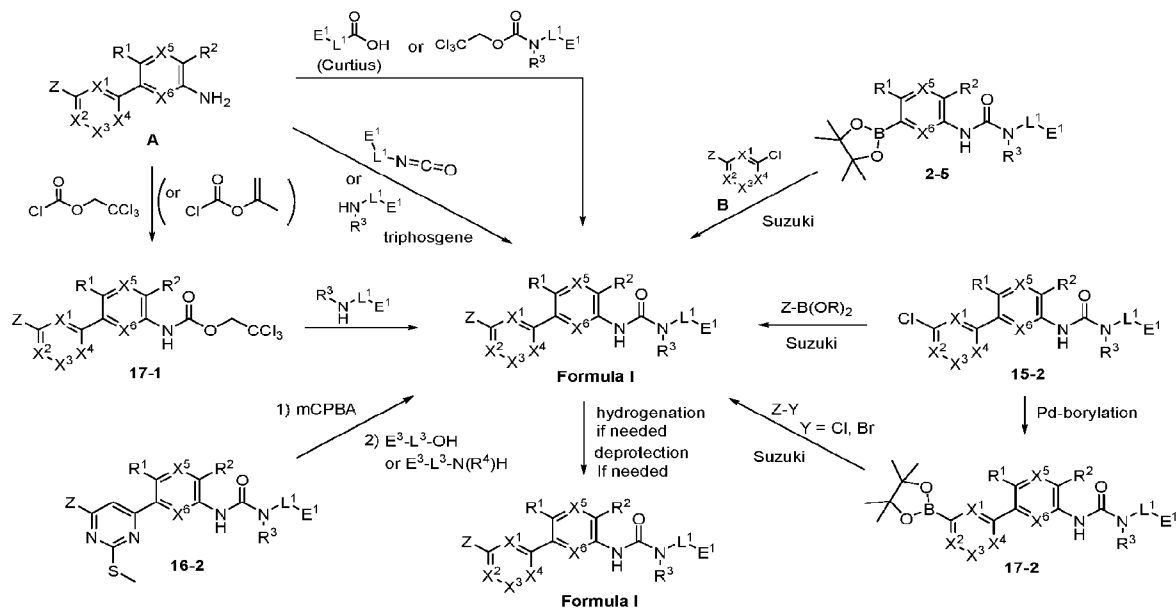
2 can be prepared by coupling reaction of **1-5**, **6-3** and **13-4** with isocyanates E^1-L^1-NCO (commercially available or synthesized by suitable method well known to those skilled in the art), or by coupling reaction of **1-5**, **6-3** and **13-4** with amines $E^1-L^1-N(R^3)H$ in the presence of triphosgene, or by Curtius rearrangement of **1-5**, **6-3** and **13-4** with carboxylic acid E^1-L^1-COOH , or by coupling reaction of **1-5**, **6-3** and **13-4** with $E^1-L^1-N(R^3)COOCH_2CCl_3$ which can be obtained by activation of $E^1-L^1-N(R^3)H$ with 2,2,2-trichloroethyl chloroformate under Schotten-Baumann conditions. Alternatively, compounds **15-2** can be prepared by coupling reaction of **15-1** with amines $E^1-L^1-N(R^3)H$ in the presence of base such as DIEA.

Scheme 16



[000249] Scheme 16 illustrates an exemplary preparation of intermediates **16-2**. Activation of **8-4** with 2,2,2-trichloroethyl chloroformate under Schotten-Baumann conditions produces **16-1** which is reacted with amines $E^1-L^1-N(R^3)H$ to obtain **16-2**.

Scheme 17



A: 1-6, 3-4, 4-4a, 4-4b, 5-4, 6-4, 6-5, 7-4a, 7-4b, 7-4c, 10-2a, 10-2b, 11-4a, 11-4b, 12-4a, 12-4b, 13-3, and 14-3
B: 3-2, 6-2, 6-5, 7-3a, 7-3c, 11-3a, 11-3b, 12-3a, 12-3b, 13-2, and 14-2b

[000250] Scheme 17 illustrates an exemplary preparation of compounds of Formula I. Activation of **A** (1-6, 3-4, 4-4a, 4-4b, 5-4, 6-4, 6-5, 7-4a, 7-4b, 7-4c, 10-2a, 10-2b, 11-4a, 11-4b, 12-4a, 12-4b, 13-3, and 14-3) with 2,2,2-trichloroethyl chloroformate (or isopropenyl chloroformate) under Schotten-Baumann conditions affords intermediates **17-1**. Compounds of Formula I can be prepared by coupling reaction of **17-1** with amines $E^1-L^1-N(R^3)H$ in the presence of base such as DIEA or by coupling reaction of compounds **A** with isocyanates E^1-L^1-NCO (commercially available or synthesized by suitable method well known to those skilled in the art), or by coupling reaction of compounds **A** with amines $E^1-L^1-N(R^3)H$ in the presence of triphosgene, or by Curtius rearrangement of compounds **A** with carboxylic acid E^1-L^1-COOH , or by coupling reaction of compounds **A** with $E^1-L^1-N(R^3)COOCH_2CCl_3$ which can be obtained by activation of $E^1-L^1-N(R^3)H$ with 2,2,2-trichloroethyl chloroformate under Schotten-Baumann conditions or by Suzuki reaction of **15-2** with $Z-B(OR)_2$. Pd-borylation of **15-2** with bis(pinacolato)diboron in the presence of a palladium catalyst (example, $Pd(dppf)Cl_2$) affords boronates or **17-2**. Compound **17-2** can be converted to compound of Formula I under Suzuki conditions with $Z-Y$ ($Y = Cl, Br$, commercially available or synthesized by suitable method well known to those skilled in the art). In a

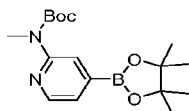
similar manner, boronates **2-5** can be converted to compound of Formula **I** under Suzuki conditions with compounds **B** (**3-2**, **6-2**, **6-5**, **7-3a**, **7-3c**, **11-3a**, **11-3b**, **12-3a**, **12-3b**, **13-2**, and **14-2b**). Alternatively, compound of Formula **I** can be prepared by oxidation of **16-2** with mCPBA, followed by S_NAr reaction with alcohols E^3-L^3-OH or amines $E^3-L^3-N(R^4)H$. Finally, compounds of Formula **I** which contains an unsaturated functionality such as a double bond, can be hydrogenated in the presence of Pd catalyst. When Formula **I** contain a nitrogen protecting group such as Boc, the protecting group can be removed under acidic conditions (trifluoroacetic acid or HCl in 1,4-dioxane). In another embodiment, Formula **I** which contains an oxygen protecting group such as TBDMS, the protecting group can be deprotected using TBAF.

Preparation of Intermediates.

[000251] Using the synthetic procedures and methods described herein and methods known to those skilled in the art, the following compounds were made:

General Method A: Borylation

[000252] Intermediate **A1**: tert-butyl methyl(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-2-yl)carbamate

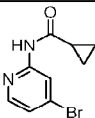
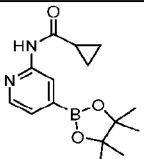
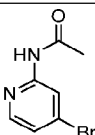
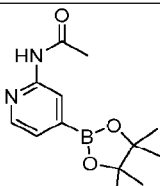
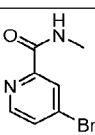
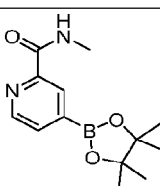
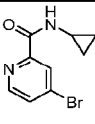
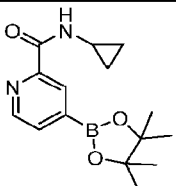
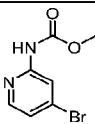
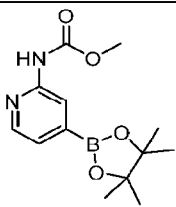
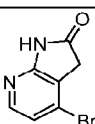
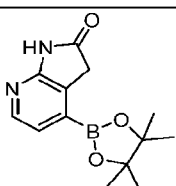


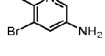
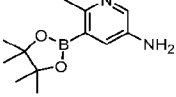
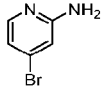
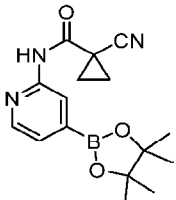
[000253] A mixture of tert-butyl (4-bromopyridin-2-yl)(methyl)carbamate (0.82 g, 2.9 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (0.87 g, 3.4 mmol) and KOAc (0.84 g, 8.6 mmol) in DMF (15 mL) was allowed to stir at rt. The reaction mixture was sparged with Ar for 10 min. Pd(dppf)Cl₂.DCM adduct (0.12 g, 0.14 mmol) was added and the reaction mixture was sealed and heated to 80 °C overnight. The reaction was cooled to rt and diluted with EtOAc (30 mL). The organic layer was separated and washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to afford a brown oil. The brown oil was treated with hexanes (20 mL) and the solid was filtered. The filtrate was concentrated to dryness under vacuum to afford tert-butyl methyl(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-2-yl)carbamate (**A1**, 1.09 g, 100%) as a brown solid. ¹H NMR (400 MHz, DMSO-d₆): δ 8.40 (d, J = 4.8 Hz, 1H), 7.90 (s,

1H), 7.27 (d, J = 4.8 Hz, 1H), 3.29 (s, 3H), 1.48 (s, 9H), 1.30 (s, 12H); MS (ESI) m/z: 335.2 (M+H⁺).

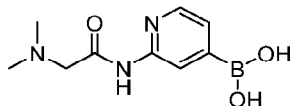
[000254] Using the General Method A above, the following Intermediates of Table A were prepared.

Table A.

Ex. No.	SM	Product	Yield (%)	¹ H NMR (400 or 500 MHz, DMSO-d ₆): δ	MS (m/z: M+H ⁺)
A2			crude	10.7 (s, 1H), 8.28 (m, 2H), 7.22 (d, J = Hz, 1H), 1.15 (s, 12H), 1.06 (brs, 1H), 0.86 (m, 4H).	288.9
A3			crude	10.4 (s, 1H), 8.31 (brs, 1H), 7.92 (s, 1H), 7.23 (d, J = 5.2 Hz, 1H), 2.09 (s, 3H), 1.30 (s, 12H).	263.3
A4			57	8.78 (d, J = 5.6 Hz, 1H), 8.66 (d, J = 4.7 Hz, 1H), 8.22 (s, 1H), 7.73 (dd, J = 1.2 and 4.7 Hz, 1H), 2.81 (d, J = 4.9 Hz, 3H), 1.32 (s, 12H).	No Data
A5			crude	10.7 (s, 1H), 8.28 (m, 2H), 7.22 (d, J = Hz, 1H), 1.15 (s, 12H), 1.06 (brs, 1H), 0.86 (m, 4H).	288.9
A6			42	10.2 (s, 1H), 8.28 (dd, J = 1.0 and 4.7 Hz, 1H), 8.10 (d, J = 1.0 Hz, 1H), 7.20 (d, J = 0.9 Hz, 1H), 3.66 (s, 3H), 1.30 (s, 12H).	No Data
A7			crude	No Data	179.0

A8			crude	No Data	153.2 (boronic acid)
A10			61	10.3 (s, 1H), 8.39 (d, J = 4.4 Hz, 1H), 8.17 (s, 1H), 7.33 (d, J = 4.4 Hz, 1H), 1.72 (m, 2H), 1.69 (m, 2H), 1.30 (s, 12H).	314.3

[000255] Preparation of intermediate **A9**

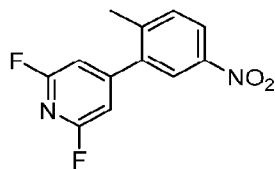


[000256] A solution of 4-bromopyridin-2-amine (4.0 g, 23 mmol) in DCM (100 ml) was cooled to 0 °C. DIEA (16 mL, 92 mmol) and 2-chloroacetyl chloride (2.0 mL, 25 mmol) were added dropwise to the solution. The reaction mixture was allowed to warm to rt and then stirred at rt for 4 h. Dimethylamine (2.0 M in THF, 58 mL, 116 mmol) was added to the reaction mixture and the solution was allowed to stir at rt overnight. The reaction mixture was quenched with sat'd NaHCO₃ (aq, 50 mL) and then the solution was extracted with DCM (3 x 50 mL). The combined organics were dried over anhydrous Na₂SO₄, filtered, and concentrated to dryness to afford a black oil. The black oil was purified by silica gel column chromatography (0 to 10% MeOH/DCM) to obtain N-(4-bromopyridin-2-yl)-2-(dimethylamino)acetamide (2.16 g, 36%) as a brown solid. ¹H NMR (500 MHz, DMSO-d₆): δ 10.1 (s, 1H), 8.32 (d, J = 1.8 Hz, 1H), 8.21 (d, J = 5.4 Hz, 1H), 7.38 (dd, J = 1.8 and 5.4 Hz, 1H), 3.14 (s, 2H), 2.28 (s, 6H); MS (ESI) m/z: 258.0 (M+H⁺) and 260.0.

[000257] (2-(2-(dimethylamino)acetamido)pyridin-4-yl)boronic acid (**A9**, crude, 100%) was prepared by Method A. MS (ESI) m/z: 224.0 (M+H⁺).

General Method B: Suzuki Coupling Reaction

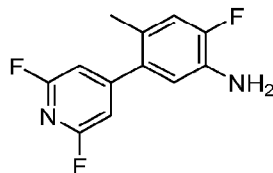
[000258] Intermediate **B1**: 2,6-difluoro-4-(2-methyl-5-nitrophenyl)pyridine



[000259] A solution of 2-bromo-1-methyl-4-nitrobenzene (4.0 g, 19 mmol) in DME (90 mL) was treated with 2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (5.4 g, 22 mmol). Na_2CO_3 (28 mL, 56 mmol, 2.0 M solution) was added and stirred at rt. The reaction mixture was degassed by bubbling argon for two minutes and treated with $\text{Pd}(\text{dppf})\text{Cl}_2\cdot\text{DCM}$ adduct (0.76 g, 0.93 mmol). The resulting reaction mixture was heated at 60 °C for 3 h. The reaction was filtered through a pad of celite and washed using EtOAc. The organic layer was separated and concentrated under reduced pressure to afford a brown oil. The brown oil was then suspended in MeOH and the solid was filtered to obtain 2,6-difluoro-4-(2-methyl-5-nitrophenyl)pyridine (4.1 g, 89%) as a tan solid. ^1H NMR (500 MHz, $\text{DMSO}-d_6$): δ 8.24 (dd, $J = 2.5$ and 8.5 Hz, 1H), 8.15 (d, $J = 2.5$ Hz, 1H), 7.67 (d, $J = 8.5$ Hz, 1H), 7.37 (s, 2H), 2.39 (s, 3H).

General Method C: Suzuki Coupling Reaction

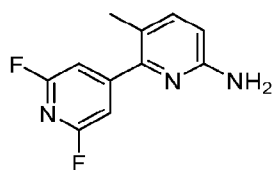
[000260] Intermediate **B2**: 5-(2,6-difluoropyridin-4-yl)-2-fluoro-4-methylaniline



[000261] A solution of 5-bromo-2-fluoro-4-methylaniline (1.43 g, 7.0 mmol) and 2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) pyridine (1.40 g, 5.8 mmol) in 1,4-dioxane (10 mL) and water (2 mL) was treated with K_2CO_3 (0.81 g, 5.8 mmol). The reaction mixture was purged with nitrogen gas for 20 min then, $\text{Pd}(\text{dppf})\text{Cl}_2\cdot\text{DCM}$ adduct (0.10 g, 0.38 mmol) was added. The reaction mixture was heated at 90 °C for another 2 h and the mixture was cooled to rt. The solution was filtered through a pad of celite and washed with EtOAc (750 mL). The filtrate was washed with water (250 mL). The combined organics were dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure to obtain the crude. The crude was purified by silica gel column chromatography (0 to 20 % EtOAc/heptane) to obtain 5-(2,6-difluoropyridin-4-yl)-2-fluoro-4-methylaniline (1.23 g, 88%) as a light brown solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 7.14 (s, 2H), 6.99 (d, $J = 12.3$ Hz, 1H), 6.69 (d, $J = 9.2$ Hz, 1H), 5.12 (s, 2H), 2.10 (s, 3H); MS (ESI) m/z : 239.0 ($\text{M}+\text{H}^+$).

General Method D: Suzuki Coupling Reaction

[000262] Intermediate **B3**: 2',6'-difluoro-3-methyl-[2,4'-bipyridin]-6-amine

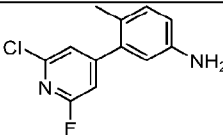
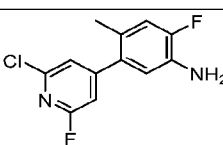
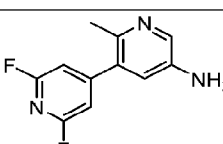
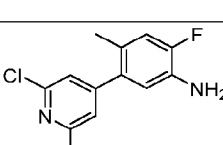
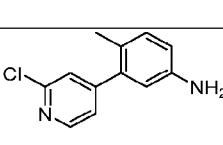
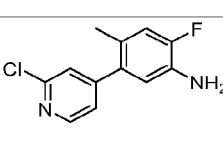
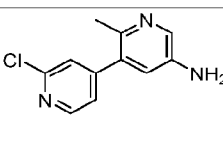
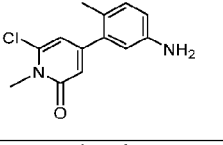
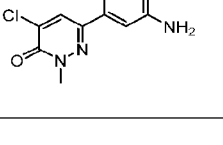


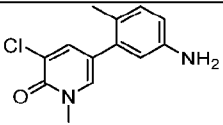
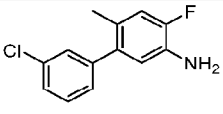
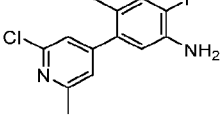
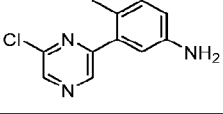
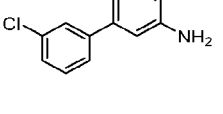
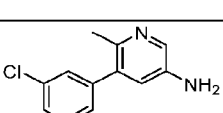
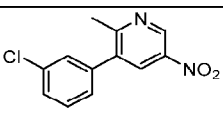
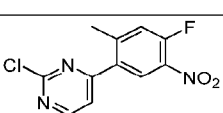
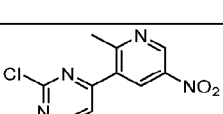
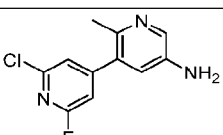
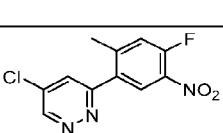
[000263] A solution of 6-bromo-5-methylpyridin-2-amine (2.0 g, 11 mmol), 2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (3.1 g, 13 mmol), and K_2CO_3 (3.7 g, 27 mmol) in 1,4-dioxane (48 mL) and water (5.4 mL) was sparged with Ar for 2 min. XPhos Pd G2 (0.17 g, 0.21 mmol) was added and then sparged with Ar for 2 min. The reaction solution was heated to 85 °C for 2.5 h. The reaction was cooled to rt and diluted with DCM (100 mL). The solution was filtered through a pad of celite and the filtrate was washed with sat'd $NaHCO_3$ solution (100 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to yield the crude. The crude was purified silica gel column chromatography (0 to 25 % (10 % $NH_4OH:MeOH$)\DCM) to produce 2',6'-difluoro-3-methyl-[2,4'-bipyridin]-6-amine (1.8 g, 68%) as a tan solid. MS (ESI) m/z : 222.2 ($M+H^+$).

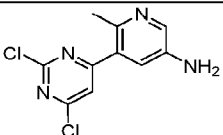
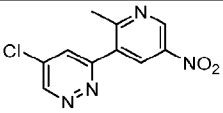
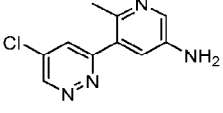
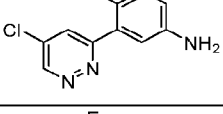
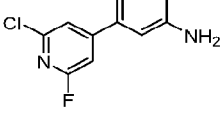
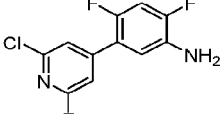
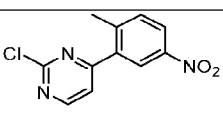
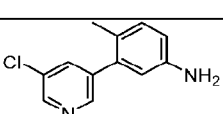
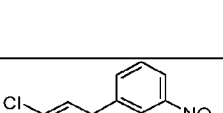
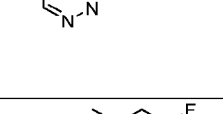
[000264] Using the General Methods B-D above, the following Intermediates of Table B were prepared.

Table B.

Exp No	Product	Method	Yield (%)	^1H NMR (400 or 500 MHz, DMSO- d_6): δ	MS (m/z : $M+H^+$)
B4		B	70	9.34 (d, $J = 2.0$ Hz, 1H), 8.56 (d, $J = 5.2$ Hz, 1H), 8.52 (d, $J = 2.0$ Hz, 1H), 7.77 (s, 1H), 7.62 (d, $J = 4.8$ Hz, 1H), 2.58 (s, 3H).	250.0
B5		C	88	7.14 (s, 2H), 6.97 (d, $J = 8.4$ Hz, 1H), 6.58 (dd, $J = 2.0$ and 8.0 Hz, 1H), 6.49 (s, 1H), 5.0 (brs, 2H), 2.09 (s, 3H).	221.0
B6		C	92	No Data	253.0

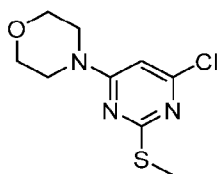
B7		C	82	No Data	237.0
B8		C	80	7.45 (d, J = 1.2 Hz, 1H), 7.22 (t, J = 1.2 Hz, 1H), 6.98 (d, J = 12.4 Hz, 1H), 6.69 (d, J = 9.2 Hz, 1H), 5.12 (s, 2H), 2.10 (s, 3H).	255.0
B9		C	95	7.93 (d, J = 2.6 Hz, 1H), 7.23 (s, 2H), 6.83 (d, J = 2.6 Hz, 1H), 5.29 (s, 2H), 2.26 (s, 3H).	222.2
B10		B	67	7.52 (s, 2H), 6.95 (d, J = 10.0 Hz, 1H), 6.69 (d, J = 9.2 Hz, 1H), 5.1 (s, 2H), 2.10 (s, 3H).	271.0
B11		B	99	8.41 (d, J = 5.1 Hz, 1H), 7.42 (s, 1H), 7.35 (dd, J = 1.5 and 5.1 Hz, 1H), 6.96 (d, J = 8.2 Hz, 1H), 6.56 (dd, J = 2.4 and 8.1 Hz, 1H), 6.46 (d, J = 2.4 Hz, 1H), 5.04 (s, 2H), 2.06 (s, 3H).	219.0
B12		B	56	8.42 (d, J = 5.1 Hz, 1H), 7.43 (s, 1H), 7.35 (m, 1H), 6.97 (d, J = 12.4 Hz, 1H), 6.66 (d, J = 9.2 Hz, 1H), 5.09 (s, 2H), 2.08 (s, 3H).	237.0
B13		B	60	8.46 (d, J = 4.8 Hz, 1H), 7.91 (s, 1H), 7.52 (s, 1H), 7.42 (d, J = 5.2 Hz, 1H), 6.81 (s, 1H), 5.2 (brs, 2H), 2.31 (s, 3H).	219.8
B14		C	57	6.92 (d, J = 8.0 Hz, 1H), 6.53 (dd, J = 8.0 Hz & 2.4 Hz, 1H), 6.44 (s, 2H), 6.26 (s, 1H), 5.0 (brs, 2H), 3.58 (s, 3H), 2.08 (s, 3H).	248.8
B15		C	38	6.94 (d, J = 8.0 Hz, 1H), 6.88 (s, 1H), 6.56 (dd, J = 8.0 Hz & 2.0 Hz, 1H), 6.35 (s, 1H), 5.0 (brs, 2H), 3.66 (s, 3H), 1.96 (s, 3H).	250.2

B16		C	54	7.72 (s, 2H), 6.90 (d, J = 8.4 Hz, 1H), 6.48 (dd, J = 2.4 and 8.0 Hz, 1H), 6.42 (d, J = 2.4 Hz, 1H), 4.90 (brs, 2H), 3.59 (s, 3H), 2.08 (s, 3H).	248.8
B17		C	97	No Data	236.0
B18		C	crude	No Data	251.0
B19		C	63	8.76 (s, 1H), 8.74 (s, 1H), 6.99 (d, J = 8.0 Hz, 1H), 6.71 (s, 1H), 6.63 (m, 1H), 5.0 (brs, 2H), 2.18 (s, 3H).	219.8
B20		C	90	7.37-7.45 (m, 2H), 7.30 (s, 1H), 7.24 (br d, J = 7.2 Hz, 1H), 6.92 (d, J = 8.0 Hz, 1H), 6.50 (brd, J = 8.0 Hz, 1H), 6.43 (s, 1H), 4.94 (brs, 2H), 2.03 (s, 3H).	217.9
B21		C	87	No Data	219.2
B22		B	92	9.28 (d, J = 2.4 Hz, 1H), 8.37 (d, J = 2.8 Hz, 1H), 7.62 (d, J = 0.8 Hz, 1H), 7.57 (d, J = 5.2 Hz, 1H), 7.54 (s, 1H), 7.49 (m, 1H), 2.56 (s, 3H).	249.0
B23		B	62	8.90 (dd, J = 2.4 and 5.2 Hz, 1H), 8.31 (d, J = 7.6 Hz, 1H), 7.90 (d, J = 5.2 Hz, 1H), 7.68 (d, J = 12.4 Hz, 1H), 2.49 (s, 3H).	268.1
B24		B	73	9.38 (d, J = 2.4 Hz, 1H), 8.96 (d, J = 5.2 Hz, 1H), 8.68 (d, J = 2.4 Hz, 1H), 8.01 (d, J = 5.2 Hz, 1H), 2.73 (s, 3H).	251.0
B25		C	57	7.92 (d, J = 2.7 Hz, 1H), 7.54 (t, J = 1.1 Hz, 1H), 7.31 (t, J = 1.3 Hz, 1H), 6.83 (d, J = 2.7 Hz, 1H), 5.29 (s, 2H), 2.25 (s, 3H).	238.0
B26		B	55	No Data	268.0

B27		C	90	7.98 (m, 2H), 7.11 (d, J = 2.8 Hz, 1H), 5.37 (br s, 2H), 2.40 (s, 3H).	256.9
B28		B	77	9.53 (d, J = 2.4 Hz, 1H), 9.40 (d, J = 2.4 Hz, 1H), 8.74 (d, J = 2.4 Hz, 1H), 8.41 (d, J = 2.4 Hz, 1H), 2.67 (s, 3H).	250.8
B29		reduction with Fe	43	No Data	221.0
B30		C	91	No Data	220.0
B31		B	62	No Data	241.0
B32		B	58	No Data	259.0
B33		B	70	8.91 (d, J = 5.1 Hz, 1H), 8.34 (d, J = 2.5 Hz, 1H), 8.28 (dd, J = 2.5 and 8.4 Hz, 1H), 7.92 (d, J = 5.1 Hz, 1H), 7.68 (d, J = 8.5 Hz, 1H), 2.51 (s, 3H).	250.0
B34		C	67	8.60 (s, 1H), 8.46 (s, 1H), 7.88 (s, 1H), 6.96 (d, J = 8.4 Hz, 1H), 6.55 (dd, J = 2.4 and 8.4 Hz, 1H), 6.46 (d, J = 2.0 Hz, 1H), 5.09 (s, 2H), 2.05 (s, 3H).	218.9
B35		B	72	9.47 (d, J = 2.04 Hz, 1H), 9.01 (s, 1H), 8.75 (d, J = 2.4 Hz, 1H), 8.65 (dd, J = 20.4, 12.8 Hz, 1H), 8.40 (dd, J = 1.2 and 8.0 Hz, 1H), 7.87 (t, J = 8.0 Hz, 1H).	No Data
B36		C	87	No Data	237.0

General Method E: Aromatic Substitution Reactions

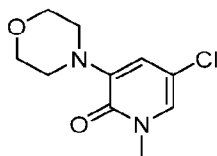
[000265] Intermediate C1: 4-(6-chloro-2-(methylthio)pyrimidin-4-yl)morpholine



[000266] A solution of 4,6-dichloro-2-(methylthio)pyrimidine (3.0 g, 15 mmol) in EtOH (80 mL) was treated with DIPA (29 mL, 17 mmol). Morpholine (1.4 mL 15 mmol) was added and the reaction mixture was stirred at rt for 16 h. The reaction mixture was concentrated to around a quarter volume and MeCN (10 mL) was added. The mixture was sonicated for 5 min. then the solid was filtered to obtain 4-(6-chloro-2-(methylthio)pyrimidin-4-yl)morpholine (3.3 g, 87%) as a white solid. ^1H NMR (500 MHz, DMSO- d_6): δ 6.66 (s, 1H), 3.63 (brm, 8H), 2.42 (s, 3H); MS (ESI) m/z : 246.0 ($\text{M}+\text{H}^+$).

General Method F: Pd coupling Reactions

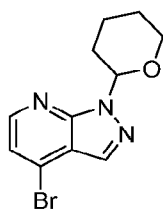
[000267] Intermediate **C2**: 5-chloro-1-methyl-3-morpholinopyridin-2(1H)-one



[000268] A solution of 3-bromo-5-chloro-1-methylpyridin-2(1H)-one (1.14 g, 5.1 mmol), morpholine (0.47 mL, 5.4 mmol) in 1,4-dioxane (26 mL) was treated with Cs_2CO_3 (3.36 g, 10.3 mmol). The reaction mixture was sparged with Ar for 2 min. $\text{Pd}_2(\text{dba})_3$ (0.24 g, 0.26 mmol) and xantphos (0.21 g, 0.36 mmol) were then added. The reaction mixture was heated to 100 °C for 20 h. The reaction was cooled to rt and the solution was diluted with DCM (75 mL). The solution was filtered through a pad of celite and then the solution was washed with sat'd NaHCO_3 solution (150 mL). The solution was extracted with DCM (2 x 40 mL) and the combined organics were dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure to yield 5-chloro-1-methyl-3-morpholinopyridin-2(1H)-one (1.49 g, 127%) as a tan solid. ^1H NMR (500 MHz, DMSO- d_6): δ 7.58 (d, J = 2.6 Hz, 1H), 6.65 (d, J = 2.7 Hz, 1H), 3.68 (t, J = 4.6 Hz, 4H), 3.39 (s, 3H), 3.08 (t, J = 4.5 Hz, 4H); MS (ESI) m/z : 229.2 ($\text{M}+\text{H}^+$).

General Method G: Protection

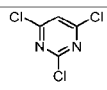
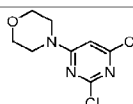
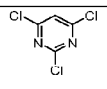
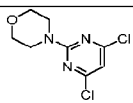
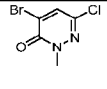
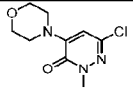
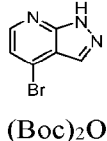
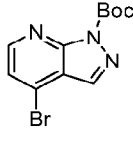
[000269] Example **C3**: 4-bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridine

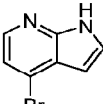
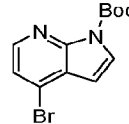
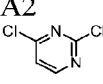
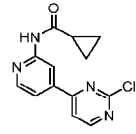
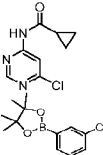
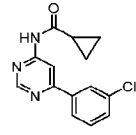
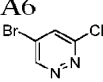
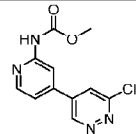
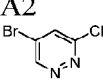
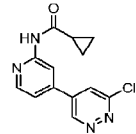
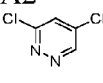
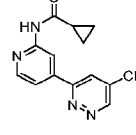
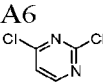
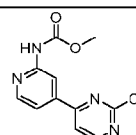
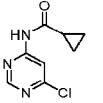
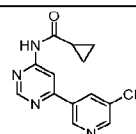


[000270] A solution of 4-bromo-1H-pyrazolo[3,4-b]pyridine (1.61 g, 8.1 mmol) in EtOAc (30 mL) was treated with 3,4-dihydro-2H-pyran (2 mL, 22 mmol). 4-Methylbenzenesulfonic acid (0.075 g, 0.39 mmol) was added and then the reaction was allowed to stir at rt overnight. The reaction turned orange and a precipitate was present. K_2CO_3 (0.35 g) was added and the suspension was stirred for about 15 min and then filtered through a pad of celite. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (0 to 60% EtOAc/hexanes) to afford 4-bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridine (1.01 g, 44%) as a colorless oil. ^1H NMR (500 MHz, DMSO- d_6): δ 8.44 (d, J = 4.9 Hz, 1H), 8.24 (s, 1H), 7.60 (d, J = 4.9 Hz, 1H), 6.02 (dd, J = 2.5 and 10.3 Hz, 1H), 3.94 (m, 1H), 3.63-3.76 (m, 1H), 2.41-2.50 (m, 1H), 2.04 (m, 1H), 1.92 (m, 1H), 1.65-1.83 (m, 1H), 1.38-1.65 (m, 2H); MS (ESI) m/z : 304.0 ($M+Na+H^+$) and 306.0.

[000271] Using the General Methods E, F and G above, the following Intermediates of Table C were prepared.

Table C.

Exp No	SM	Product	Method	Yield (%)	^1H NMR (400 or 500 MHz, DMSO- d_6): δ	MS (m/z : $M+H^+$)
C4			E	72	7.02 (s, 1H), 3.64 (brm, 8H).	234.0
C5			E	22	6.96 (s, 1H), 3.67 (m, 4H), 3.63 (m, 4H).	234.0
C6			E	97	6.55 (s, 1H), 3.67 (t, J = 4.8 Hz, 4H), 3.55 (s, 3H), 3.51 (t, J = 4.7 Hz, 4H).	230.2
C7	 (Boc) $_2$ O		G	91	8.55 (d, J = 5.0 Hz, 1H), 8.47 (s, 1H), 7.74 (d, J = 5.0 Hz, 1H), 1.62 (s, 9H).	320.0 ($M+Na+H^+$) 322.0

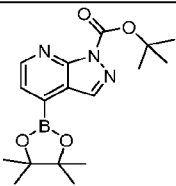
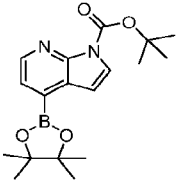
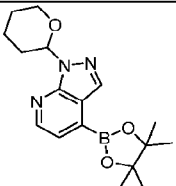
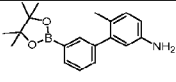
	DMAP					
C8	 (Boc) ₂ O DMAP		G	crude	8.26 (d, J = 5.2 Hz, 1H), 7.90 (d, J = 4.1 Hz, 1H), 7.57 (d, J = 5.2 Hz, 1H), 6.65 (d, J = 4.0 Hz, 1H), 1.60 (s, 9H).	319.0 (M+Na+H ⁺) 321.0
C9	A2 		F	85	1.06 (s, 1H), 8.93 (d, J = 5.2 Hz, 1H), 8.82 (s, 1H), 8.52 (d, J = 5.2 Hz, 1H), 8.17 (d, J = 5.2 Hz, 1H), 7.78 (dd, J = 1.6 and 5.2 Hz, 1H), 2.03 (m, 1H), 0.81-0.87 (m, 4H).	275.2
C10			F	75	No Data	274.0
C11	A6 		F	91	10.5 (s, 1H), 9.61 (d, J = 1.9 Hz, 1H), 8.46 (d, J = 5.2 Hz, 1H), 8.29 (d, J = 1.9 Hz, 1H), 8.23 (d, J = 1.5 Hz, 1H), 7.59 (dd, J = 1.7 and 5.2 Hz, 1H), 3.71 (s, 3H).	265.2
C12	A2 		F	74	No Data	275.0
C13	A2 		F	88	11.0 (s, 1H), 9.49 (d, J = 2.4 Hz, 1H), 8.88 (s, 1H), 8.54 (d, J = 2.0 Hz, 1H), 8.51 (d, J = 5.2 Hz, 1H), 7.81 (dd, J = 1.6 and 5.2 Hz, 1H), 2.05 (m, 1H), 0.82-0.87 (m, 4H).	275.2
C14	A6 		F	80	10.4 (brs, 1H), 8.94 (d, J = 5.2 Hz, 1H), 8.58 (s, 1H), 8.47 (d, J = 5.2 Hz, 1H), 8.18 (d, J = 5.2 Hz, 1H), 7.75 (dd, J = 1.6 and 5.2 Hz, 1H), 3.71 (s, 3H). m/z: 265.04	265.0
C15			F	84	11.4 (s, 1H), 9.12 (d, J = 1.8 Hz, 1H), 8.99 (s, 1H), 8.78 (d, J = 2.2 Hz, 1H), 8.58 (s, 1H), 8.44 (d, J = 2.3 Hz, 1H), 2.07 (m, 1H), 0.87-0.94 (m, 4H).	275.0

C16			F	27	11.0 (brs, 1H), 9.13 (s, 1H), 8.93 (s, 1H), 8.79 (d, J = 1.6 Hz, 1H), 8.46 (brm, 1H), 8.36 (s, 1H), 3.75 (s, 3H).	264.9
C17			F	47	No Data	407.1
C18			F	71	9.42 (d, J = 1.3 Hz, 1H), 9.38 (d, J = 1.9 Hz, 1H), 9.08 (dd, J = 3.8 and 8.6 Hz, 1H), 8.83 (d, J = 2.4 Hz, 1H), 8.75 (t, J = 2.2 Hz, 1H), 8.65 (d, J = 1.3 Hz, 1H), 2.86 (d, J = 4.8 Hz, 3H).	249.0
C19			F	59	10.42 (s, 1H), 8.61 (s, 1H), 8.45 (d, J = 5.2 Hz, 1H), 8.14 (s, 1H), 7.78 (d, J = 5.2 Hz, 1H), 3.71 (s, 3H), 2.71 (s, 3H).	278.8

[000272] Using the General Method A above, the following Intermediates of Table D were prepared.

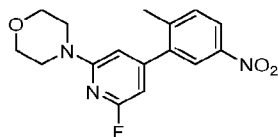
Table D.

Ex. No.	SM	Product	Yield (%)	¹ H NMR (400 or 500 MHz, DMSO-d ₆): δ	MS (m/z: M+H ⁺)
D1	B22		crude	9.28 (d, J = 2.4 Hz, 1H), 8.37 (d, J = 2.4 Hz, 1H), 7.77 (d, J = 7.2 Hz, 1H), 7.69 (s, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.55 (t, J = 7.2 Hz, 1H), 2.53 (s, 3H), 1.30 (s, 12H).	341.1
D2	B17		92	No Data	328.2

D3	C7		crude	No Data	286.2 (boronic acid)
D4	C8		crude	No Data	No Data
D5	C3		crude	No Data	248.2 (boronic acid)
D6	B20		crude	No Data	310.2

General Method H: Aromatic Substitution Reactions

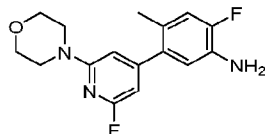
[000273] Intermediate **E1**: 4-(6-fluoro-4-(2-methyl-5-nitrophenyl)pyridine-2-yl)morpholine



[000274] A solution of 2,6-difluoro-4-(2-methyl-5-nitrophenyl)pyridine (**B1**, 4.1 g, 16 mmol) and DIEA (8.6 mL, 49 mmol) in EtOH (82 mL) was treated with morpholine (4.2 mL, 49 mmol). The reaction mixture was sealed and heated to 65 °C for 6 h. The reaction was cooled to rt and was diluted with water. The solid was filtered and washed with water. The solid was dried under high vacuum overnight to obtain 4-(6-fluoro-4-(2-methyl-5-nitrophenyl)pyridine-2-yl)morpholine pyridine (4.4 g, 84%) as a tan solid. ¹H NMR (500 MHz, DMSO-d₆): δ 8.19 (dd, J = 2.5 and 8.5 Hz, 1H), 8.04 (d, J = 2.5 Hz, 1H), 7.62 (d, J = 8.5 Hz, 1H), 6.72 (s, 1H), 6.42 (s, 1H), 3.68 (t, J = 4.8 Hz, 4 H), 3.49 (t, J = 4.8 Hz, 4H), 2.36 (s, 3H); MS (ESI) m/z: 318.2 (M+H⁺).

General Method I: Aromatic Substitution Reactions

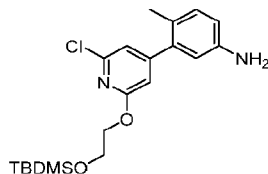
[000275] Intermediate **E2**: 2-fluoro-5-(2-fluoro-6-morpholinopyridin-4-yl)-4-methylaniline



[000276] A solution of 5-(2,6-difluoropyridin-4-yl)-2-fluoro-4-methylaniline (**B2**, 1.2 g, 5.2 mmol) in MeCN (10 mL), was treated with morpholine (0.5 g, 5.7 mmol). The reaction mixture was heated at 70 °C for 20 h. The reaction mixture was cooled to rt and quenched with water (15 mL). The solution was extracted with DCM (3x). The combined organic extracts were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to obtain 2-fluoro-5-(2-fluoro-6-morpholinopyridin-4-yl)-4-methylaniline (1.0 g, 65%) as a white solid. ¹H NMR (400 MHz, DMSO-d₆): δ 6.94 (d, J = 12.4 Hz, 1H), 6.66 (d, J = 9.3 Hz, 1H), 6.53 (s, 1H), 6.23 (s, 1H), 5.02 (s, 2H), 3.69 (t, J = 4.8 Hz, 4H), 3.47 (t, J = 4.8 Hz, 4H), 2.07 (s, 3H); MS (ESI) m/z: 306.2 (M+H⁺).

General Method J: Aromatic Substitution Reactions

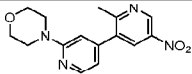
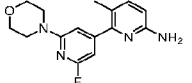
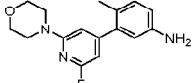
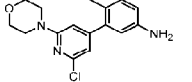
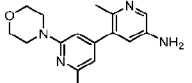
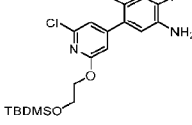
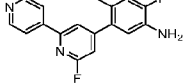
[000277] Intermediate **E3**: 3-(2-(2-((tert-butyldimethylsilyl)oxy)ethoxy)-6-chloropyridin-4-yl)-4-methylaniline

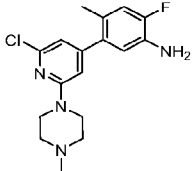
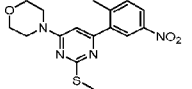
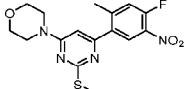
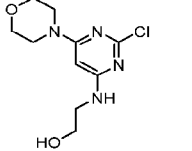
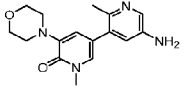
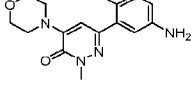
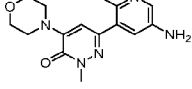
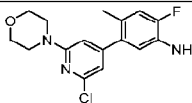
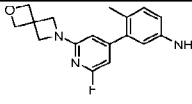


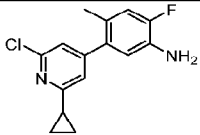
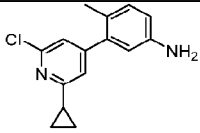
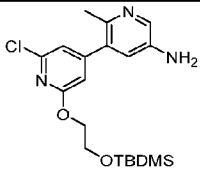
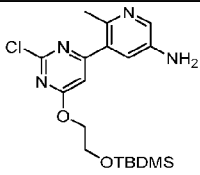
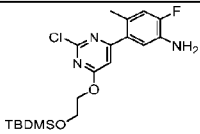
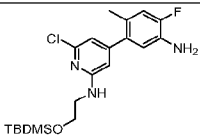
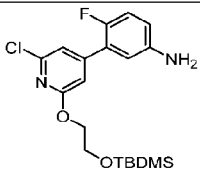
[000278] A solution of 2-((tert-butyldimethylsilyl)oxy)ethan-1-ol (0.42 g, 2.4 mmol) in DMF (5.0 mL) was treated with NaH (0.15 g, 3.8 mmol, 60 % in mineral oil) slowly under an ice-water bath and the reaction mixture was stirred under the same conditions for 30 min. A solution of 3-(2-chloro-6-fluoropyridin-4-yl)-4-methylaniline (**B7**, 0.45 g, 1.9 mmol) in DMF (1 mL) was added into the reaction mixture and the reaction mixture was heated at 40 °C for 2 h. The reaction mixture was quenched with water (20 mL) under an ice-water bath. The solution was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (5 to 10 % EtOAc/hexanes) to obtain 3-(2-(2-((tert-butyldimethylsilyl)oxy)ethoxy)-6-chloropyridin-4-yl)-4-methylaniline (0.47 g, 62%). MS (ESI) m/z: 393.2 (M+H⁺).

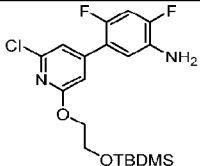
[000279] Using the General Methods C, D, H, I and J above, the following Intermediates of Table E were prepared.

Table E.

Exp No	SM	Product	Method	Yield (%)	¹ H NMR (400 or 500 MHz, DMSO-d ₆): δ	MS (m/z: M+H ⁺)
E4	B4		H	72	9.30 (d, J = 2.8 Hz, 1H), 8.38 (d, J = 2.4 Hz, 1H), 8.24 (d, J = 5.2 Hz, 1H), 6.93 (s, 1H), 6.81 (d, J = 5.2 Hz, 1H), 3.71 (m, 4), 3.51 (m, 4H), 2.58 (s, 3H).	301.3
E5	B3		I	crude	7.30 (d, J = 8.3 Hz, 1H), 6.67 (s, 1H), 6.43 (t, J = 6.2 Hz, 1H), 6.35 (s, 1H), 5.83 (s, 2H), 3.67 (t, J = 4.8 Hz, 4H), 3.44 (t, J = 4.8 Hz, 4H), 2.09 (s, 3H).	289.2
E6	B5		H	96	6.97 (d, J = 8.4 Hz, 1H), 6.53 (m, 2H), 6.44 (s, 1H), 6.23 (s, 1H), 4.90 (brs, 2H), 3.66 (m, 4H), 3.46 (m, 4H), 2.06 (s, 3H).	288.0
E7	B6		J	75	6.92 (d, J = 8.1 Hz, 1H), 6.63 (s, 1H), 6.59 (s, 1H), 6.52 (dd, J = 2.4 and 8.1 Hz, 1H), 6.43 (d, J = 2.4 Hz, 1H), 4.97 (s, 2H), 3.67 (t, J = 4.8 Hz, 4H), 3.46 (t, J = 4.8 Hz, 4H), 2.05 (s, 3H).	304.2
E8	B9		H	50	No Data	289.2
E9	B8		J	76	6.99 (d, J = 1.1 Hz, 1H), 6.94 (d, J = 12.4 Hz, 1H), 6.66 (d, J = 1.1 Hz, 1H), 6.63 (d, J = 9.2 Hz, 1H), 5.08 (s, 2H), 4.33 (t, J = 4.8 Hz, 2H), 3.90 (t, J = 4.8 Hz, 2H), 2.06 (s, 3H), 0.83 (t, J = 0.3 Hz, 9H), 0.02 (m, 6H).	411.2
E10	B8		C	91	8.71 (d, J = 4.6 Hz, 2H), 8.07 (m, 3H), 7.25 (s, 1H), 7.02 (d, J = 12.4 Hz, 1H), 6.76 (d, J = 9.2 Hz, 1H), 5.13 (s, 2H).	298.2

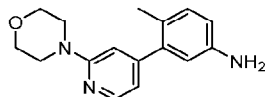
					2.14 (s, 3H).	
E11	B8		J	95	No Data	335.2
E12	C1		D	crude	8.19 (m, 2H), 7.60 (d, J = 8.8 Hz, 1H), 6.76 (s, 1H), 3.67 (m, 8H), 2.47 (s, 3H), 2.45 (s, 3H).	No Data
E13	C1		D	31	8.15 (d, J = 7.8 Hz, 1H), 7.60 (d, J = 12.5 Hz, 1H), 6.75 (s, 1H), 3.66 (brm, 8H), 2.46 (s, 3H), 2.44 (s, 3H).	365.2
E14	C4		J	51	6.97 (brs, 1H), 6.07 (brs, 1H), 4.61 (brs, 1H), 3.60 (d, J = 5.0 Hz, 4H), 3.51 (s, 4H), 3.44 (t, J = 6.5 Hz, 2H), 3.25 (t, J = 7.5 Hz, 2H).	259.2
E15	C2		D	18	No Data	301.2
E16	C6		C	76	No Data	301.2
E17	C6		C	30	7.86 (d, J = 2.7 Hz, 1H), 6.90 (d, J = 2.7 Hz, 1H), 6.57 (s, 1H), 5.18 (s, 2H), 3.70 (t, J = 4.5 Hz, 4H), 3.65 (s, 3H), 3.45 (t, J = 4.5 Hz, 4H), 2.30 (s, 3H).	No Data
E18	B10		J	42	7.24 (d, J = 9.2 Hz, 1H), 6.78 (s, 2H), 6.47 (d, J = 9.6 Hz, 1H), 5.5 (s, 2H), 3.70 (brs, 4H), 3.47 (brs, 4H), 2.10 (s, 3H).	321.9
E19	B5		I	91	6.91 (d, J = 8.2 Hz, 1H), 6.51 (dd, J = 2.4 and 8.1 Hz, 1H), 6.41 (d, J = 2.4 Hz, 1H), 6.17 (s, 1H), 6.08 (s, 1H), 4.96 (s, 2H), 4.70 (s, 4H), 4.12 (s, 4H), 2.04 (s, 3H).	300.2

E20	B10		C	crude	No Data	453.0
E21	B6		C	71	7.25 (s, 1H), 7.12 (s, 1H), 6.95 (d, J = 8.4 Hz, 1H), 6.54 (m, 1H), 6.48 (s, 1H), 5.0 (brs, 2H), 2.14 (m, 1H), 2.08 (s, 3H), 1.02 (m, 2H), 0.88 (m, 2H).	259.2
E22	B25		J	87	7.85 (s, 1H), 7.03 (d, J = 1.1 Hz, 1H), 6.74 (d, J = 2.7 Hz, 1H), 6.71 (d, J = 1.1 Hz, 1H), 5.21 (s, 2H), 4.28-4.34 (m, 2H), 3.85-3.91 (m, 2H), 2.19 (s, 3H), 0.79 (s, 9H), 0.01 (s, 6H).	394.2
E23	B27		J	58	7.94 (dd, J = 5.6, 2.8 Hz, 1H), 7.09 (s, 1H), 7.03 (d, J = 2.4 Hz, 1H), 5.30 (s, 2H), 4.48 (t, J = 4.4 Hz, 2H), 3.91 (t, J = 4.4 Hz, 2H), 2.34 (s, 3H), 0.82 (s, 9H), 0.04 (s, 6H).	395.1
E24	B10		J	73	6.99 (s, 1H), 6.95 (d, J = 10.2 Hz, 1H), 6.66 (d, J = 6.4 Hz, 1H), 5.08 (s, 2H), 4.34 (t, J = 4.0 Hz, 2H), 3.91 (m, J = 4.8 Hz, 2H), 2.07 (s, 3H), 0.85 (s, 9H), 0.04 (s, 6H).	411.0
E25	B8		J	33	6.97 (t, J = 5.6 Hz, 1H), 6.46 (s, 1H), 6.39 (d, J = 9.6 Hz, 2H), 6.31 (s, 1H), 5.02 (br s, 2H), 3.69 (t, J = 6.0 Hz, 2H), 3.32- 3.37 (m, 2H), 2.11 (s, 3H), 0.84 (s, 9H), 0.02 (s, 6H).	410.0
E26	B31		J	45	No Data	397.2

E27	B32		J	67	No Data	415.2
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General Method K: Reduction

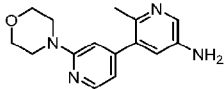
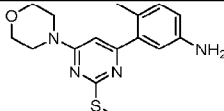
[000280] Intermediate **F1**: 4-methyl-3-(2-morpholinopyridin-4-yl)aniline

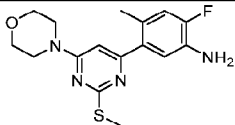


[000281] A solution of 3-(2-chloro-6-morpholinopyridin-4-yl)-4-methylaniline (**E7**, 0.20 g, 0.70 mmol) in EtOH (3 mL) was treated with 10% palladium on carbon (50% wet with water) (0.15 g, 0.07 mmol). The reaction mixture was hydrogenated under 50 psi for 4 h. The reaction mixture was filtered through a pad of celite and washed with EtOH. The filtrate was then concentrated under reduced pressure and the residue was purified by reverse-phase column chromatography (0 to 100% (0.4% TFA:H₂O)/CH₃CN) to afford 4-methyl-3-(2-morpholinopyridin-4-yl)aniline (0.10 g, 55%) as an off-white solid. ¹H NMR (500 MHz, DMSO-d₆): δ 8.11 (d, J = 5.1 Hz, 1H), 6.91 (d, J = 8.1 Hz, 1H), 6.65 (s, 1H), 6.59 (d, J = 5.1 Hz, 1H), 6.50 (dd, J = 2.4 and 8.1 Hz, 1H), 6.42 (d, J = 2.4 Hz, 1H), 4.93 (s, 2H), 3.68 (t, J = 4.8 Hz, 4H), 3.44 (t, J = 4.8 Hz, 4H), 2.04 (s, 3H).

[000282] Using the General Method K above, the following Intermediates of Table F were prepared.

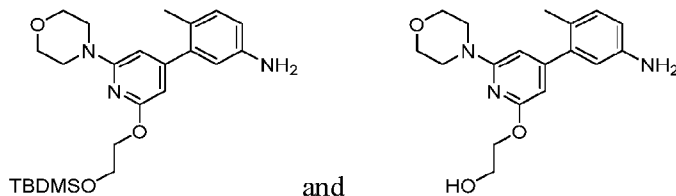
Table F.

Exp No	SM	Product	Yield (%)	¹ H NMR (400 or 500 MHz, DMSO-d ₆): δ	MS (m/z: M+H ⁺)
F2	E4		98	8.16 (d, J = 4.8 Hz, 1H), 7.86 (d, J = 2.4 Hz, 1H), 6.77 (d, J = 2.8 Hz, 1H), 6.73 (s, 1H), 6.65 (d, J = 5.2 Hz, 1H), 5.2 (s, 2H), 3.69 (m, 4), 3.47 (m, 4H), 2.23 (s, 3H).	271.3
F3	E12		crude	No Data	317.2

F4	E13		35	No Data	335.2
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General Method L: Aromatic Substitution Reactions

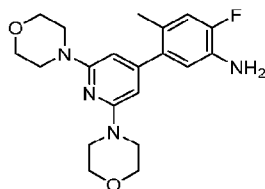
[000283] Intermediate **G1**: 3-(2-(2-((tert-butyldimethylsilyl)oxy)ethoxy)-6-morpholinopyridin-4-yl)-4-methylaniline and intermediate **G2**: 2-((4-(5-amino-2-methylphenyl)-6-morpholinopyridin-2-yl)oxy)ethan-1-ol



[000284] A solution of 2-((tert-butyldimethylsilyl)oxy)ethan-1-ol (37 g, 209 mmol) in 1,4-dioxane and NMP (4:1, 150 mL) was treated with NaH (5.2 g, 131 mmol, 60% dispersion in mineral oil) slowly. The resultant mixture was stirred at rt for 15 min under Ar atmosphere. 3-(2-Fluoro-6-morpholinopyridin-4-yl)-4-methylaniline (**E6**, 15 g, 52 mmol) was added and then the reaction mixture was heated at 120 °C for 2 h. The reaction mixture was cooled to rt and poured into cold sat'd NH₄Cl solution (200 mL). The mixture was extracted with DCM (3 x 200 mL). The combined organics were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The crude was purified by silica gel column chromatography (0 to 40% EtOAc/hexanes) to obtain two major products: 3-(2-(2-((tert-butyldimethylsilyl)oxy)ethoxy)-6-morpholinopyridin-4-yl)-4-methylaniline (**G1**, 7.0 g, 30%) as a brown liquid. ¹H NMR (400 MHz, DMSO-d₆): δ 6.89 (d, J = 8.0 Hz, 1H), 6.48 (dd, J = 2.4 and 8.0 Hz, 1H), 6.41 (s, 1H), 6.16 (s, 1H), 5.91 (s, 1H), 4.9 (brs, 2H), 4.28 (t, J = 5.2 Hz, 2H), 3.89 (t, J = 5.2 Hz, 2H), 3.68 (m, 4H), 3.42 (m, 4H), 2.01 (s, 3H), 0.85 (s, 9H), 0.04 (s, 6H); MS (ESI) m/z: 444.1 (M+H⁺) and 2-((4-(5-amino-2-methylphenyl)-6-morpholinopyridin-2-yl)oxy)ethan-1-ol (**G2**, 6.5 g, 55%) as a brown liquid. ¹H NMR (400 MHz, DMSO-d₆): δ 6.89 (d, J = 8.2 Hz, 1H), 6.48 (dd, J = 2.0 and 8.0 Hz, 1H), 6.41 (brs, 1H), 6.16 (m, 1H), 5.95 (m, 1H), 4.9 (brs, 2H), 4.78 (t, J = 5.6 Hz, 1H), 4.23 (t, J = 5.2 Hz, 2H), 3.69 (m, 6H), 3.39 (m, 4H), 2.01 (s, 3H); MS (ESI) m/z: 330.0 (M+H⁺).

General Method M: Aromatic Substitution Reactions at high temperature

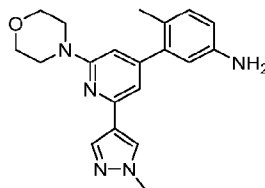
[000285] Intermediate **G3**: 5-(2,6-dimorpholinopyridin-4-yl)-2-fluoro-4-methylaniline



[000286] A solution of 2-fluoro-5-(2-fluoro-6-morpholinopyridin-4-yl)-4-methylaniline (**E2**, 0.4 g, 1.3 mol) and morpholine (2.3 g, 27 mmol) and in DMSO (2 mL) was heated at 160 °C for 4 h. The reaction mixture was quenched with water (10 mL) and the solution was extracted with EtOAc (2 x 30 mL). The combined organics were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The crude was purified by silica gel column chromatography (30 to 40% EtOAc/hexanes) to obtain 5-(2,6-dimorpholinopyridin-4-yl)-2-fluoro-4-methylaniline (0.42 g, 85%) as a white solid. ¹H NMR (400 MHz, DMSO-d₆): δ 6.88 (m, 1H), 6.60 (m, 1H), 5.95 (s, 2H), 4.94 (brs, 2H), 3.66 (t, J = 4.7 Hz, 8H), 3.38 (t, J = 4.7 Hz, 8H), 2.06 (s, 3H); MS (ESI) m/z: 373.2 (M+H⁺).

General Method N: Suzuki Reaction

[000287] Intermediate **G4**: 4-methyl-3-(2-(1-methyl-1H-pyrazol-4-yl)-6-morpholinopyridin-4-yl)aniline

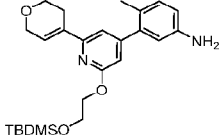
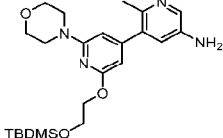
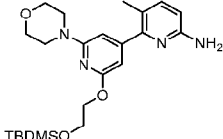
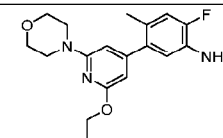
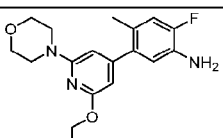


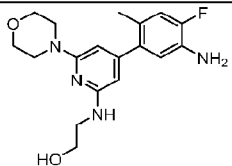
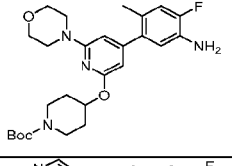
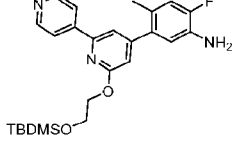
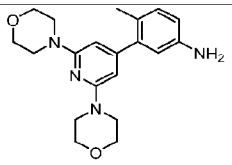
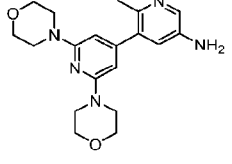
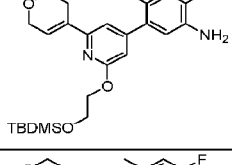
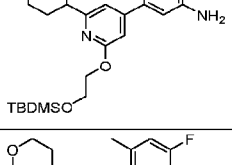
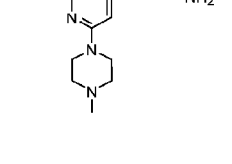
[000288] A solution of 3-(2-chloro-6-morpholinopyridin-4-yl)-4-methylaniline (**E7**, 0.80 g, 2.6 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (0.66 g, 3.2 mmol) in 1,4-dioxane (25 mL) was treated with K₂CO₃ (2 N, 2.6 mL, 5.3 mmol). The reaction mixture was sparged with Ar for 2 min and then Pd(dppf)Cl₂.DCM adduct (0.22 g, 0.26 mmol) was added. The reaction mixture was heated at 80 °C for 1h and then cooled to rt. The reaction mixture was quenched with water (100 mL) and then the solution was extracted with EtOAc (3 x 40 mL). The combined organics were dried over anhydrous MgSO₄, filtered, concentrated under reduced pressure to obtain the crude. The crude was purified by silica gel column chromatography (0 to 70% EtOAc/hexanes) to afford 4-methyl-3-(2-(1-methyl-1H-pyrazol-4-yl)-6-morpholinopyridin-4-yl)aniline (0.72 g, 78%) as an off-

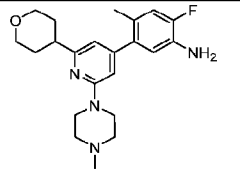
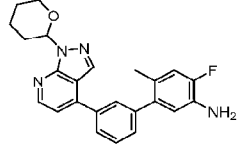
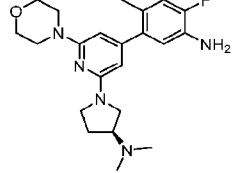
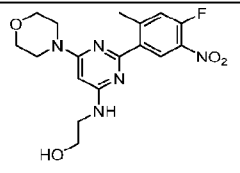
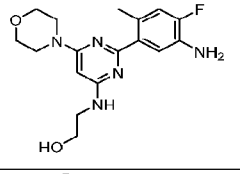
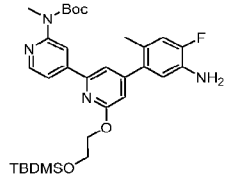
white solid. ^1H NMR (500 MHz, DMSO-d_6): δ 8.21 (s, 1H), 7.94 (s, 1H), 6.92 (d, $J = 8.1\text{ Hz}$, 1H), 6.87 (s, 1H), 6.50 (dd, $J = 2.4$ and 8.1 Hz , 1H), 6.46 (s, 1H), 6.45 (s, 1H), 4.93 (s, 2H), 3.85 (s, 3H), 3.71 (t, $J = 4.7\text{ Hz}$, 4H), 3.50 (t, $J = 4.7\text{ Hz}$, 4H), 2.07 (s, 3H); MS m/z : 350.2 ($\text{M}+\text{H}^+$).

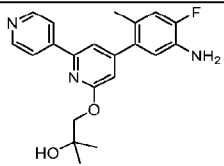
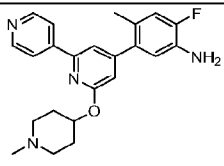
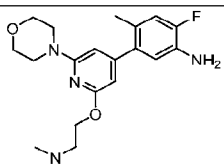
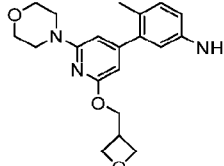
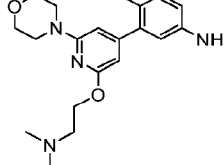
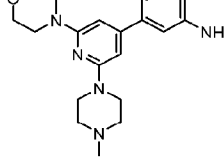
[000289] Using the General Methods K, L, M and N above, the following Intermediates of Table G were prepared.

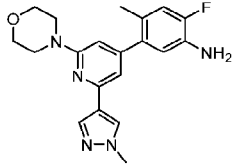
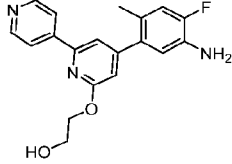
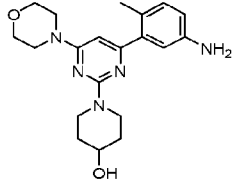
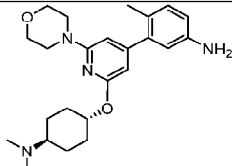
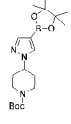
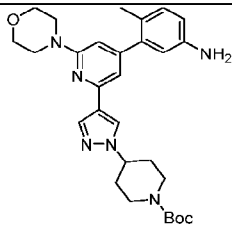
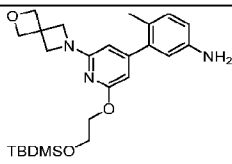
Table G.

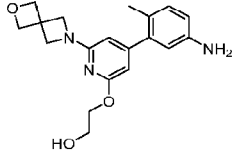
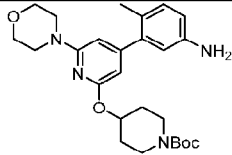
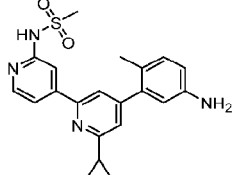
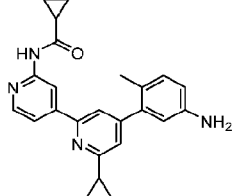
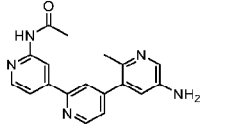
Exp No	SM	Product	Method	Yield (%)	^1H NMR (400 or 500 MHz, DMSO-d_6): δ	MS (m/z : $\text{M}+\text{H}^+$)
G5			N	28	No Data	441.2
G6			L	30	No Data	445.2
G7			L	58	7.27 (d, $J = 8.3\text{ Hz}$, 1H), 6.39 (d, $J = 8.3\text{ Hz}$, 1H), 6.29 (s, 1H), 6.05 (s, 1H), 5.76 (s, 2H), 4.27 (t, $J = 5.0\text{ Hz}$, 2H), 3.89 (t, $J = 5.0\text{ Hz}$, 2H), 3.68 (t, $J = 4.8\text{ Hz}$, 4H), 3.41 (t, $J = 4.8\text{ Hz}$, 4H), 2.07 (s, 3H), 0.85 (s, 9H), 0.04 (2, 6H).	445.2
G8			L	48	6.85 (d, $J = 12.4\text{ Hz}$, 1H), 6.57 (d, $J = 9.4\text{ Hz}$, 1H), 6.12 (s, 1H), 5.87 (s, 1H), 4.94 (s, 2H), 4.24 (t, $J = 5.2\text{ Hz}$, 2H), 3.85 (t, $J = 5.2\text{ Hz}$, 2H), 3.64 (t, $J = 4.8\text{ Hz}$, 4H), 3.38 (t, $J = 4.8\text{ Hz}$, 4H), 2.01 (s, 3H), 0.81 (s, 9H), 0.01 (t, $J = 4.1\text{ Hz}$, 6H).	462.2
G9			L	53	No Data	348.2

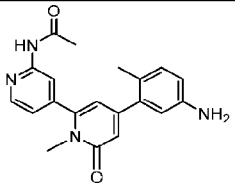
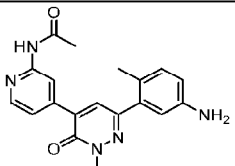
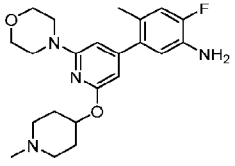
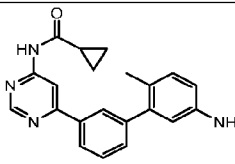
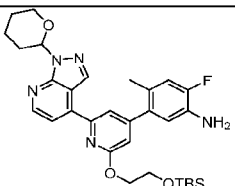
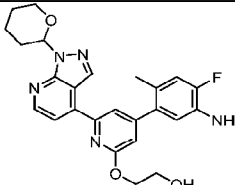
G10	E2 		L	61	No Data	347.2
G11	E2 		L	crude	No Data	487.2
G12	E10 		L	67	8.67 (m, 2H), 8.09 (m, 2H), 7.65 (d, J = 1.1Hz, 1H), 6.97 (d, J = 12.4 Hz, 1H), 6.74 (d, J = 1.1Hz, 1H), 6.71 (d, J = 9.3 Hz, 1H), 5.08 (s, 2H), 4.51 (t, J = 4.9 Hz, 2H), 3.98 (m, 2H), 2.11 (s, 3H), 0.83 (m, 9H), 0.04 (s, 6H).	454.2
G13	E6 		M	95	No Data	355.2
G14	E8 		M	47	No Data	356.2
G15	E9 		N	78	No Data	459.2
G16	G15 		K	crude	No Data	461.2
G17	E11 		N	38	6.91 (d, J = 12.4 Hz, 1H), 6.72 (brs, 1H), 6.63 (m, 2H), 6.54 (s, 1H), 4.99 (s, 2H), 4.23 (m, 2H), 3.78 (t, J = 5.4 Hz, 2H), 3.51 (brm, 4H), 2.38 (m, 4H), 2.20 (s, 3H), 2.06 (s, 3H), 1.23-1.26 (m, 2H).	383.2

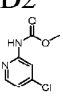
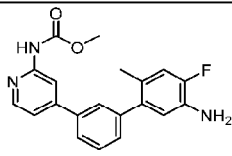
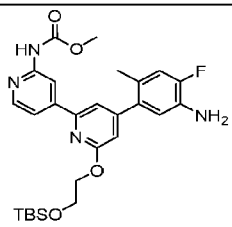
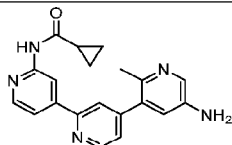
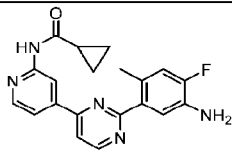
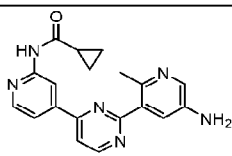
G18	G17		K	66	6.90 (d, J = 12.4 Hz, 1H), 6.61 (d, J = 9.4 Hz, 1H), 6.47 (s, 1H), 6.42 (s, 1H), 4.97 (m, 2H), 3.91 (m, 2H), 3.50 (brm, 4H), 3.41 (m, 2H), 2.72-2.80 (m, 1H), 2.42 (brm, 4H), 2.23 (s, 3H), 2.06 (s, 3H), 1.73 (m, 4H).	385.2
G19	C3 D2		N	79	No Data	403.2
G20	E2 		L	82	6.86 (d, J = 12.4 Hz, 1H), 6.59 (d, J = 9.5 Hz, 1H), 5.80 (s, 1H), 5.61 (s, 1H), 4.94 (s, 2H), 3.64 9m, 4H), 3.56 (m, 2H), 3.37 (m, 4H), 3.23-3.30 (m, 2H), 3.04 (m, 1H), 2.18 (s, 6H), 2.06 (s, 3H), 1.89 (m, 1H), 1.72 (m, 1H).	No Data
G21	E14 		N	36	CDCl ₃ , 8.08 (d, J = 7.9 Hz, 1H), 7.54 (m, 1H), 6.65 (brs, 1H), 6.21 (s, 1H), 4.63 (brm, 1H), 3.64 (m, 4H), 3.56 (m, 4H), 3.48 (s, 2H), 3.28 (m, 2H), 2.46 (s, 3H).	378.2
G22	G21		K	92	No Data	348.2
G23	E9 A1		N	60	8.44 (d, J = 5.3 Hz, 1H), 8.26 (s, 1H), 7.81 (m, 1H), 7.57 (d, J = 1.2 Hz, 1H), 6.97 (d, J = 12.4 Hz, 1H), 6.72 (m, 2H), 5.08 (s, 2H), 4.50 (t, J = 5.0 Hz, 2H), 3.98 (t, J = 4.9 Hz, 2H), 3.31 (s, 3H), 2.10 (s, 3H), 1.45 (s, 9H), 0.83 (s, 9H), 0.03 (s, 6H).	583.3

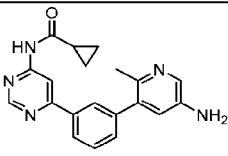
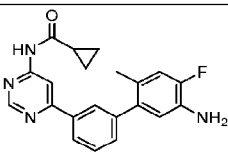
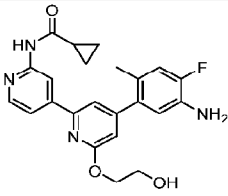
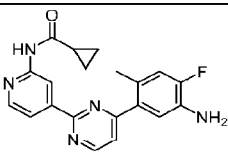
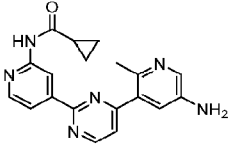
G24	E10 		L	crude	8.68 (d, J = 5.4 Hz, 2H), 8.09 (d, J = 5.5 Hz, 2H), 7.65 (s, 1H), 6.98 (d, J = 12.4 Hz, 1H), 6.76 (s, 1H), 6.73 (d, J = 9.3 Hz, 1H), 5.06 (s, 2H), 4.65 (s, 1H), 4.22 (s, 2H), 2.68 (s, 6H), 2.13 (s, 3H).	368.2
G25	E10 		L	89	No Data	393.2
G26	E2 		L	95	6.88 (d, J = 12.4 Hz, 1H), 6.60 (d, J = 12.4 Hz, 1H), 6.15 (s, 1H), 5.91 (d, J = 0.9 Hz, 1H), 4.98 (s, 2H), 4.29 (t, J = 6.0 Hz, 2H), 3.68 (t, J = 4.7 Hz, 4H), 3.42 (t, J = 4.7 Hz, 4H), 2.58 (t, J = 6.0 Hz, 2H), 2.19 (s, 6H), 2.05 (s, 3H).	375.2
G27	E6 		L	70	6.90 (d, J = 8.0 Hz, 1H), 6.50 (m, 1H), 6.42 (m, 1H), 6.18 (s, 1H), 5.94 (s, 1H), 4.90 (brs, 2H), 4.69 (m, 2H), 4.45 (d, J = 6.8 Hz, 2H), 4.40 (t, J = 6.8 Hz, 2H), 3.70 (m, 4H), 3.43 (m, 4H), 3.38 (m, 1H), 2.04 (s, 3H).	356.1
G28	E6 		L	66	6.89 (d, J = 8.0 Hz, 1H), 6.48 (d, J = 6.8 Hz, 1H), 6.41 (s, 1H), 6.16 (s, 1H), 5.92 (s, 1H), 4.90 (brs, 2H), 4.29 (t, J = 5.6 Hz, 2H), 3.69 (brm, 4H), 3.43 (brm, 4H), 2.58 (t, J = 6.0 Hz, 2H), 2.19 (s, 6H), 2.04 (s, 3H).	357.1
G29	E7 		L	80	6.88 (d, J = 8.0 Hz, 1H), 6.48 (brs, 1H), 6.41 (s, 1H), 5.95 (s, 1H), 5.92 (s, 1H), 4.80 (brs, 2H), 3.67 (brm, 4H), 3.42 (brm, 4H), 3.43 (brm, 4H), 2.32 (brm, 4H), 2.20 (s, 3H), 2.04 (s,	368.5

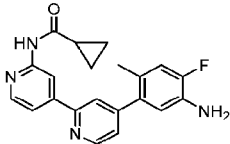
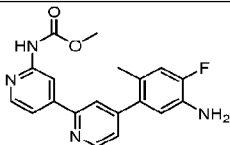
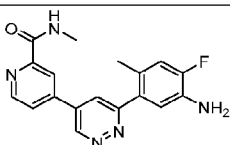
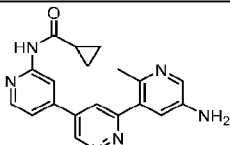
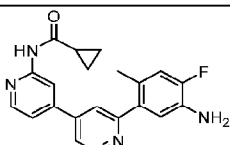
					3H).	
G30	E18 		N	66	8.33 (s, 1H), 7.91 (s, 1H), 7.22 (d, J = 8.8 Hz, 1H), 7.05 (s, 1H), 6.62 (s, 1H), 6.45 (d, J = 13.6 Hz, 1H), 5.40 (s, 2H), 3.81 (s, 3H), 3.72 (brm, 4H), 3.51 (brm, 4H), 2.08 (s, 3H).	368.0
G31	E10 		L	43	8.67 (d, J = 5.5 Hz, 2H), 8.09 (d, J = 5.5 Hz, 2H), 7.64 (s, 1H), 6.98 (d, J = 12.3 Hz, 1H), 6.76 (s, 1H), 6.72 (d, J = 9.3 Hz, 1H), 5.06 (s, 2H), 4.86 (t, J = 5.4 Hz, 1H), 4.45 (t, J = 5.2 Hz, 2H), 3.78 (m, 2H), 2.12 (s, 3H).	No Data
G32	E12 Mcpb 		oxidation, substitution, & K	crude	No Data	370.2
G33	E6 		L	34	6.89 (d, J = 8.0 Hz, 1H), 6.48 (d, J = 8.8 Hz, 1H), 6.41 (brs, 1H), 6.13 (s, 1H), 5.88 (s, 1H), 4.9 (brs, 2H), 4.75 (m, 1H), 3.69 (brs, 4H), 3.41 (brs, 4H), 2.35 (brs, 5H), 2.28 (brs, 3H), 2.17 (brs, 3H), 1.97 (s, 3H), 1.85 (4H).	411.5
G34	E7 		N	59	8.35 (s, 1H), 7.97 (s, 1H), 6.93 (brs, 2H), 6.50 (d, J = 7.6 Hz, 1H), 6.45 (d, J = 6.4 Hz, 2H), 4.9 (brs, 2H), 4.36 (m, 1H), 4.03 (brs, 2H), 3.71 (brs, 4H), 3.51 (brs, 4H), 2.89 (brs, 2H), 2.07 (s, 3H), 2.01 (m, 2H), 1.81 (m, 2H), 1.41 (s, 9H).	519.3
G35	E19 		L	34	6.88 (d, J = 8.1 Hz, 1H), 6.48 (dd, J = 2.4 and 8.1 Hz, 1H), 6.38 (d, J = 2.4 Hz, 1H), 5.86 (s, 1H), 5.74 (s, 1H), 4.91 (s, 2H), 4.70 (s, 4H), 4.25 (t, J = 5.1 Hz,	456.2

					2H), 4.07 (s, 4H), 3.88 (t, J = 5.1 Hz, 2H), 2.01 (s, 3H), 0.85 (s, 9H), 0.04 (s, 6H).	
G36	E19 		L	41	6.89 (d, J = 8.1 Hz, 1H), 6.48 (dd, J = 2.4 and 8.1 Hz, 1H), 6.39 (d, J = 2.4 Hz, 1H), 5.88 (s, 1H), 5.75 (s, 1H), 4.94 (s, 2H), 4.79 (t, J = 5.5 Hz, 1H), 4.70 (s, 4H), 4.20 (m, 2H), 4.07 (s, 4H), 3.68 (m, 2H), 2.02 (s, 3H).	342.2
G37	E6 		L	58	6.89 (d, J = 8.0 Hz, 1H), 6.47 (dd, J = 2.4 and 8.0 Hz, 1H), 6.44 (s, 1H), 6.23 (s, 1H), 5.92 (s, 1H), 5.50 (m, 1H), 4.9 (brs, 2H), 3.67 (m, 4H), 3.45 (m, 4H), 3.03 (m, 2H), 2.69 (m, 2H), 2.19 (m, 2H), 2.17 (s, 3H), 1.60 (m, 2H), 1.40 (s, 9H).	469.4
G38	E21 		N	40	10.9 (brs, 1H), 8.30 (s, 1H), 7.73 (s, 1H), 7.63 (m, 2H), 7.73 (s, 1H), 7.98 (d, J = 8.0 Hz, 1H), 6.56 (dd, J = 2.4 and 8.0 Hz, 1H), 6.52 (s, 1H), 5.0 (brs, 2H), 2.22 (m, 1H), 2.10 (s, 3H), 1.98 (s, 3H), 1.02 (m, 2H), 1.09 (m, 2H).	395.3
G39	E21 A2		N	44	10.9 (s, 1H), 8.75 (s, 1H), 8.38 (d, J = 5.2 Hz, 1H), 7.72 (m, 1H), 7.55 (s, 1H), 7.26 (s, 1H), 6.96 (m, 1H), 6.56 (m, 1H), 6.44 (s, 1H), 4.9 (brs, 2H), 2.20 (m, 1H), 2.09 (s, 3H), 1.98 (m, 1H), 1.02 (m, 4H), 0.85 (m, 4H).	385.4
G40	A3 B13		N	64	10.5 (s, 1H), 8.83 (s, 1H), 8.78 (d, J = 5.2 Hz, 1H), 8.41 (d, J = 4.8 Hz, 1H), 7.90 (m, 2H), 7.80 (d, J = 5.2 Hz, 1H), 7.49 (brm, 1H), 6.89 (brm, 1H), 5.20 (brs, 2H), 2.32 (s, 3H), 2.12 (s, 3H).	320.0

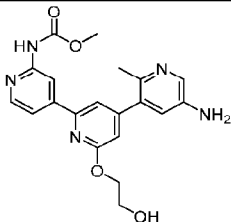
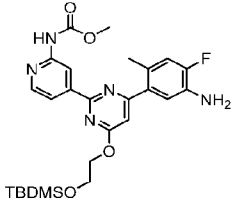
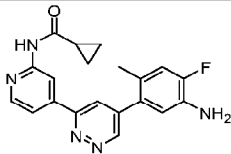
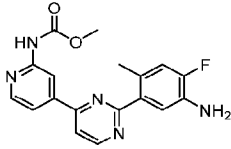
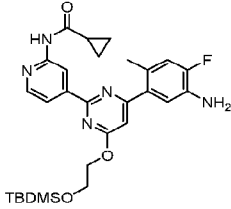
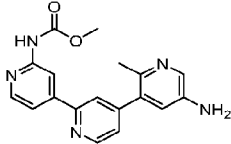
G41	A3 B14		N	64	10.7 (s, 1H), 8.43 (d, J = 8.0 Hz, 1H), 8.15 (s, 1H), 7.51 (m, 2H), 7.29 (d, J = 4.0 Hz, 1H), 6.93 (d, J = 8.0 Hz, 1H), 6.33 (s, 1H), 6.11 (s, 1H), 4.9 (brs, 2H), 3.28 (s, 3H), 2.12 (s, 3H), 2.07 (s, 3H).	349.1
G42	A3 B15		N	57	10.5 (s, 1H), 8.17 (s, 1H), 8.07 (d, J = 5.2 Hz, 1H), 6.81 (m, 2H), 6.62 (d, J = 4.8 Hz, 1H), 6.48 (brm, 1H), 6.32 (brm, 1H), 4.90 (brs, 2H), 3.78 (s, 3H), 2.10 (s, 3H), 1.78 (s, 3H).	350.0
G43	E2 		L	72	6.88 (d, J = 12.4 Hz, 1H), 6.61 (d, J = 9.4 Hz, 1H), 6.13 (s, 1H), 5.89 (s, 1H), 4.95 (s, 2H), 4.88 (m, 1H), 3.68 (t, J = 4.7 Hz, 4H), 3.39 (t, J = 4.8 Hz, 4H), 2.61 (d, J = 10.3 Hz, 2H), 2.14 (m, 5H), 2.06 (s, 3H), 1.95 (m, 2H), 1.64 (m, 2H).	401.2
G44	D6 		N	72	11.3 (s, 1H), 8.95 (brs, 1H), 8.60 (s, 1H), 8.01 (d, J = 7.6 Hz, 1H), 7.91 (brs, 1H), 7.58 (t, J = 7.6 Hz, 1H), 7.45 (br d, J = 8.0 Hz, 1H), 6.95 (d, J = 8.0 Hz, 1H), 6.51 (m, 2H), 4.93 (brs, 2H), 2.06 (s, 3H), 2.02-2.12 (m, 1H), 0.85-0.92 (m, 4H).	345.1
G45	D5 E9		N	crude	No Data	578.2
G45 a	G45		K	37	8.78 (s, 1H), 8.64 (d, J = 4.9 Hz, 1H), 7.92 (d, J = 5.0 Hz, 1H), 7.76 (d, J = 1.2 Hz, 1H), 6.99 (d, J = 12.4 Hz, 1H), 6.84 (d, J = 1.1 Hz, 1H), 6.77 (d, J = 9.3 Hz, 1H), 6.10 (dd, J = 2.5 and 10.3 Hz, 1H), 5.07	464.2

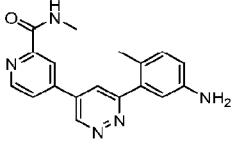
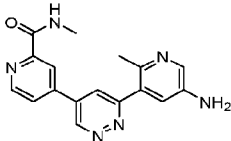
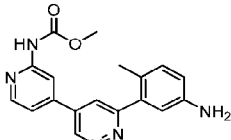
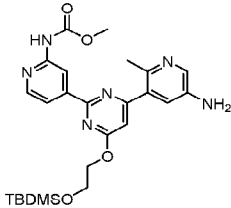
					(s, 2H), 4.91 (t, J = 5.5 Hz, 1H), 4.52 (m, 2H), 3.96 (m, 1H), 3.83 (m, 2H), 3.67-3.75 (m, 1H), 2.50-2.59 (m, 1H), 2.16 (s, 3H), 2.06 (m, 1H), 1.98 (s, 1H), 1.79 (m, 1H), 1.60 (m, 2H).	
G46	D2 		N	33	10.3 (s, 1H), 8.31 (dd, J = 0.7 and 5.3 Hz, 1H), 8.15 (dd, J = 0.7 and 1.7 Hz, 1H), 7.69 (m, 1H), 7.53-7.59 (m, 2H), 7.35-7.44 (m, 2H), 6.94 (d, J = 12.4 Hz, 1H), 6.69 (d, J = 9.4 Hz, 1H), 4.99 (s, 2H), 3.68 (s, 3H), 2.09 (s, 3H).	352.2
G47	A6 E9		N	74	No Data	527.2
G48	A2 B13		N	63	No Data	346.2
G49	C9 		N & K	60	11.0 (s, 1H), 9.03 (d, J = 5.2 Hz, 1H), 8.91 (s, 1H), 8.51 (d, J = 4.8 Hz, 1H), 7.97 (d, J = 5.2 Hz, 1H), 7.85 (dd, J = 1.2 and 5.2 Hz, 1H), 7.42 (d, J = 9.6 Hz, 1H), 6.99 (d, J = 12.4 Hz, 1H), 5.09 (brs, 2H), 2.44 (s, 3H), 2.02 (m, 1H), 0.81-0.86 (m, 4H).	364.0
G50	C9 		N & K	82	11.0 (s, 1H), 9.07 (brm, 1H), 8.93 (brs, 1H), 8.52 (brs, 1H), 8.03 (s, 1H), 8.03 (s, 1H), 7.86 (m, 1H), 7.50 (brm, 1H), 5.27 (brs, 2H), 2.66 (s, 3H), 2.04 (m, 1H), 0.81-0.86 (m, 4H).	347.1

G51	D1 		N & K	73	11.3 (s, 1H), 8.95 (s, 1H), 8.60 (s, 1H), 8.04 (d, J = 7.6 Hz, 1H), 7.99 (s, 1H), 7.88 (d, J = 2.4 Hz, 1H), 7.62 (t, J = 7.6 Hz, 1H), 7.53 (d, J = 7.6 Hz, 1H), 6.84 (d, J = 2.4 Hz, 1H), 5.20 (brs, 2H), 2.25 (s, 3H), 2.06 (m, 1H), 0.85-0.90 (m, 4H).	346.2
G52	C10 		N	60	11.3 (s, 1H), 8.94 (d, J = 1.2 Hz, 1H), 8.60 (d, J = 1.3 Hz, 1H), 8.01 (m, 1H), 7.91 (t, J = 1.8 Hz, 1H), 7.58 (t, J = 7.7 Hz, 1H), 7.46 (dt, J = 1.4 and 7.7 Hz, 1H), 6.95 (d, J = 12.4 Hz, 1H), 6.70 (d, J = 9.3 Hz, 1H), 5.02 (s, 2H), 3.17 (d, J = 5.2 Hz, 1H), 2.03-2.13 (m, 1H), 0.86-0.92 (m, 6H).	363.2
G53	A2 E9		N & R	78	10.9 (s, 1H), 8.76 (s, 1H), 8.40 (d, J = 5.2 Hz, 1H), 7.76 (dd, J = 1.2 and 5.2 Hz, 1H), 7.44 (s, 1H), 6.98 (d, J = 12.4 Hz, 1H), 6.77 (s, 1H), 6.71 (d, J = 9.2 Hz, 1H), 5.07 (s, 2H), 4.87 (t, J = 5.2 Hz, 1H), 4.43 (t, J = 4.8 Hz, 2H), 3.78 (q, J = 5.2 Hz, 2H), 2.11 (s, 3H), 2.04 (m, 1H), 0.79-0.85 (m, 4H).	423.3
G54	A2 B23		K & N	81	12.0 (s, 1H), 9.10 (s, 1H), 8.98 (d, J = 4.8 Hz, 1H), 8.49 (d, J = 4.8 Hz, 1H), 7.99 (d, J = 4.0 Hz, 1H), 7.64 (d, J = 5.2 Hz, 1H), 7.05 (s, 1H), 7.02 (t, J = 4.0 Hz, 1H), 5.17 (s, 2H), 2.31 (s, 3H), 2.04 (m, 1H), 0.82 (d, J = 8.4 Hz, 4H).	364.1
G55	A2 B24		K & N	65	10.9 (s, 1H), 9.11 (s, 1H), 9.03 (d, J = 5.2 Hz, 1H), 8.48 (d, J = 5.2 Hz, 1H), 7.99 (m, 2H), 7.77 (d, J = 5.6 Hz, 1H), 7.14 (d, J =	347.1

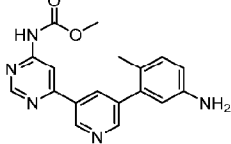
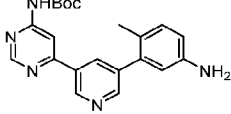
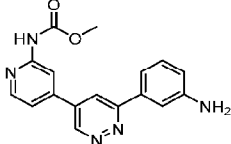
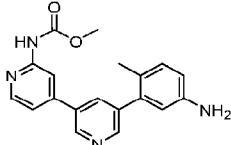
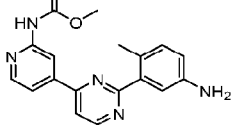
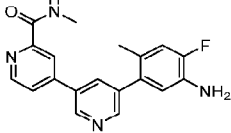
					2.4 Hz, 1H), 5.33 (s, 2H), 2.46 (s, 3H), 2.05 (m, 1H), 0.81-0.86 (m, 4H).	
G56	A2 B12		N	crude	10.9 (s, 1H), 8.83 (br s, 1H), 8.73 (d, J = 4.8 Hz, 1H), 8.41 (d, J = 5.2 Hz, 1H), 7.86 (brs, 1H), 7.79 (d, J = 5.6 Hz, 1H), 7.41 (d, J = 4.8 Hz, 1H), 7.00 (d, J = 12.4 Hz, 1H), 6.73 (d, J = 8.8 Hz, 1H), 5.10 (brs, 2H), 2.11 (brs, 3H), 2.01 (q, J = 6.4 Hz, 1H), 0.86 (m, 4H).	363.1
G57	A6 B12		N	crude	10.3 (brs, 1H), 8.75 (d, J = 4.8 Hz, 1H), 8.67 (brs, 1H), 8.36 (d, J = 4.8 Hz, 1H), 7.88 (s, 1H), 7.74 (d, J = 4.8 Hz, 1H), 7.41 (d, J = 4.8 Hz, 1H), 7.00 (d, J = 12.4 Hz, 1H), 6.74 (d, J = 9.2 Hz, 1H), 5.09 (brs, 2H), 3.69 (brs, 3H), 2.13 (br s, 3H).	353.0
G58	A4 B26		N & K	crude	No Data	338.2
G59	A8 C12		N	36	11.0 (s, 1H), 9.58 (d, J = 2.2 Hz, 1H), 8.53 (d, J = 1.6 Hz, 1H), 8.50 (d, J = 5.2 Hz, 1H), 8.11 (d, J = 2.2 Hz, 1H), 7.98 (d, J = 2.7 Hz, 1H), 7.66 (dd, J = 1.7 and 5.2 Hz, 1H), 7.10 (d, J = 2.7 Hz, 1H), 5.30 (s, 2H), 2.33 (s, 3H), 2.04 (m, 1H), 0.79-0.88 (m, 4H).	347.2
G60	A2 B26		N & K	93	11.03 (s, 1H), 9.54 (s, 1H), 8.43-8.61 (m, 2H), 8.00 (s, 1H), 7.65 (d, J = 5.5 Hz, 1H), 7.02 (d, J = 12.3 Hz, 1H), 6.95 (d, J = 9.3 Hz, 1H), 5.12 (s, 2H), 2.17 (s, 3H), 2.07 (m, 1H), 0.86-0.80 (m, 4H).	364.2

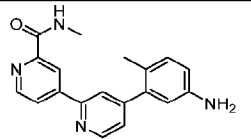
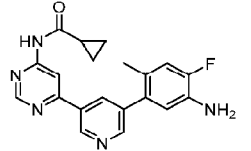
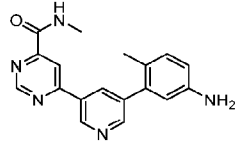
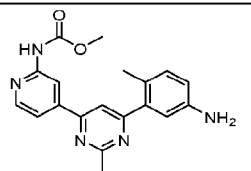
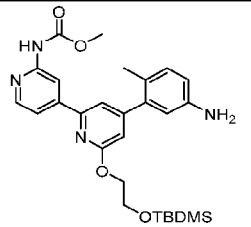
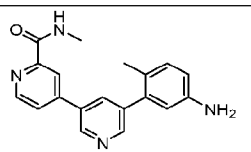
G61	A2 E22		N & R	86	10.77 (s, 1H), 8.40 (d, J = 5.2 Hz, 1H), 7.91 (d, J = 2.0 Hz, 1H), 7.77 (d, J = 5.2 Hz, 1H), 7.55 (m, 4H), 6.89 (br s, 2H), 4.87 (t, J = 5.6 Hz, 1H), 4.43 (t, J = 4.8 Hz, 2H), 3.80 (t, J = 4.8 Hz, 2H), 2.27 (s, 3H), 1.98-2.04 (m, 1H), 0.78-0.84 (m, 4H).	406.4
G62	A6 B23		K & N	60	10.35 (s, 1H), 9.00 (d, J = 5.2 Hz, 1H), 8.88, (s, 1H), 8.44 (d, J = 4.8 Hz, 1H), 7.96 (d, J = 4.8 Hz, 1H), 7.65 (d, J = 4.8 Hz, 1H), 7.05 (m, 1H), 7.02 (s, H), 5.17 (br d, 2H), 3.70 (s, 3H), 2.33 (s, 3H).	354.0
G63	D1 	N & K	69	8.84 (s, 1H), 8.34 (s, 1H), 8.04 (d, J = 6.8 Hz, 2H), 7.88 (s, 1H), 7.62 (t, J = 7.6 Hz, 1H), 7.53 (d, J = 7.2 Hz, 1H), 6.96 (s, 1H), 6.85 (s, 1H), 3.70 (s, 3H), 2.26 (s, 2H). 3Hs are under solvent.	336.1	
G64	C11 	N	crude	No Data	354.2	
G65	A6 B24		N & K	59	10.38 (s, 1H), 9.04 (d, J = 5.2 Hz, 1H), 8.90 (s, 1H), 8.44 (d, J = 5.2 Hz, 1H), 7.99 (d, J = 2.8 Hz, 2H), 7.74 (d, J = 5.2 Hz, 1H), 7.15 (d, J = 2.4 Hz, 1H), 5.36 (s, 2H), 3.70 (s, 3H). 3Hs are under solvent.	337.0
G66	A2 E23		N	66	10.96 (s, 1H), 9.06 (s, 1H), 8.85 (s, 1H), 8.49 (d, J = 6.4 Hz, 1H), 7.96 (dd, J = 4.4, 1.2 Hz, 1H), 7.08 (d, J = 2.8 Hz, 1H), 7.05 (s, 1H), 5.28 (s, 2H), 4.62 (t, J = 4.4 Hz, 2H), 4.00 (t, J = 5.2 Hz, 2H), 2.41 (s, 3H), 2.03 (m, 1H), 0.83 (m, 13H).	521.2

					0.04 (s, 6H).	
G67	A6 E22		N & deprote ction with HCl	60	No Data	396.2
G68	A6 E24		N	68	10.31 (s, 1H), 8.83 (s, 1H), 8.43 (d, J = 5.2 Hz, 1H), 7.93 (d, J = 4.0 Hz, 1H), 7.04 (s, 1H), 7.02 (m, 1H), 6.96 (m, 1H), 5.11 (s, 2H), 4.62 (t, J = 4.4 Hz, 2H), 4.01 (t, J = 4.8 Hz, 2H), 3.28 (s, 3H), 2.29 (s, 3H), 0.82 (s, 9H), 0.52 (s, 6H).	528.1
G69	C13 		N	30	11.0 (s, 1H), 9.31 (d, J = 2.0 Hz, 1H), 8.91 (s, 1H), 8.49 (d, J = 5.2 Hz, 1H), 8.16 (d, J = 2.0 Hz, 1H), 7.86 (dd, J = 1.6 and 5.2 Hz, 1H), 7.05 (d, J = 12.0 Hz, 1H), 6.80 (d, J = 8.4 Hz, 1H), 5.17 (brs, 2H), 2.16 (s, 3H), 2.05 (m, 1H), 0.82-0.87 (m, 4H).	364.3
G70	C14 		N	crude	No Data	354.1
G71	A2 E24		N	55	10.9 (s, 1H), 9.05 (s, 1H), 8.47 (brm, 1H), 7.96 (brm, 1H), 6.97 (d, J = 12.4 Hz, 1H), 6.94 (s, 2H), 5.12 (br s, 2H), 4.60 (brm, 2H), 4.01 (brm, 2H), 2.26 (s, 3H), 2.03 (m, 1H), 0.85 (s, 9H), 0.80-0.85 (m, 4H), 0.04 (s, 6H).	538.2
G72	A6 B13		N	71	10.3 (s, 1H), 8.77 (d, J = 5.0 Hz, 1H), 8.60 (t, J = 1.1 Hz, 1H), 8.36 (d, J = 5.3 Hz, 1H), 7.96 (d, J = 1.2 Hz, 1H), 7.92 (d, J = 2.6 Hz, 1H), 7.75 (dd, J = 1.6	336.0

					and 5.2 Hz, 1H), 7.48 (dd, J = 1.5 and 5.0 Hz, 1H), 6.88 (d, J = 2.7 Hz, 1H), 5.26 (s, 2H), 3.69 (s, 3H), 2.28 (s, 3H).	
G73	A4 B30		crude	47	9.71 (d, J = 2.0 Hz, 1H), 8.88 (brm, 1H), 8.81 (d, J = 5.2 Hz, 1H), 8.49 (d, J = 0.8 Hz, 1H), 8.21 (d, J = 4.4 Hz, 1H), 8.18 (dd, J = 2.0 and 5.2 Hz, 1H), 7.02 (d, J = 8.4 Hz, 1H), 6.76 (d, J = 2.0 Hz, 1H), 6.63 (dd, J = 2.0 and 8.4 Hz, 1H), 5.05 (brs, 2H), 2.85 (d, J = 4.8 Hz, 3H), 2.18 (s, 3H).	320.1
G74	A4 B29		N	74	9.75 (d, J = 2.4 Hz, 1H), 8.87 (brd, J = 4.8 Hz, 1H), 8.82 (d, J = 5.2 Hz, 1H), 8.52 (s, 1H), 8.33 (d, J = 2.0 Hz, 1H), 8.19 (dd, J = 4.8, 1.6 Hz, 1H), 7.98 (d, J = 2.4 Hz, 1H), 7.13 (d, J = 2.8 Hz, 1H), 5.29 (brs, 2H), 2.85 (d, J = 4.8 Hz, 3H), 2.36 (s, 3H).	321.0
G75	A6 B30		N	35	10.4 (s, 1H), 9.56 (s, 1H), 8.45 (d, J = 5.1 Hz, 1H), 8.27 (s, 1H), 8.01 (s, 1H), 7.63 (d, J = 5.5 Hz, 1H), 7.02 (d, J = 8.1 Hz, 1H), 6.74 (s, 1H), 6.64 (d, J = 8.2 Hz, 1H), 5.06 (s, 2H), 3.92 (s, 3H), 2.16 (s, 3H).	336.2
G76	A6 E23		N	47	10.3 (s, 1H), 8.85 (s, 1H), 8.42 (d, J = 5.2 Hz, 1H), 7.96 (d, J = 2.4 Hz, 1H), 7.93 (d, J = 5.6 Hz, 1H), 7.09 (d, J = 2.4 Hz, 1H), 7.07 (s, 1H), 5.30 (br s, 2H), 4.62 (t, J = 4.8 Hz, 2H), 4.01 (t, J = 4.4 Hz, 2H), 3.69 (s, 3H), 2.43 (s, 3H), 0.83 (s, 9H), 0.05 (s, 6H).	511.4

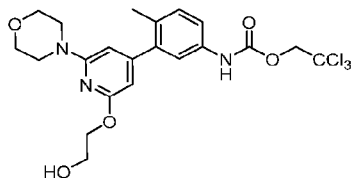
G77	A6 E26		N	48	No Data	513.2
G78	A6 E27		N	78	No Data	531.2
G79	A6 B33		N & K	85	No Data	336.2
G80	A6 B28		N & K	48	10.5 (brs, 1H), 9.60 (s, 1H), 8.45 (d, J = 3.6 Hz, 1H), 8.28 (s, 1H), 8.14 (s, 1H), 7.99 (s, 1H), 7.63 (brm, 1H), 7.12 (s, 1H), 5.32 (br s, 2H), 3.70 (s, 3H), 2.35 (s, 3H).	337.1
G81	C15 		N	84	11.4 (s, 1H), 9.16 (d, J = 2.1 Hz, 1H), 9.00 (d, J = 1.2 Hz, 1H), 8.68 (d, J = 2.0 Hz, 1H), 8.63 (s, 1H), 8.23 (t, J = 2.4 Hz, 1H), 7.00 (d, J = 8.1 Hz, 1H), 6.58 (dd, J = 2.4 and 8.1 Hz, 1H), 6.53 (d, J = 2.4 Hz, 1H), 5.03 (s, 2H), 2.07 (s, 3H), 2.06 (m, 1H), 0.85-0.95 (m, 4H).	346.2
G82	A2 B34		N	35	10.9 (s, 1H), 8.88 (d, J = 1.6 Hz, 1H), 8.59 (d, J = 1.6 Hz, 1H), 8.45 (s, 1H), 8.41 (d, J = 5.2 Hz, 1H), 7.96 (s, 1H), 7.53 (d, J = 4.4 Hz, 1H), 6.99 (d, J = 8.4 Hz, 1H), 6.57 (dd, J = 2.0 and 8.0 Hz, 1H), 6.53 (s, 1H), 5.00 (s, 2H), 2.08 (s, 3H), 2.03 (m, 1H), 0.81-	345.3

					0.86 (m, 4H).	
G83	C16 		N	42	9.01-9.23 (m, 2H), 8.88 (s, 1H), 8.66 (s, 1H), 8.32 (s, 1H), 8.19- 8.24 (m, 1H), 6.99 (d, J = 8.4 Hz, 1H), 8.57 (d, J = 7.2 Hz, 1H), 6.54 (s, 1H), 4.99 (brs, 2H), 3.71 (s, 3H), 2.09 (s, 3H).	336.0
G84	C17 		N	26	10.5 (s, 1H), 9.16 (d, J = 1.6 Hz, 1H), 8.90 (s, 1H), 8.66 (d, J = 2.0 Hz, 1H), 8.35 (s, 1H), 8.24 (t, J = 2.0 Hz, 1H), 7.00 (d, J = 8.0 Hz, 1H), 6.57 (dd, J = 2.4 and 8.0 Hz, 1H), 6.53 (d, J = 2.0 Hz, 1H), 5.02 (s, 2H), 2.09 (s, 3H), 1.48 (s, 9H).	378.1
G85	A6 B35		N & K	15	10.4 (s, 1H), 9.51 (d, J = 2.0 Hz, 1H), 8.47 (d, J = 5.2 Hz, 1H), 8.27 (d, J = 1.6 Hz, 2H), 7.65 (d, J = 1.6 Hz, 1H), 7.49 (s, 1H), 7.34 (d, J = 7.6 Hz, 1H), 7.22 (t, J = 8.0 Hz, 1H), 6.76 (t, J = 1.2 Hz, 1H), 5.32 (s, 2H), 3.71 (s, 3H).	322.2
G86	A6 B34		N	60	10.4 (s, 1H), 8.89 (d, J = 5.0 Hz, 1H), 8.61 (d, J = 2.0 Hz, 1H), 8.53 (d, J = 4.0 Hz, 1H), 8.18 (s, 1H), 7.99 (s, 1H), 7.50 (m, 1H), 6.95 (d, J = 8.0 Hz, 1H), 6.56 (s, 2H), 5.02 (s, 2H), 3.69 (s, 3H), 2.11 (s, 3H).	335.1
G87	C14 		N & K	crude	No Data	336.0
G88	A4 B36		N	36	No Data	337.2

G89	A4 B11		N	84	No Data	319.2
G90	C15 		N	39	No Data	364.2
G91	C18 		N	97	9.40 (s, 1H), 9.37 (d, J = 2.1 Hz, 1H), 9.06 (q, J = 4.9 Hz, 1H), 8.70 (d, J = 2.1 Hz, 1H), 8.62 (s, 1H), 8.51 (m, 1H), 6.99 (d, J = 8.0 Hz, 1H), 6.53-6.60 (m, 2H), 5.02 (s, 2H), 2.86 (d, J = 4.8 Hz, 3H), 2.10 (s, 3H).	320.2
G92	C19 		N	64	No Data	350.2
G93	A6 E3		N	70	10.3 (s, 1H), 8.56 (s, 1H), 8.35 (d, J = 5.6 Hz, 1H), 7.72 (dd, J = 1.2 and 5.6 Hz, 1H), 7.48 (s, 1H), 6.97 (d, J = 8.4 Hz, 1H), 6.75 (s, 1H), 6.57 (dd, J = 2.4 and 8.4 Hz, 1H), 6.51 (d, J = 2.0 Hz, 1H), 5.03 (s, 2H), 4.51 (t, J = 4.4 Hz, 2H), 4.01 (t, J = 8.4 Hz, 2H), 3.69 (s, 3H), 2.09 (s, 3H), 0.84 (s, 9H), 0.05 (s, 6H).	509.2
G94	A4 B34		N	61	9.02 (d, J = 2.1 Hz, 1H), 8.86 (q, J = 4.8 Hz, 1H), 8.74 (d, J = 5.1 Hz, 1H), 8.64 (d, J = 2.0 Hz, 1H), 8.37 (d, J = 1.8 Hz, 1H), 8.17 (t, J = 2.2 Hz, 1H), 8.06 (dd, J = 2.0 and 5.2 Hz, 1H), 7.00 (d, J = 7.9 Hz, 1H), 6.58 (m, 1H), 6.57 (s, 1H), 5.02 (s, 2H), 2.86 (d, J = 4.8 Hz, 3H), 2.12 (s, 3H).	319.2

General Method O: Activation of Amine

[000290] Intermediate **H1**: 2,2,2-trichloroethyl (3-(2-(2-hydroxyethoxy)-6-morpholinopyridin-4-yl)-4-methylphenyl)carbamate



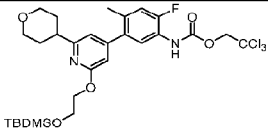
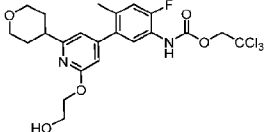
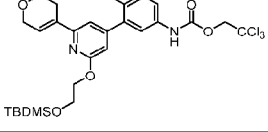
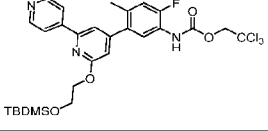
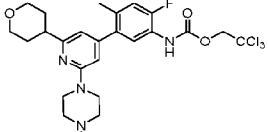
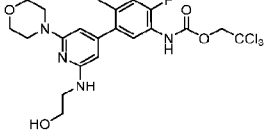
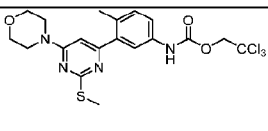
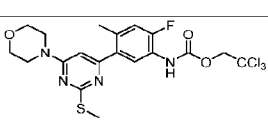
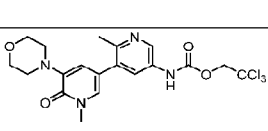
[000291] A solution of 2-((4-(5-amino-2-methylphenyl)-6-morpholinopyridin-2-yl)oxy)ethan-1-ol (**G2**, 0.78 g, 1.5 mmol) in EtOAc (15 mL) was treated with sat'd NaHCO₃ solution (15 mL). 2,2,2-Trichloroethyl chloroformate (0.20 mL, 1.5 mmol) was then added dropwise and the reaction mixture was stirred vigorously at rt for 2 h. The organic layer was separated and the aqueous layer was extracted with DCM (3x). The combined organics were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to afford a yellow oil. The yellow oil was purified using silica gel column chromatography (0 to 30% EtOAc/hexanes) to afford 2,2,2-trichloroethyl (3-(2-(2-hydroxyethoxy)-6-morpholinopyridin-4-yl)-4-methylphenyl)carbamate (0.55 g, 72%) as a white foam. ¹H NMR (500 MHz, DMSO-d₆): δ 10.1 (s, 1H), 7.42 (d, J = 8.2 Hz, 1H), 7.34 (s, 1H), 7.21 (d, J = 8.3 Hz, 1H), 6.19 (s, 1H), 5.97 (s, 1H), 4.92 (s, 2H), 4.78 (brs, 1H), 4.23 (t, J = 5.3 Hz, 2H), 3.68 (t, J = 4.8 Hz, 6H), 3.43 (t, J = 4.7 Hz, 4H), 2.16 (s, 3H).

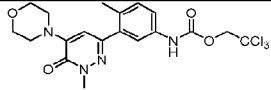
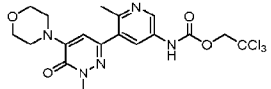
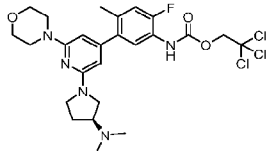
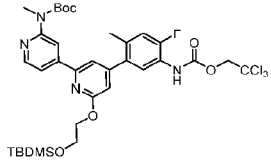
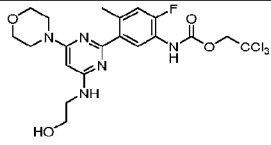
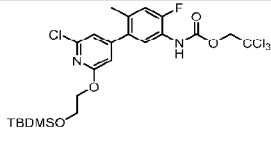
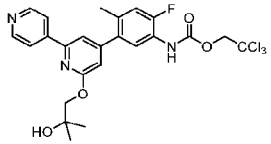
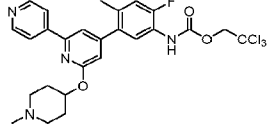
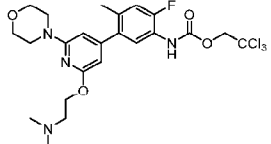
[000292] Using the General Method O above, the following Intermediates of Table H were prepared.

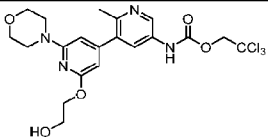
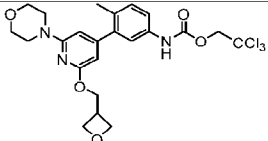
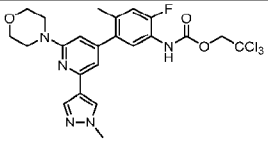
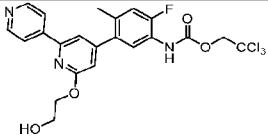
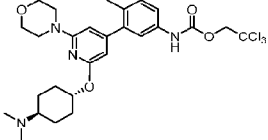
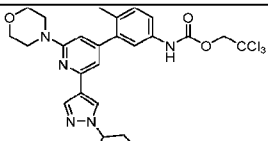
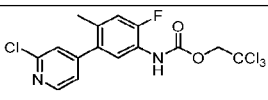
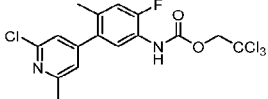
Table H.

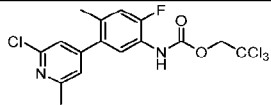
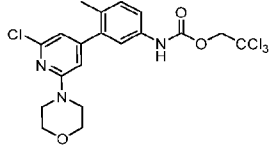
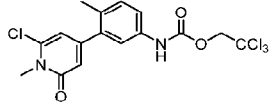
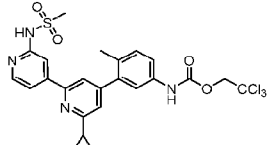
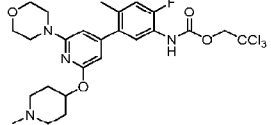
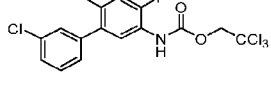
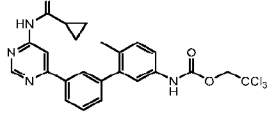
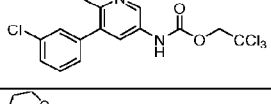
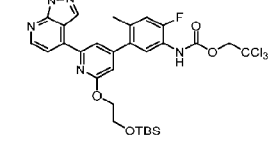
Exp No	SM	Product	Yield (%)	¹ H NMR (400 or 500 MHz, DMSO-d ₆): δ	MS (m/z: M+H ⁺)
H2	F1		98	No Data	444.0
H3	F2		82	10.4 (brs, 1H), 8.61 (s, 1H), 8.20 (d, J = 4.8 Hz, 1H), 6.80 (m, 2H), 6.70 (d, J = 4.8 Hz, 1H), 4.96 (s, 2H), 3.69 (m, 4H), 3.50 (m, 4H), 2.37 (s, 3H).	444.9
H4	E2		crude	No Data	480.0

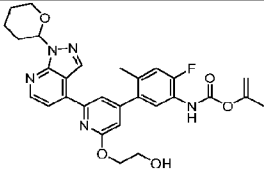
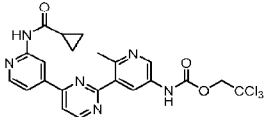
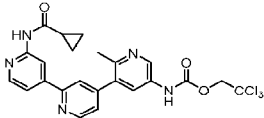
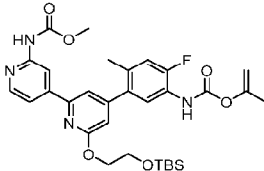
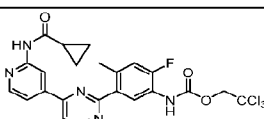
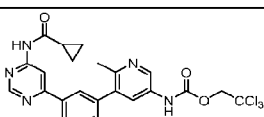
H5	G13		crude	10.1 (s, 1H), 7.41 (d, J = 8.4 Hz, 1H), 7.32 (s, 1H), 7.19 (d, J = 8.3 Hz, 1H), 5.99 (s, 2H), 4.91 (s, 2H), 3.66 (t, J = 4.6 Hz, 8H), 3.39 (t, J = 4.7 Hz, 8H), 2.17 (s, 3H).	529.0
H6	G3		93	No Data	547.2
H7	G1		87	10.1 (brs, 1H), 7.39 (d, J = 8.2 Hz, 1H), 7.30 (s, 1H), 7.17 (d, J = 8.4 Hz, 1H), 6.16 (s, 1H), 5.91 (s, 1H), 4.88 (s, 2H), 4.25 (t, J = 5.0 Hz, 2H), 3.86 (t, J = 5.0 Hz, 2H), 3.64 (t, J = 4.7 Hz, 4H), 3.40 (t, J = 4.7 Hz, 4H), 2.12 (s, 3H), 0.81 (s, 9H), 0.01 (s, 6H).	618.2
H8	G11		crude	No Data	661.2
H9	G4		89	No Data	524.0
H10	G14		92	No Data	530.0
H11	G8		73	No Data	636.2
H12	G9		51	7.34 (d, J = 8.0 Hz, 1H), 7.21 (d, J = 11.6 Hz, 1H), 6.20 (s, 1H), 5.97 (s, 1H), 4.91 (s, 2H), 4.79 (t, J = 5.5 Hz, 1H), 4.23 (t, J = 5.3 Hz, 2H), 3.68 (m, 6H), 3.43 (m, 4H), 2.20 (s, 3H).	522.0
H13	G15		92	No Data	635.2

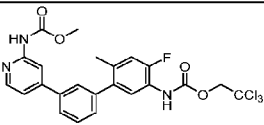
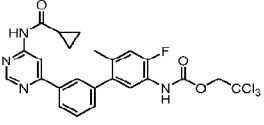
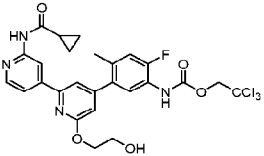
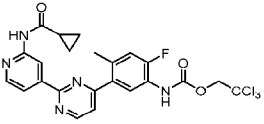
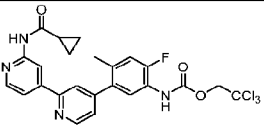
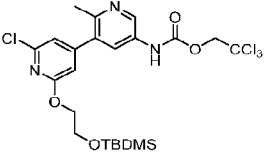
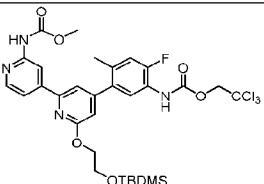
H14	G16		32	7.38 (d, J = 7.9 Hz, 1H), 7.24 (d, J = 11.6 Hz, 1H), 6.82 (m, 1H), 6.53 (d, J = 1.2 Hz, 1H), 4.91 (s, 2H), 4.37 (t, J = 5.0 Hz, 2H), 3.90-4.02 (m, 5H), 3.38-3.48 (m, 2H), 2.83-2.91 (m, 1H), 2.20 (s, 3H), 1.76 (m, 4H), 0.83 (s, 9H), 0.26 (s, 6H).	635.2 637.2
H15	G16		13	7.39 (brm, 1H), 7.24 (d, J = 11.6 Hz, 1H), 6.79 (s, 1H), 6.55 (d, J = 1.2 Hz, 1H), 4.91 (s, 2H), 4.82 (t, J = 5.5 Hz, 1H), 4.31 (t, J = 5.2 Hz, 2H), 3.93 (m, 2H), 3.72 (m, 2H), 3.42 (m, 2H), 2.86 (m, 1H), 2.21 (s, 3H), 1.77 (m, 4H).	521.0
H16	G5		77	No Data	615.2
H17	G12		crude	No Data	628.2 630.2
H18	G18		41	9.88 (brs, 1H), 7.34 (d, J = 7.9 Hz, 1H), 7.22 (d, J = 11.6 Hz, 1H), 6.52 (s, 1H), 6.46 (s, 1H), 4.91 (s, 2H), 3.91 (m, 2H), 3.51 (m, 4H), 3.40 (m, 2H), 2.73-2.81 (m, 1H), 2.40 (brm, 4H), 2.21 (s, 3H), 2.20 (s, 3H), 1.69-1.77 (m, 4H).	559.2
H19	G10		36	No Data	521.0
H20	F3		66	No Data	491.0
H21	F4		crude	No Data	509.0 511.0
H22	E15		crude	No Data	457.0

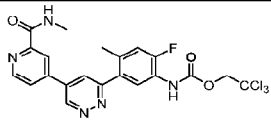
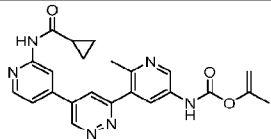
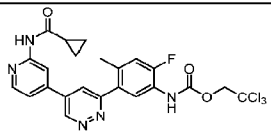
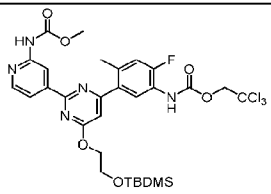
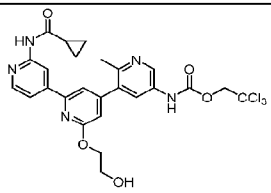
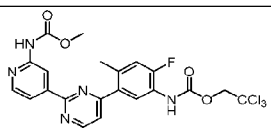
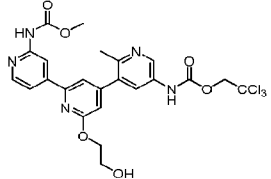
H23	E16		68	No Data	475.0 477.0
H24	E17		crude	No Data	476.2
H25	G20		99	No Data	574.2 576.2
H26	G23		93	9.95 (brs, 1H), 8.45 (m, 1H), 8.26 (d, J = 7.5 Hz, 1H), 7.85 (m, 1H), 7.65 (m, 1H), 7.49 (s, 1H), 7.29 (m, 1H), 6.85 (m, 1H), 4.91 (s, 2H), 4.51 (m, 1H), 4.45 (m, 1H), 4.02 (s, 3H), 3.98 (m, 1H), 3.78 (m, 1H), 1.44 (s, 9H), 0.83 (s, 9H), 0.03 (s, 6H).	643.2 (loss of TBDMS)
H27	G22		30	No Data	522.0 524.0
H28	E9		92	9.93 (s, 1H), 7.43 (d, J = 7.9 Hz, 1H), 7.26 (d, J = 11.5 Hz, 1H), 7.06 (d, J = 1.1 Hz, 1H), 6.77 (d, J = 1.1 Hz, 1H), 4.91 (s, 2H), 4.85 (s, 1H), 4.24-4.31 (m, 2H), 3.71 (t, J = 5.0 Hz, 2H), 2.22 (s, 3H).	587.0
H29	G24		96	No Data	542.2 544.2
H30	G25		89	No Data	567.2 569.2
H31	G26		21	9.88 (brs, 1H), 7.34 (d, J = 8.1 Hz, 1H), 7.22 (d, J = 11.6 Hz, 1H), 6.20 (s, 1H), 5.96 (s, 1H), 4.91 (s, 2H), 4.30 (t, J = 6.0 Hz, 2H), 3.68 (t, J = 4.7 Hz, 4H), 3.44 (t, J = 4.7 Hz, 4H), 2.58 (m, 2H), 2.20 (s, 3H).	549.0 551.0

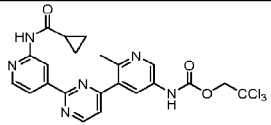
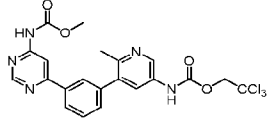
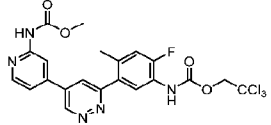
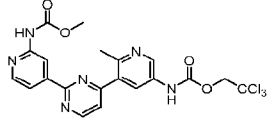
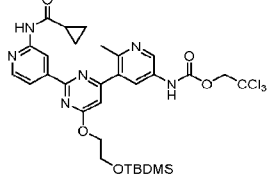
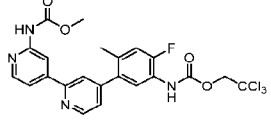
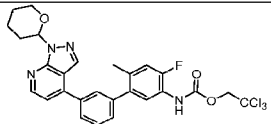
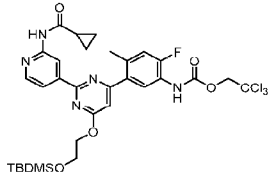
				2.19 (s, 6H).	
H32	G6		crude	No Data	505.0 507.0
H33	G27		67	10.1 (s, 1H), 7.41 (m, 1H), 7.35 (brs, 1H), 7.22 (d, J = 8.0 Hz, 1H), 6.22 (s, 1H), 5.98 (s, 1H), 4.92 (s, 2H), 4.69 (m, 2H), 4.46 (m, 2H), 4.41 (m, 2H), 3.69 (m, 4H), 3.46 (m, 4H), 3.35 (m, 1H), 2.16 (s, 3H).	532.0 534.0
H34	G30		crude	9.90 (brs, 1H), 8.25 (s, 1H), 7.97 (s, 1H), 7.51 (brs, 1H), 7.25 (d, J = 11.6 Hz, 1H), 6.92 (s, 1H), 6.52 (s, 1H), 4.91 (s, 2H), 3.86 (s, 3H), 3.72 (brm, 4H), 3.53 (brm, 4H), 2.24 (s, 3H).	542.0 544.0
H35	G31		88	No Data	514.0 516.0
H36	G33		crude	No Data	585.4 587.4
H37	G34		95	10.1 (brs, 1H), 8.36 (s, 1H), 7.98 (s, 1H), 7.44 (brs, 1H), 7.38 (brs, 1H), 7.23 (m, 1H), 6.97 (s, 1H), 6.48 (s, 1H), 4.93 (brs, 2H), 4.36 (m, 1H), 4.02 (brs, 2H), 3.72 (brs, 4H), 3.52 (brs, 4H), 2.90 (brs, 2H), 2.19 (s, 3H), 2.01 (m, 2H), 1.79 (m, 2H), 1.41 (s, 9H).	695.0
H38	B12		crude	No Data	413.0
H39	E20		crude	No Data	453.0

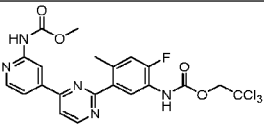
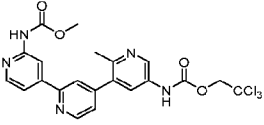
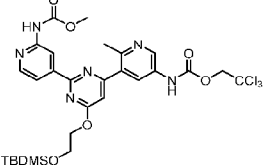
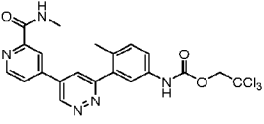
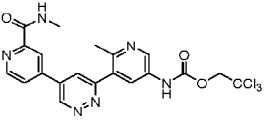
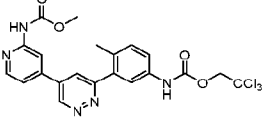
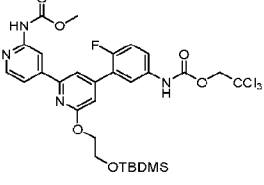
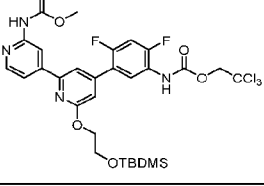
H40	B18		crude	No Data	427.0
H41	E7		crude	No Data	480.0
H42	B14		93	No Data	422.8
H43	G38		88	No Data	570.8
H44	G43		crude	No Data	575.2
H45	B17		crude	No Data	412.0
H46	G44		86	11.3 (s, 1H), 10.2 (brs, 1H), 8.95 (s, 1H), 8.60 (s, 1H), 8.05 (brd, J = 7.6 Hz, 1H), 7.94 (brs, 1H), 7.62 (t, J = 7.6 Hz, 1H), 7.52 (brd, J = 7.6 Hz, 1H), 7.44 (brm, 2H), 7.27 (d, J = 8.0 Hz, 1H), 4.86 (s, 2H), 2.18 (s, 3H), 2.02-2.14 (m, 1H), 0.86-0.93 (m, 4H).	519.0
H47	B21		95	No Data	395.0
H48	G45		84	9.94 (s, 1H), 8.77 (s, 1H), 8.65 (d, J = 4.9 Hz, 1H), 7.92 (d, J = 5.0 Hz, 1H), 7.81 (d, J = 1.2 Hz, 1H), 7.52 (d, J = 7.9 Hz, 1H), 7.30 (d, J = 11.5 Hz, 1H), 6.89 (d, J = 1.1 Hz, 1H), 6.10 (dd, J = 2.5 and 10.3 Hz, 1H), 4.92 (s, 2H), 4.53-4.66 (m, 2H), 3.89-3.99 (m, 1H), 3.67-3.75	754.2

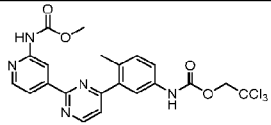
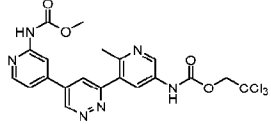
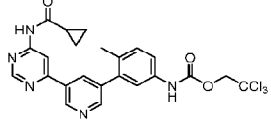
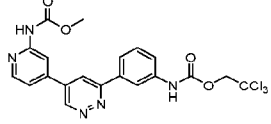
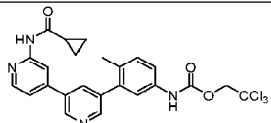
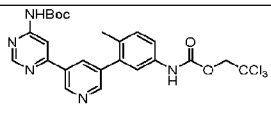
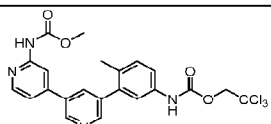
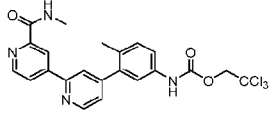
				(m, 1H), 2.54 (m, 1H), 2.29 (s, 3H), 2.02-2.12 (m, 1H), 1.98 (s, 2H), 1.95 (m, 1H), 1.71 (m, 1H), 1.57-1.65 (m, 2H), 0.83 (s, 9H), 0.05 (s, 6H).	
H49	G45a		95	9.69 (brs, 1H), 8.78 (s, 1H), 8.65 (d, J = 4.9 Hz, 1H), 7.93 (d, J = 4.9 Hz, 1H), 7.82 (d, J = 1.2 Hz, 1H), 7.60 (s, 1H), 7.29 (d, J = 11.7 Hz, 1H), 6.92 (d, J = 1.1 Hz, 1H), 6.10 (dd, J = 2.5 and 10.4 Hz, 1H), 4.91 (t, J = 5.5 Hz, 1H), 4.68-4.74 (m, 2H), 4.53 (m, 2H), 3.96 (m, 1H), 3.83 (m, 2H), 3.71 (m, 1H), 2.50-2.59 (m, 1H), 2.29 (s, 3H), 2.06 (m, 1H), 1.94 (m, 1H), 1.91 (s, 3H), 1.74-1.86 (m, 1H), 1.60 (m, 2H).	548.2
H50	G50		crude	No Data	521.2
H51	G48		71	No Data	520.0
H52	G47		71	No Data	611.2
H53	G49		70	11.0 (s, 1H), 9.93 (brs, 1H), 9.08 (d, J = 5.2 Hz, 1H), 8.93 (s, 1H), 8.52 (d, J = 5.2 Hz, 1H), 8.03 (d, J = 5.6 Hz, 1H), 7.85 (d, J = 6.0 Hz, 1H), 7.32 (d, J = 11.6 Hz, 1H), 6.81 (t, J = 6.8 Hz, 1H), 4.93 (s, 2H), 2.60 (s, 3H), 2.08 (m, 1H), 0.82-0.87 (m, 4H).	540.2
H54	G51		crude	11.3 (s, 1H), 10.4 (s, 1H), 8.96 (s, 1H), 8.61 (m, 1H), 8.08 (d, J = 7.6 Hz, 1H), 8.01 (s, 1H), 7.81 (brs, 1H), 7.66 (t, J = 7.6 Hz, 1H), 7.58 (d, J = 8.0 Hz, 1H), 6.81 (t, J = 6.4 Hz, 1H), 4.95 (s, 2H), 2.39 (s, 3H), 2.08 (m, 1H), 0.85-0.90 (m, 4H).	520.1

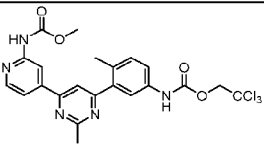
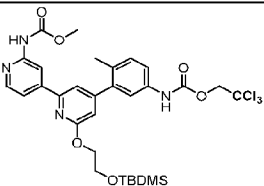
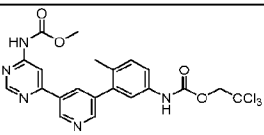
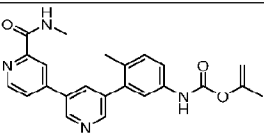
H55	G46		67	No Data	526.0
H56	G52		crude	11.3 (s, 1H), 8.90 (d, J = 1.2 Hz, 1H), 8.55 (d, J = 1.3 Hz, 1H), 8.00 (q, J = 1.6 Hz, 1H), 7.89 (t, J = 1.8 Hz, 1H), 7.57 (t, J = 7.7 Hz, 1H), 7.47 (dt, J = 1.5 and 7.6 Hz, 1H), 7.38 (dd, J = 4.5 and 8.0 Hz, 1H), 7.21 (d, J = 11.6 Hz, 1H), 6.76 (t, J = 6.9 Hz, 1H), 4.87 (s, 2H), 2.17 (s, 3H), 2.02 (m, 1H), 0.84 (m, 4H).	539.0
H57	G53		88	10.9 (s, 1H), 8.76 (s, 1H), 8.39 (d, J = 5.2 Hz, 1H), 7.76 (m, 2H), 7.49 (m, 1H), 7.45 (s, 1H), 7.29 (d, J = 11.6 Hz, 1H), 6.86 (m, 1H), 4.92 (s, 2H), 4.88 (s, 1H), 4.43 (t, J = 4.8 Hz, 2H), 3.78 (m, 2H), 2.25 (s, 3H), 1.98 (m, 1H), 0.78-0.90 (m, 4H).	597.0
H58	G54		crude	10.9 (s, 1H), 10.0 (s, 1H), 9.10 (s, 1H), 9.03 (d, J = 5.2 Hz, 1H), 8.48 (d, J = 5.2 Hz, 1H), 7.98 (dd, J = 1.2 and 4.8 Hz, 1H), 7.79 (t, J = 8.8 Hz, 1H), 7.72 (d, J = 5.2 Hz, 1H), 6.80 (t, J = 6.8 Hz, 1H), 4.93 (s, 2H), 2.49 (s, 3H), 2.03 (m, 1H), 0.80-0.85 (m, 4H).	537.9
H59	G56		83	No Data	536.8
H60	E22		crude	No Data	570.0
H61	G47		crude	10.3 (brs, 1H), 9.93 (brs, 1H), 8.56 (brs, 1H), 8.35 (d, J = 5.2 Hz, 1H), 7.72 (d, J = 5.2 Hz, 1H), 7.54 (br s, 1H), 7.47 (d, J = 7.6 Hz, 1H), 7.29 (d, J = 11.6 Hz, 1H), 6.83 (brs, 1H), 4.92 (brs, 2H), 4.51 (t, J = 4.8 Hz, 2H), 4.01 (t, J = 2 Hz, 2H), 3.69 (brs, 3H), 2.25 (brs, 3H), 0.84 (s,	701.1

				9H), 0.05 (s, 6H).	
H62	G58		78	No Data	512.2
H63	G59		crude	No Data	449.2 (M + H + 18)
H64	G60		crude	No data	538.0 540.0
H65	G68		94	10.34 (s, 1H), 9.95 (br s, 1H), 9.20 (s, 1H), 8.43 (d, J = 5.2 Hz, 1H), 7.92 (d, J = 4.4 Hz, 1H), 7.77 (d, J = 3.2 Hz, 1H), 7.33 (d, J = 11.6 Hz, 1H), 7.18 (s, 1H), 4.93 (s, 2H), 4.63 (t, J = 4.8 Hz, 2H), 4.01 (t, J = 4.4 Hz, 2H), 3.69 (s, 3H), 2.43 (s, 3H), 0.82 (s, 9H), 0.05 (s, 6H).	702.01
H66	G61		62	10.88 (s, 1H), 8.78 (s, 1H), 8.66 (s, 1H), 8.41 (d, J = 4.8 Hz, 1H), 7.81 (dd, J = 14.0, 10.0 Hz, 2H), 7.50 (m, 2H), 6.94 (s, 1H), 4.97 (s, 2H), 4.90 (t, J = 6.4 Hz, 1H), 4.45 (t, J = 4.8 Hz, 2H), 3.79 (t, J = 4.4 Hz, 2H), 2.04 (m, 1H), 0.79-0.86 (m, 4H). 3Hs are under solvent.	580.0
H67	G62		69	10.37 (s, 1H), 10.20 (s, 1H), 9.05 (d, J = 5.2 Hz, 1H), 8.88 (s, 1H), 8.44 (d, J = 4.8 Hz, 1H), 7.96 (d, J = 4.8 Hz, 1H), 7.80 (d, J = 8.4 Hz, 1H), 7.74 (d, J = 5.2 Hz, 1H), 7.37 (d, J = 11.2 Hz, 1H), 4.93 (s, 2H), 3.70 (s, 3H), 2.45 (s, 3H).	528.0
H68	G67		crude	No data	570.0 572.0

H69	G55		90	11.03 (s, 1H), 10.52 (s, 1H), 9.13 (d, J = 5.2 Hz, 1H), 8.95 (s, 1H), 8.70 (s, 1H), 8.54 (d, J = 4.4 Hz, 2H), 8.10 (d, J = 5.2 Hz, 1H), 7.88 (d, J = 4.4 Hz, 1H), 4.25 (s, 2H), 2.74 (s, 3H), 2.04 (m, 1H), 0.83 (m, 4H).	521.0
H70	G63		90	10.89 (s, 1H), 8.90 (s, 1H), 8.63 (s, 1H), 8.38 (s, 1H), 8.10 (s, 1H), 8.03 (s, 1H), 7.83 (s, 1H), 7.61 (d, J = 6.4 Hz, 1H), 6.83 (t, J = 6.8 Hz, 1H), 4.96 (s, 2H), 3.70 (s, 3H), 3.39 (s, 3H). NH missing.	511.1
H71	G64		crude	No Data	528.0
H72	G65		61	No Data	510.8
H73	G66		82	10.92 (s, 1H), 10.49 (s, 1H), 9.06 (s, 1H), 8.70 (s, 1H), 8.48 (d, J = 5.2 Hz, 1H), 8.11 (s, 1H), 7.97 (d, J = 5.2 Hz, 1H), 7.17 (s, 1H), 4.97 (s, 2H), 4.00-4.05 (m, 2H), 3.32 (s, 3H), 2.50 (m, 2H), 2.03 (m, 1H), 0.83 (m, 4H), 0.82 (s, 9H), 0.04 (s, 6H).	695.1
H74	G57		85	10.37 (s, 1H), 10.02 (s, 1H), 8.79 (d, J = 5.2 Hz, 1H), 8.60 (s, 1H), 8.37 (d, J = 5.6 Hz, 1H), 7.95 (s, 1H), 7.76 (d, J = 6.0 Hz, 1H), 7.49 (d, J = 4.0 Hz, 2H), 7.32 (d, J = 12.0 Hz, 1H), 4.92 (s, 2H), 3.69 (s, 3H), 2.27 (s, 3H).	527.1
H75	G19		crude	No Data	577.2
H76	G71		89	10.9 (s, 1H), 9.96 (brs, 1H), 9.04 (s, 1H), 8.46 (d, J = 5.2 Hz, 1H), 7.95 (d, J = 5.2 Hz, 1H), 7.69 (d, J = 8.0 Hz, 1H), 7.29 (d, J = 11.6 Hz, 1H), 7.06 (s, 1H), 4.93 (s, 2H), 4.62 (t, J = 4.4 Hz, 2H), 4.01 (t, J = 4.4 Hz, 2H), 2.41 (s, 3H), 2.03 (m, 1H),	712.0

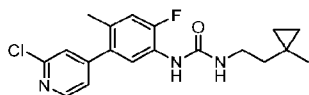
				0.85 (s, 9H), 0.80-0.85 (m, 4H), 0.04 (s, 6H).	
H77	G70		crude	No Data	528.0 530.0
H78	G72		91	No Data	510.0 512.0
H79	G76		81	No Data	685.0
H80	G73		50	10.2 (s, 1H), 9.76 (d, J = 2.2 Hz, 1H), 8.87 (q, J = 4.7 Hz, 1H), 8.82 (d, J = 5.4 Hz, 1H), 8.57 (m, 1H), 8.31 (d, J = 2.2 Hz, 1H), 8.19 (dd, J = 1.9 and 5.1 Hz, 1H), 7.69 (m, 1H), 7.56 (m, 1H), 7.34 (d, J = 8.4 Hz, 1H), 4.94 (s, 2H), 2.85 (d, J = 4.8 Hz, 3H), 2.29 (s, 3H).	494.0 496.0
H81	G74		64	No Data	495.2 497.2
H82	G75		38	No Data	510.0 512.0
H83	G77		crude	No Data	687.0 689.0
H84	G78		77	No Data	705.0 707.0

H85	G79		16	No Data	510.0 512.0
H86	G80		JCL	No Data	510.7 512.7
H87	G81		75	No Data	520.0 522.0
H88	G85		87	10.5 (s, 1H), 10.4 (s, 1H), 9.51 (m, 2H), 8.47 (d, J = 4.0 Hz, 1H), 8.39 (s, 1H), 8.29 (s, 1H), 7.90 (d, J = 8.8 Hz, 1H), 7.69 (dd, J = 8.0 and 16.8 Hz, 2H), 7.66 (t, J = 4.0 Hz, 1H), 4.98 (s, 2H), 3.72 (s, 3H).	495.8 497.8
H89	G82		67	11.0 (s, 1H), 10.2 (brs, 1H), 8.92 (s, 1H), 8.64 (d, J = 2.0 Hz, 1H), 8.45 (d, J = 2.0 Hz, 1H), 8.42 (d, J = 5.2 Hz, 1H), 8.03 (t, J = 2.4 Hz, 1H), 7.79 (m, 1H), 7.53 (dd, J = 1.6 and 5.2 Hz, 1H), 7.45 (brs, 1H), 7.31 (d, J = 8.4 Hz, 1H), 4.92 (s, 2H), 2.21 (s, 3H), 2.05 (m, 1H), 0.80-0.85 (m, 4H).	519.1 521.1
H90	G84		51	10.4 (brs, 2H), 9.21 (d, J = 2.4 Hz, 1H), 8.90 (d, J = 0.8 Hz, 1H), 8.72 (d, J = 2.4 Hz, 1H), 8.35 (d, J = 1.2 Hz, 1H), 8.29 (t, J = 2.0 Hz, 1H), 7.48 (brs, 2H), 7.32 (d, J = 8.4 Hz, 1H), 4.93 (s, 2H), 2.21 (s, 3H), 1.50 (s, 9H).	551.8 553.8
H91	G86		82	10.4 (s, 1H), 10.2 (brs, 1H), 8.93 (d, J = 2.4 Hz, 1H), 8.65 (d, J = 2.0 Hz, 1H), 8.38 (d, J = 5.2 Hz, 1H), 8.19 (s, 1H), 8.06 (t, J = 2.0 Hz, 1H), 7.50 (m, 2H), 7.47 (s, 1H), 7.32 (d, J = 7.4 Hz, 1H), 4.94 (s, 2H), 3.69 (s, 3H), 2.27 (s, 3H).	508.9 510.9
H92	G89		crude	No Data	493.0 495.0

H93	G92		35	10.2 (s, 1H), 8.66 (d, J = 8.0 Hz, 1H), 7.91 (s, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.39 (s, 1H), 7.00 (d, J = 7.6 Hz, 1H), 6.77 (d, J = 2.4 Hz, 1H), 6.62 (d, J = 8.0 Hz, 1H), 5.06 (s, 2H), 4.94 (s, 2H), 3.71 (s, 3H), 2.72 (s, 3H), 2.32 (s, 3H).	524.0 526.0
H94	G93		46	10.3 (s, 1H), 8.35 (d, J = 5.2 Hz, 1H), 7.65 (m, 1H), 7.73 (dd, J = 1.6 and 5.6 Hz, 1H), 7.54 (d, J = 0.8 Hz, 1H), 7.44 (s, 1H), 7.38 (m, 2H), 7.29 (d, J = 8.0 Hz, 1H), 6.81 (s, 1H), 4.91 (s, 2H), 4.52 (t, J = 4.4 Hz, 2H), 4.01 (t, J = 4.4 Hz, 2H), 3.69 (s, 3H), 2.21 (s, 3H), 0.81 (s, 9H), 0.05 (s, 6H).	No Data
H95	G83		55	11.0 (s, 1H), 10.2 (s, 1H), 9.21 (s, 1H), 8.94 (s, 1H), 8.73 (s, 1H), 8.41 (s, 1H), 8.31 (s, 1H), 7.49 (brs, 2H), 7.32 (d, J = 8.4 Hz, 1H), 4.94 (s, 2H), 3.74 (s, 3H), 2.22 (s, 3H).	510.0
H96	G94		42	9.97 (s, 1H), 9.07 (t, J = 2.0 Hz, 1H), 8.86 (q, J = 4.8 Hz, 1H), 8.75 (d, J = 5.2 Hz, 1H), 8.68 (brs, 1H), 8.38 (brs, 1H), 8.25 (br m, 1H), 8.07 (brd, J = 5.2 Hz, 1H), 7.42-7.50 (m, 2H), 7.31 (d, J = 8.0 Hz, 1H), 4.75 (s, 1H), 4.73 (s, 1H), 2.86 (d, J = 4.8 Hz, 3H), 2.23 (s, 3H), 1.94 (s, 3H).	403.2

General Method P: Coupling Reaction

[000293] Example 11: 1-(5-(2-chloropyridin-4-yl)-2-fluoro-4-methylphenyl)-3-(2-(1-methylcyclopropyl)ethyl)urea

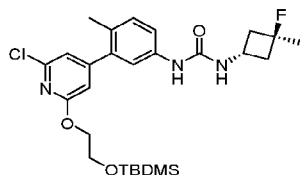


[000294] A solution of 2,2,2-trichloroethyl (5-(2-chloropyridin-4-yl)-2-fluoro-4-methylphenyl)carbamate (**H38**, 0.30 g, 0.73 mmol) and DIEA (0.57 mL, 3.3 mmol) in DMSO (7 mL) was treated with 2-(1-methylcyclopropyl)ethan-1-amine hydrochloride (0.16 g, 1.2 mmol). The reaction was stirred at 80 °C 2.5 h and RT overnight. The reaction was diluted with DCM (30 mL), filtered through a pad of celite, and washed with DCM (20 mL). The filtrate was treated with sat'd NaHCO₃ (50 mL) and the organic layer was extracted with

DCM (2x). The combined organics were dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The crude was purified by silica gel column chromatography (0 to 50% EtOAc/hexanes) to afford 1-(5-(2-chloropyridin-4-yl)-2-fluoro-4-methylphenyl)-3-(2-(1-methylcyclopropyl)ethyl)urea (0.16 g, 59%) as a white solid. ^1H NMR (500 MHz, DMSO): δ 8.45 (d, J = 5.1 Hz, 1H), 8.34 (s, 1H), 8.05 (d, J = 8.6 Hz, 1H), 7.47 (d, J = 1.4 Hz, 1H), 7.38 (dd, J = 1.5 and 5.1, Hz, 1H), 7.18 (d, J = 12.3 Hz, 1H), 6.51 (t, J = 5.6 Hz, 1H), 3.15 (m, 2 H), 2.16 (s, 3H), 1.35 (t, J = 7.5 Hz, 2H), 1.00 (s, 3H), 0.26 (m, 2 H), 0.20 (m, 2H); MS (ESI) m/z : 362.2 ($\text{M}+\text{H}^+$).

General Method Q: Curtius rearrangement

[000295] Example 12: 1-(3-(2-(2-((tert-butyldimethylsilyl)oxy)ethoxy)-6-chloropyridin-4-yl)-4-methylphenyl)-3-((1r,3r)-3-fluoro-3-methylcyclobutyl)urea

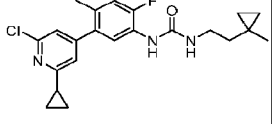
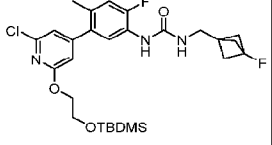
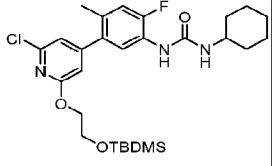
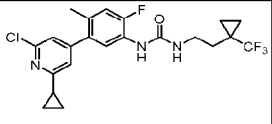
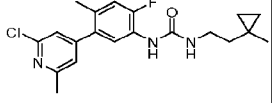
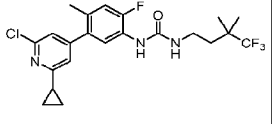


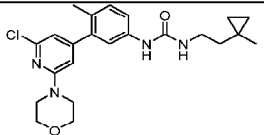
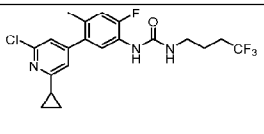
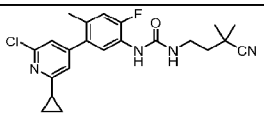
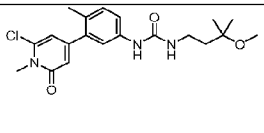
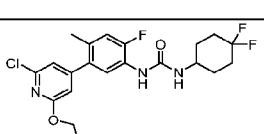
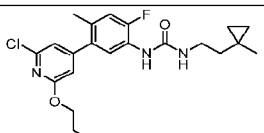
[000296] A mixture of 3-(2-(2-((tert-butyldimethylsilyl)oxy)ethoxy)-6-chloropyridin-4-yl)-4-methylaniline (**E3**, 0.40 g, 1.02 mmol), (1r,3r)-3-fluoro-3-methylcyclobutane-1-carboxylic acid (0.20 g, 1.5 mmol), DIEA (0.71 mL, 4.1 mmol) and diphenyl phosphorazidate (0.57 mL, 2.6 mmol) in 1,4-dioxane (10 mL) was sealed and a needle was placed through the septa and the reaction was then heated to 70 °C for 5 h. The reaction was cooled to rt and was diluted with sat'd NaHCO_3 (aq). The solution was extracted with EtOAc (4x). The combined organics were dried over anhydrous Na_2SO_4 , filtered, and concentrated to dryness to afford a brown oil. The brown oil was purified by silica gel column chromatography (0 to 60% EtOAc/hexanes) to obtain 1-(3-(2-(2-((tert-butyldimethylsilyl)oxy)ethoxy)-6-chloropyridin-4-yl)-4-methylphenyl)-3-((1r,3r)-3-fluoro-3-methylcyclobutyl)urea (0.36 g, 69%) as a yellow solid. MS (ESI) m/z : 522.2 ($\text{M}+\text{H}^+$).

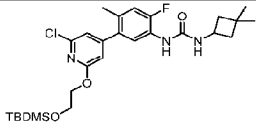
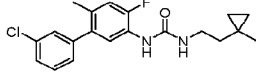
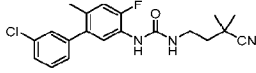
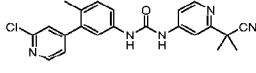
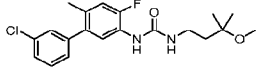
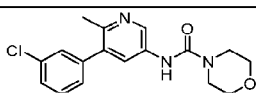
[000297] Using the General Methods P & Q above, the following Intermediates of Table I were prepared.

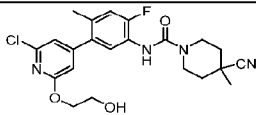
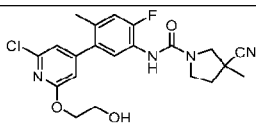
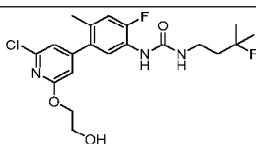
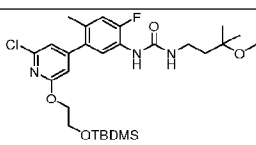
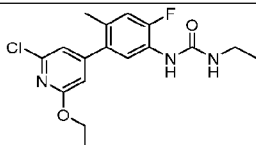
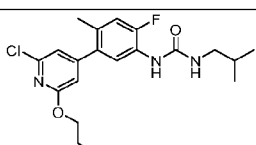
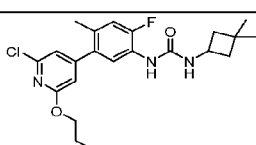
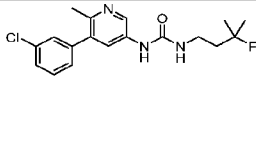
Table I.

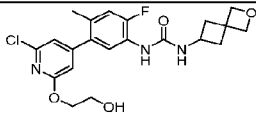
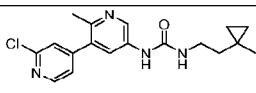
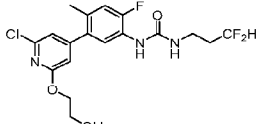
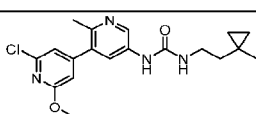
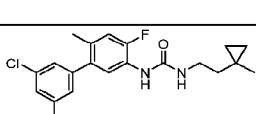
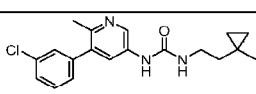
Ex. No	SM	Product	Method	Yield (%)	^1H NMR (400 or 500 MHz, DMSO- d_6): δ	MS (m/z : $\text{M}+\text{H}^+$)
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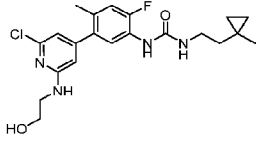
I3	H39 		P	80	No Data	402.2
I4	H28 		P	60	8.34 (s, 1H), 8.00 (d, J = 8.3 Hz, 1H), 7.17 (d, J = 12.3 Hz, 1H), 7.02 (s, 1H), 6.70 (s, 1H), 6.62 (t, J = 5.7 Hz, 1H), 4.35 (t, J = 4.8 Hz, 2H), 3.91 (t, J = 4.8 Hz, 2H), 3.38 (d, J = 5.6 Hz, 2H), 2.15 (s, 3H), 1.92 (d, J = 2.6 Hz, 6H), 0.83 (s, 9H), 0.04 (s, 6H).	552.2
I5	H28 		P	98	8.20 (s, 1H), 8.03 (d, J = 8.3 Hz, 1H), 7.16 (d, J = 12.3 Hz, 1H), 7.02 (s, 1H), 6.70 (s, 1H), 6.57 (d, J = 7.6 Hz, 1H), 4.35 (t, J = 4.8 Hz, 2H), 4.02 (d, J = 6.8 Hz, 1H), 3.91 (t, J = 4.8 Hz, 2H), 2.15 (s, 3H), 1.77 (m, 2H), 1.62 (t, J = 11.7 Hz, 2H), 1.04-1.33 (m, 6H), 0.83 (s, 9H), 0.04 (s, 6H).	536.2
I6	I139 		P	92	8.39 (s, 1H), 8.00 (d, J = 8.4 Hz, 1H), 7.28 (s, 1H), 7.17 (m, 2H), 6.61 (t, J = 5.8 Hz, 1H), 3.18 (q, J = 7.0 Hz, 3H), 2.15 (m, 4H), 1.70 (t, J = 7.7 Hz, 3H), 1.00 (m, 2H), 0.93 (m, 2H), 0.89 (m, 3 9H), 0.75 (s, 2H).	456.2
I7	H40 		P	61	No Data	376.2
I8	H39 		P	81	8.35 (s, 1H), 8.00 (m, 1H), 7.28 (s, 1H), 7.16 (m, 2 H), 6.60 (t, J = 5.8 Hz, 1H), 3.15 (m, 2H), 2.15 (m, 4H), 1.61 (t, J = 8.0 Hz, 2H), 1.10 (s, 6H), 1.00 (m, 2H), 0.93 (m, 2H).	458.2

I9	H41 		P	27	8.44 (s, 1H), 7.28 (d, J = 9.8 Hz, 2H), 7.12 (d, J = 8.1 Hz, 1H), 6.67 (s, 1H), 6.63 (s, 1H), 6.00 (t, J = 5.7 Hz, 1H), 3.67 (t, J = 4.7 Hz, 4H), 3.48 (t, J = 4.7 Hz, 4H), 3.13 (m, 2H), 2.13 (s, 3H), 1.35 (t, J = 7.5 Hz, 2H), 1.01 (s, 3H), 0.26 (m, 2H), 0.20 (m, 2H).	429.2
I10	H39 		P	83	8.32 (s, 1H), 7.99 (d, J = 8.4 Hz, 1H), 7.28 (s, 1H), 7.17 (m, 2H), 6.68 (t, J = 5.8 Hz, 1H), 3.14 (m, 2H), 2.26 (m, 2H), 2.15 (m, 4H), 1.63 (m, 2H), 0.99 (m, 2H), 0.92 (m, 2H).	430.2
I11	H39 		P	90	8.38 (s, 1H), 8.01 (d, J = 8.4 Hz, 1H), 7.28 (s, 1H), 7.17 (m, 2H), 6.67 (t, J = 5.7 Hz, 1H), 3.22 (m, 2H), 2.16 (m, 4H), 1.69 (m, 2H), 1.31 (s, 6H), 1.00 (m, 2H), 0.94 (m, 2H).	415.2
I12	H42 		P	97	8.49 (s, 1H), 7.34 (d, J = 2.0 Hz, 1H), 7.27 (dd, J = 4.0 and 8.0 Hz, 1H), 7.12 (d, J = 8.0 Hz, 1H), 6.8 (t, J = 4.0 Hz, 1H), 6.50 (s, 1H), 6.28 (s, 1H), 3.59 (s, 3H), 3.15 (s, 3H), 3.09 (t, J = 12.0 Hz, 2H), 2.17 (s, 3H), 1.59 (t, J = 8.0 Hz, 2H), 1.20 (s, 6H).	392.4
I13	H28 		P	82	No Data	572.2
I14	H28 		P	77	8.32 (s, 1H), 8.02 (d, J = 8.4 Hz, 1H), 7.16 (d, J = 12.3 Hz, 1H), 7.02 (d, J = 1.0 Hz, 1H), 6.80 (t, J = 6.9 Hz, 1H), 6.70 (s, 1H), 6.50 (t, J = 5.7 Hz, 1H), 4.35 (t, J = 4.9 Hz, 1H), 4.02 (m, 2H), 3.91 (t, J = 4.9 Hz,	536.2

					2H), 3.14 (m, 2H), 2.15 (s, 3H), 1.35 (t, J = 7.5 Hz, 2H), 1.00 (s, 3H), 0.83 (s, 9H), 0.26 (m, 2H), 0.20 (m, 2H), 0.04 (m, 6H).	
I15	E9 		Q	57	No Data	536.2
I16	H45 		P		8.27 (s, 1H), 7.99 (d, J = 8.5 Hz, 1H), 7.43 (m, 2H), 7.32 (t, J = 1.8 Hz, 1H), 7.26 (dt, J = 1.6 and 7.2 Hz, 1H), 7.13 (d, J = 12.4 Hz, 1H), 6.49 (t, J = 5.6 Hz, 1H), 3.14 (m, 2H), 2.13 (s, 3H), 1.34 (t, J = 7.5 Hz, 2H), 1.00 (s, 3H), 0.25 (m, 2H), 0.21 (m, 2H).	361.2
I17	H45 		P	63	8.32 (s, 1H), 7.97 (d, J = 8.5 Hz, 1H), 7.44 (m, 2H), 7.33 (t, J = 1.8 Hz, 1H), 7.26 (dt, J = 1.6 and 7.2 Hz, 1H), 7.14 (d, J = 12.3 Hz, 1H), 6.65 (t, J = 5.8 Hz, 1H), 3.22 (m, 2H), 2.13 (s, 3H), 1.68 (m, 2H), 1.31 (s, 6H).	374.2
I18	B11 		Q	crude	No Data	406.2
I19	H45 		P	68	8.28 (s, 1H), 7.98 (d, J = 8.5 Hz, 1H), 7.43 (m, 2H), 7.32 (t, J = 1.8 Hz, 1H), 7.26 (dt, J = 1.6 and 7.2 Hz, 1H), 7.12 (d, J = 12.3 Hz, 1H), 6.50 (t, J = 5.6 Hz, 1H), 3.09 (m, 2H), 3.05 (s, 3H), 2.12 (s, 3H), 1.57 (m, 2H), 1.08 (s, 6H).	No Data
I20	H47 		P	61	No Data	332.2

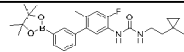
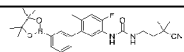
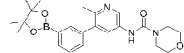
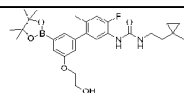
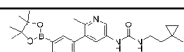
I21	H28 		P	crude	No Data	447.2
I22	H28 		P	crude	No Data	433.2
I23	II28 		P	58	No Data	428.2
I24	H28 		P	58	No Data	554.2
I25	H28 		P	62	No Data	368.2
I26	H28 		P	64	No Data	396.2
I27	I15 		Deprotection with TBAF	Crude	No Data	422.2
I28	H47 		P	crude	8.75 (s, 1H), 8.41 (d, J = 2.5 Hz, 1H), 7.79 (d, J = 2.5 Hz, 1H), 7.42-7.54 (m, 3H), 7.35 (m, 1H), 6.28 (t, J = 5.7 Hz, 1H), 3.15-3.24 (m, 2H), 2.33 (s, 3H), 1.73-1.84 (m, 2H), 1.33 (d, J = 20.0 Hz, 6H).	350.2

I29	H28 		P	crude	No Data	436.2
I30	B13 		Q	56	No Data	345.2
I31	H28 		P	25	8.40 (s, 1H), 8.00 (d, J = 8.4 Hz, 1H), 7.17 (d, J = 12.3 Hz, 1H), 7.02 (s, 1H), 6.73 (s, 1H), 6.68 (t, J = 5.8 Hz, 1H), 5.95-6.27 (tt, J = 4.4 and 5.6 Hz, 1H), 4.86 (t, J = 5.5 Hz, 1H), 4.26-4.31 (m, 2H), 3.71 (q, J = 5.3 Hz, 2H), 3.23 (q, J = 6.6 Hz, 2H), 2.17 (s, 3H), 1.92-2.07 (m, 2H).	418.0
I32	H60 		P	63	No Data	405.2
I33	H28 		P	25	8.28 (d, J = 2.3 Hz, 1H), 7.99 (d, J = 8.5 Hz, 1H), 7.12 (d, J = 12.4 Hz, 1H), 7.03 (t, J = 2.1 Hz, 1H), 6.88 (t, J = 1.6 Hz, 1H), 6.83 – 6.78 (m, 1H), 6.52 – 6.47 (m, 1H), 4.88 (br s, 1H), 4.05 (t, J = 5.0 Hz, 2H), 3.71 (t, J = 4.9 Hz, 2H), 3.19 – 3.11 (m, 2H), 2.14 (s, 2H), 1.40 – 1.32 (m, 2H), 1.13 – 1.09 (m, 1H), 1.05 – 0.96 (m, 3H), 0.30 – 0.25 (m, 2H), 0.22 – 0.19 (m, 2H).	421.2
I34	B21 		Q	32	8.63 (s, 1H), 8.40 (d, J = 2.8 Hz, 1H), 7.78 (d, J = 2.4 Hz, 1H), 7.46-7.52 (m, 2H), 7.43 (s, 1H), 7.34 (dd, J = 2.0 and 4.8 Hz, 1H), 6.19 (t, J = 6.0 Hz, 1H), 3.15 (m, 2H), 2.32 (s, 3H), 1.37 (t, J = 7.6 Hz, 2H), 1.02 (s, 3H), 0.26 (m, 2H).	344.3

					0.21 (m, 2H).	
I35	E25 		Q	10	7.01 (brm, 1H), 6.92 (d, J = 12.4 Hz, 1H), 6.59 (d, J = 9.2 Hz, 1H), 6.32- 6.42 (m, 3H), 4.70 (m, 1H), 3.50- 3.55 (m, 2H), 3.29 (m, 2H), 3.03-3.16 (m, 2H), 2.12 (s, 3H), 1.28 (m, 2H), 1.14 (s, 3H), 0.18-0.27 (m, 4H).	421.3

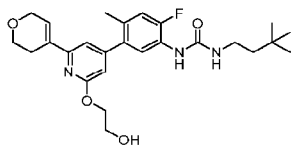
[000298] Using the General Method A above, the following Intermediates of Table J were prepared.

Table J.

Ex. No.	SM	Product	Yield (%)	¹ H NMR (400 or 500 MHz, DMSO-d ₆): δ	MS (m/z: M+H ⁺)
J1	I16		crude	No Data	453.0
J2	I17		crude	No Data	466.2
J3	I20		crude	No Data	424.0
J4	I33		crude	No Data	513.0
J5	I34		JCL	9.29 (brs, 1H), 8.43 (d, J = 2.0 Hz, 1H), 7.79 (d, J = 0.8 Hz, 1H), 7.68 (d, J = 6.8 Hz, 1H), 7.57 (s, 1H), 7.47-7.53 (m, 2H), 6.78 (brs, 1H), 3.15 (q, J = 6.0 Hz, 2H), 2.29 (s, 3H), 1.30 (s, 12H), 1.36 (m, 2H), 1.06 (s, 3H), 0.27 (m, 2H), 0.25 (m, 2H).	436.4

General Method R: Deprotection with TBAF

[000299] **Example 5:** 1-(5-(2-(3,6-dihydro-2H-pyran-4-yl)-6-(2-hydroxyethoxy)pyridin-4-yl)-2-fluoro-4-methylphenyl)-3-(3,3-dimethylbutyl)urea

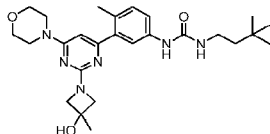


[000300] Using the General Method P, 2,2,2-trichloroethyl (5-(2-(2-((tert-butyldimethylsilyl)oxy)ethoxy)-6-(3,6-dihydro-2H-pyran-4-yl)pyridin-4-yl)-2-fluoro-4-methylphenyl)carbamate (**H13**, 0.91 g, 1.4 mmol), 3,3-dimethylbutan-1-amine (0.18 g, 1.8 mmol) and DIEA (0.75 mL, 4.3 mmol) were combined to afford 1-(5-(2-(2-((tert-butyldimethylsilyl)oxy)ethoxy)-6-(3,6-dihydro-2H-pyran-4-yl)pyridin-4-yl)-2-fluoro-4-methylphenyl)-3-(3,3-dimethylbutyl)urea (0.78 g, 93%). MS (ESI) m/z : 586.4 ($M+H^+$).

[000301] A solution of 1-(5-(2-(2-((tert-butyldimethylsilyl)oxy)ethoxy)-6-(3,6-dihydro-2H-pyran-4-yl)pyridin-4-yl)-2-fluoro-4-methylphenyl)-3-(3,3-dimethylbutyl)urea (0.78 g, 1.3 mol) in THF (5 mL) was treated with TBAF (1.0 M in THF, 4.0 mL, 4.0 mmol). The mixture was stirred at 20 °C for 1 h and then concentrated under reduced pressure. The crude was purified silica gel column chromatography (50 to 65% EtOAc/hexanes) to obtain 1-(5-(2-(3,6-dihydro-2H-pyran-4-yl)-6-(2-hydroxyethoxy)pyridin-4-yl)-2-fluoro-4-methylphenyl)-3-(3,3-dimethylbutyl)urea (**5**, 0.28 g, 45%) as a clear crystal solid. ^1H NMR (500 MHz, DMSO- d_6): δ 8.24 (s, 1H), 8.01 (d, J = 8.5 Hz, 1H), 7.14 (m, 1H), 6.95 (s, 1H), 6.84 (s, 1H), 6.56 (s, 1H), 6.47 (t, J = 5.5 Hz, 1H), 4.34 (t, J = 5.2 Hz, 2H), 4.26 (d, J = 3.1 Hz, 2H), 3.81 (t, J = 5.4 Hz, 2H), 3.73 (t, J = 5.2 Hz, 2H), 3.39 (brm, 2H), 3.07 (m, 2H), 2.16 (s, 3H), 1.32 (m, 2H), 0.88 (s, 9H). MS (ESI) m/z : 472.2 ($M+H^+$).

General Method S: Coupling, Oxidation and Substitution

[000302] **Example 1:** 1-(3,3-dimethylbutyl)-3-(3-(2-(3-hydroxy-3-methylazetidin-1-yl)-6-morpholinopyrimidin-4-yl)-4-methylphenyl)urea



[000303] A solution of 2,2,2-trichloroethyl (4-methyl-3-(2-(methylthio)-6-morpholinopyrimidin-4-yl)phenyl)carbamate (**H20**, 0.98 g, 2.0 mmol), 3,3-dimethylbutan-1-amine (0.53 mL, 4.0 mmol), and DIPEA (1.4 mL, 7.9 mmol) in DMSO (5 mL) was heated to 60 °C for 17 h. The reaction was diluted with DCM (45 mL) and sat'd $NaHCO_3$ solution (75 mL). The aqueous layer was extracted with DCM (2 x 30 mL). The combined organics were washed dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to yield a brown oily solid. The crude was purified by silica gel column chromatography (0 to 100% EtOAc/hexanes) to obtain 1-(3,3-dimethylbutyl)-3-(4-methyl-3-(2-(methylthio)-6-morpholinopyrimidin-4-yl)phenyl)urea (0.47 g, 54%) as an off-white solid. ^1H NMR (500

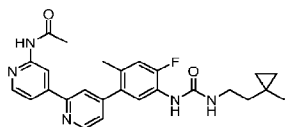
MHz, DMSO- d_6): δ 8.40 (s, 1H), 7.34 (m, 2H), 7.10 (d, J = 8.2 Hz, 1H), 6.55 (s, 1H), 5.96 (t, J = 5.6 Hz, 1H), 3.65 (m, 8H), 3.07 (m, 2H), 2.44 (s, 3H), 2.23 (s, 3H), 1.32 (m, 2H), 0.89 (s, 9H); MS (ESI) m/z : 444.2 ($M+H^+$).

[000304] A solution of 1-(3,3-dimethylbutyl)-3-(4-methyl-3-(2-(methylthio)-6-morpholinopyrimidin-4-yl)phenyl)urea (0.47 g, 1.1 mmol) in DCM (20 mL) was treated with mCPBA (0.54 g, 2.3 mmol). The reaction mixture was stirred at rt for 3 h. The reaction solution was treated with sat'd NaHCO₃ solution (25 mL) and stirred for 15 min. The aqueous layer was extracted with DCM (2 x 25 mL) and the combined organics were dried over anhydrous MgSO₄, filtered and concentrated under reduced pressure to obtain 1-(3,3-dimethylbutyl)-3-(4-methyl-3-(2-(methylsulfonyl)-6-morpholinopyrimidin-4-yl)phenyl)urea (0.50 g, 100%) which was used for the next reaction without purification.

[000305] 1-(3,3-dimethylbutyl)-3-(4-methyl-3-(2-(methylsulfonyl)-6-morpholinopyrimidin-4-yl)phenyl)urea (0.12 g, 0.25 mmol), and 3-methylazetidin-3-ol (0.055 g, 0.63 mmol) in DMF (2 mL) was treated with DIEA (0.13 mL, 0.76 mmol). The reaction mixture was heated at 90 °C for 6 h. The reaction was quenched with sat'd. NaHCO₃ solution (30 mL) and the solution was extracted with DCM (2 x 25 mL). The combined organics were washed with water (35 mL) and the organics were dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure to obtain the crude. The crude was purified by reverse phase column chromatography (0 to 100% H₂O/CH₃CN in 0.4% TFA). The fractions were collected and concentrated. The residue was dissolved in CH₃CN and treated with aqueous solution of K₂CO₃. The solution was extracted with DCM (3 x 25 mL) and the combined organics was dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure to obtain 1-(3,3-dimethylbutyl)-3-(3-(2-(3-hydroxy-3-methylazetidin-1-yl)-6-morpholinopyrimidin-4-yl)-4-methylphenyl)urea (**1**, 0.063 g, 52%) as a white solid. ¹H NMR (500 MHz, DMSO-*d*₆): δ 8.36 (s, 1H), 7.30 (m, 2H), 7.06 (d, *J* = 8.1 Hz, 1H), 6.09 (s, 1H), 5.95 (t, *J* = 5.6 Hz, 1H), 5.48 (s, 1H), 3.80 (s, 4H), 3.63 (t, *J* = 4.7 Hz, 4H), 3.53 (d, *J* = 5.0 Hz, 4H), 3.06 (m, 2H), 2.21 (s, 3H), 1.39 (s, 3H), 1.32 (m, 2H), 0.87 (m, 9H); MS (ESI) *m/z*: 483.2 (M+H⁺).

Method T: Suzuki reactions

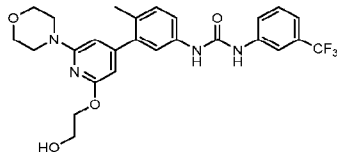
[000306] Example 2: N-(4-(4-fluoro-2-methyl-5-(3-(2-(1-methylcyclopropyl)ethyl)ureido)phenyl)-[2,4'-bipyridin]-2'-yl)acetamide



[000307] A mixture of 1-(5-(2-chloropyridin-4-yl)-2-fluoro-4-methylphenyl)-3-(2-(1-methylcyclopropyl)ethyl)urea (**I1**, 0.15 g, 0.41 mmol), N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)acetamide (**A3**, 0.24 g, 0.91 mmol), and K_2CO_3 (0.17 g, 1.2 mmol) in 1,4-dioxane (4 mL) and water (0.8 mL) was sparged with Ar for 2 min. $Pd(dppf)Cl_2$ (0.015 g, 0.02 mmol) was added and the mixture was heated to 100 °C for 3 h. The reaction was cooled to rt and diluted with DCM (30 mL). The solution was filtered through a pad of celite and the filtrate was washed with sat'd $NaHCO_3$ (aq, 30 mL). The aqueous layer was extracted with 30 mL DCM (2 x 30 mL). The combined organics were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to yield a brown oily solid. The crude was purified by silica gel column chromatography (0 to 100% EtOAc/hexanes) to obtain N-(4-(4-fluoro-2-methyl-5-(3-(2-(1-methylcyclopropyl)ethyl)ureido)phenyl)-[2,4'-bipyridin]-2'-yl)acetamide (**66**, 0.14 g, 69%) as a white solid, ^1H NMR (500 MHz, DMSO): δ 10.6 (s, 1H), 8.81 (s, 1H), 8.78 (d, J = 5.0 Hz, 1H), 8.40 (d, J = 5.3 Hz, 1H), 8.34 (s, 1H), 8.09 (d, J = 8.4 Hz, 1H), 7.88 (s, 1H), 7.77 (dd, J = 1.6 and 5.3 Hz, 1H), 7.42 (m, 1H), 7.21 (d, J = 12.3 Hz, 1H), 6.51 (t, J = 5.6 Hz, 1H), 3.14 (m, 2H), 2.20 (s, 3H), 2.11 (s, 3H), 1.34 (t, J = 7.5 Hz, 2H), 1.00 (s, 3H), 0.25 (m, 2H), 0.20 (m, 2H); MS (ESI) m/z : 462.2 ($M+H^+$).

General Method U: Coupling reaction with isocyanates

[000308] **Example 3:** 1-(3-(2-(2-hydroxyethoxy)-6-morpholinopyridin-4-yl)-4-methylphenyl)-3-(3-(trifluoromethyl)phenyl)urea

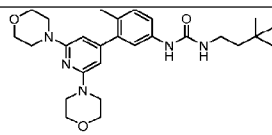
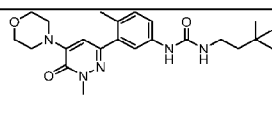
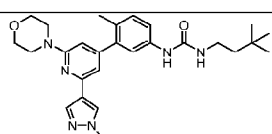


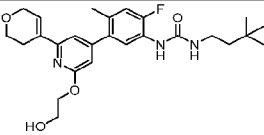
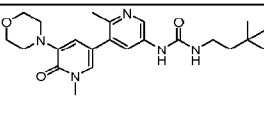
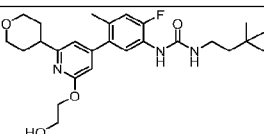
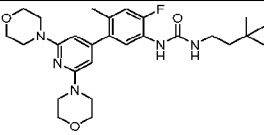
[000309] A solution of 3-(2-(2-((tert-butyldimethylsilyl)oxy)ethoxy)-6-morpholinopyridin-4-yl)-4-methylaniline (**G1**, 0.15 g, 0.34 mmol) in DCM (2 mL) was stirred at rt. TEA (0.24 mL, 1.7 mmol) and 1-isocyanato-3-(trifluoromethyl)benzene (0.19 g, 1.0 mmol) were added and then the reaction mixture was heated at 65 °C overnight. The reaction was cooled to rt and concentrated to dryness under vacuum. The crude was dissolved in THF (10 mL) and TBAF (3 eq) was added. The reaction mixture was stirred at rt overnight. The yellow solution was concentrated and the residue was purified by silica gel

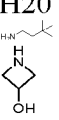
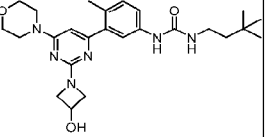
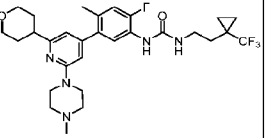
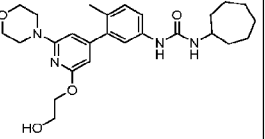
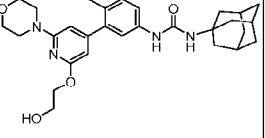
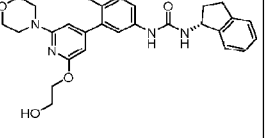
column chromatography (0 to 10% MeOH/DCM) to afford 1-(3-(2-(2-((tert-butyl)dimethylsilyl)oxy)ethoxy)-6-morpholinopyridin-4-yl)-4-methylphenyl)-3-(3-(trifluoromethyl)phenyl)urea which was deprotonated with TBAF (using General Method R) to obtain 1-(3-(2-(2-hydroxyethoxy)-6-morpholinopyridin-4-yl)-4-methylphenyl)-3-(3-(trifluoromethyl)phenyl)urea (0.061 g, 35%) as a white solid. ^1H NMR (500 MHz, $\text{DMSO}-d_6$): δ 9.00 (s, 1H), 8.70 (s, 1H), 8.01 (s, 1H), 7.54 (d, $J = 8.4$ Hz, 1H), 7.49 (m, 1H), 7.34 (brs, 2H), 7.29 (d, $J = 7.6$ Hz, 1H), 7.19 (m, 1H), 6.22 (s, 1H), 6.01 (s, 1H), 4.78 (t, $J = 5.6$ Hz, 1H), 4.25 (t, $J = 5.2$ Hz, 2H), 3.70 (m, 6H), 3.46 (brm, 4H), 2.17 (s, 3H); MS (ESI) m/z : 517.3 ($\text{M}+\text{H}^+$).

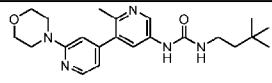
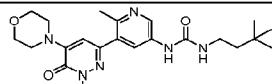
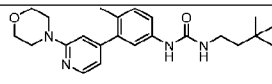
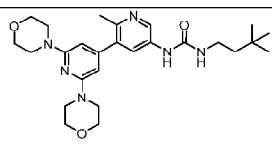
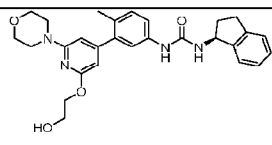
[000310] Using the General Methods I, J, N, O, Q, R, S, T, and U above, the following Examples of Compounds of Formula I as shown in Table K were prepared.

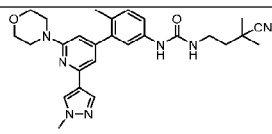
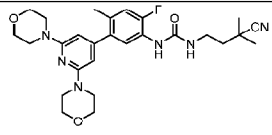
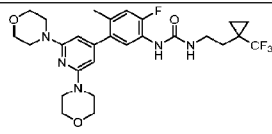
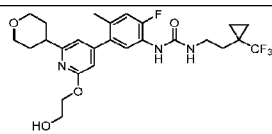
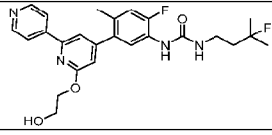
Table K.

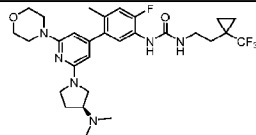
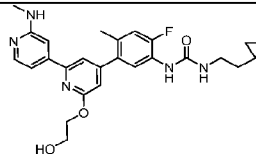
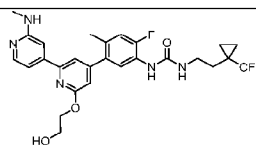
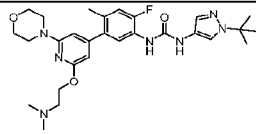
Ex. No	SM	Product	Method	Yield (%)	^1H NMR (400 or 500 MHz, $\text{DMSO}-d_6$): δ	MS (m/z : $\text{M}+\text{H}^+$)
4	H5 		P	69	8.33 (s, 1H), 7.26 (dd, $J = 2.3$ and 8.3 Hz, 1H), 7.21 (d, $J = 2.3$ Hz, 1H), 7.08 (d, $J = 8.3$ Hz, 1H), 5.98 (s, 2H), 5.94 (t, $J = 5.7$ Hz, 1H), 3.66 (t, $J = 4.7$ Hz, 8 H), 3.39 (t, $J = 4.7$ Hz, 8 H), 3.06 (m, 2H), 2.12 (s, 3H), 1.32 (m, 2H), 0.89 (s, 9H).	482.4
5	H22 		P	41	8.39 (s, 1H), 7.39 (d, $J = 2.3$ Hz, 1H), 7.29 (dd, $J = 2.3$ and 8.3 Hz, 1H), 7.10 (d, $J = 8.3$ Hz, 1H), 6.53 (s, 1H), 5.97 (t, $J = 5.6$ Hz, 1H), 3.70 (t, $J = 4.6$ Hz, 4H), 3.66 (s, 3H), 3.44 (t, $J = 4.6$ Hz, 4H), 3.07 (m, 2H), 2.20 (s, 3H), 1.32 (m, 2H), 0.89 (s, 9H).	428.2
6	H9 		P	62	8.38 (s, 1H), 8.22 (s, 1H), 7.95 (s, 1H), 7.29 (m, 2H), 7.12 (d, $J = 8.1$ Hz, 1H), 6.89 (s, 1H), 6.47 (s, 1H), 5.96 (t, $J = 5.6$ Hz, 1H),	477.2

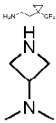
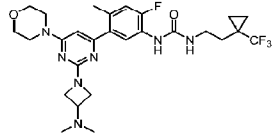
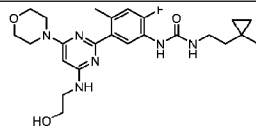
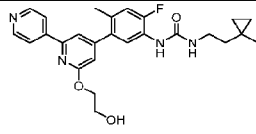
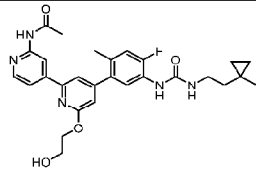
					3.85 (s, 3H), 3.71 (d, J = 4.9 Hz, 4H), 3.52 (d, J = 4.9 Hz, 4H), 3.06 (m, 2H), 2.15 (s, 3H), 1.33 (t, J = 8.0 Hz, 2H), 0.89 (s, 9H).	
7	H13 		P & R	42	8.24 (s, 1H), 8.01 (d, J = 8.5 Hz, 1H), 7.14 (m, 1H), 6.95 (s, 1H), 6.84 (s, 1H), 6.56 (s, 1H), 6.47 (t, J = 5.5 Hz, 1H), 4.34 (t, J = 5.2 Hz, 2H), 4.26 (d, J = 3.1 Hz, 2H), 3.81 (t, J = 5.4 Hz, 2H), 3.73 (t, J = 5.2 Hz, 2H), 3.39 (brm, 2H), 3.07 (m, 2H), 2.16 (s, 3H), 1.32 (m, 2H), 0.88 (s, 9H).	472.2
8	H22 		P	59	8.53 (s, 1H), 8.36 (d, J = 2.5 Hz, 1H), 7.73 (d, J = 2.5 Hz, 1H), 7.41 (d, J = 2.2 Hz, 1H), 6.69 (d, J = 2.3 Hz, 1H), 6.14 (t, J = 5.6 Hz, 1H), 3.70 (t, J = 4.5 Hz, 4H), 3.48 (s, 3H), 3.08 (m, 6H), 2.36 (s, 3H), 1.33 (m, 2H), 0.89 (s, 9H).	428.2
9	5		K	42	8.23 (s, 1H), 8.00 (d, J = 8.5 Hz, 1H), 7.13 (m, 1H), 6.76 (s, 1H), 6.51 (d, J = 1.2 Hz, 1H), 6.47 (t, J = 5.6 Hz, 1H), 4.81 (brs, 1H), 4.31 (t, J = 5.2 Hz, 2H), 3.93 (m, 2H), 3.72 (t, J = 5.1 Hz, 2H), 3.46 (m, 2H), 3.07 (m, 2H), 2.15 (s, 3H), 1.77 (m, 4H), 1.32 (m, 2H), 0.88 (s, 9H).	474.2
10	H6 		P	95	8.17 (s, 1H), 7.93 (d, J = 8.5 Hz, 1H), 7.07 (m, 1H), 6.44 (t, J = 5.5 Hz, 1H), 5.95 (s, 2H), 3.66 (t, J = 4.7 Hz, 8H), 3.39 (t, J = 4.7 Hz, 8H), 3.06 (m, 2H), 2.13 (s, 3H), 1.31 (m, 2H), 0.88 (s, 9H).	500.2

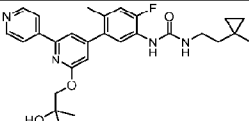
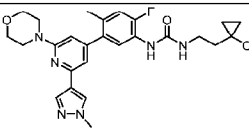
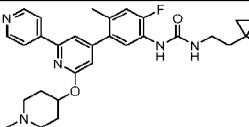
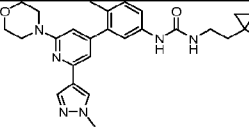
11	H20 		S	32	8.35 (s, 1H), 7.29 (m, 2H), 7.06 (d, J = 8.5 Hz, 1H), 6.09 (s, 1H), 5.94 (t, J = 5.6 Hz, 1H), 5.56 (d, J = 6.5 Hz, 1H), 4.48 (m, 1H), 4.13 (t, J = 7.8 Hz, 2H), 3.70 (dd, J = 4.6 and 9.1 Hz, 2H), 3.63 (s, 4H), 3.53 (s, 4H), 3.07 (m, 2H), 2.21 (s, 3H), 1.32 (m, 2H), 0.89 (s, 9H).	469.2
12	H18 		P	17	8.36 (s, 1H), 7.93 (d, J = 8.5 Hz, 1H), 7.12 (d, J = 12.3 Hz, 1H), 6.64 (t, J = 5.8 Hz, 1H), 6.54 (s, 1H), 6.46 (s, 1H), 3.92 (m, 2H), 3.44 (m, 2H), 3.31 (m, 4H), 3.16 (m, 2H), 2.79 (m, 1H), 2.36 (m, 7H), 2.13 (s, 3H), 1.67-1.78 (m, 6H), 0.89 (m, 2H), 0.75 (s, 2H).	564.2
13	H1 		P	35	8.20 (s, 1H), 7.25 (s, 1H), 7.22 (dd, J = 2.2 and 8.2 Hz, 1H), 7.09 (d, J = 8.2 Hz, 1H), 6.18 (s, 1H), 6.0 (d, J = 7.8 Hz, 1H), 5.97 (s, 1H), 4.78 (t, J = 5.6 Hz, 1H), 4.24 (t, J = 5.1 Hz, 2H), 3.69 (m, 7H), 3.43 (brm, 4H), 2.13 (s, 3H), 1.81 (m, 2H), 1.50 (m, 10H).	469.3
14	H1 		P	40	8.20 (s, 1H), 7.25 (s, 1H), 7.16 (dd, J = 2.1 and 8.1 Hz, 1H), 7.08 (d, J = 8.2 Hz, 1H), 6.18 (s, 1H), 5.9 (s, 1H), 5.81 (s, 1H), 4.78 (t, J = 5.5 Hz, 1H), 4.24 (t, J = 5.1 Hz, 2H), 3.69 (m, 6H), 3.44 (brm, 4H), 2.12 (s, 3H), 2.01 (brm, 3H), 1.91 (brm, 6H), 1.61 (brm, 6H).	507.4
15	H1 		P	49	8.30 (s, 1H), 7.24 (m, 6H), 7.13 (d, J = 7.9 Hz, 1H), 6.4 (d, J = 8.0 Hz, 1H), 6.20 (s, 1H), 5.98 (s, 1H), 5.14 (t, J = 7.7 Hz, 1H),	489.2

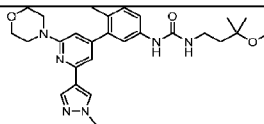
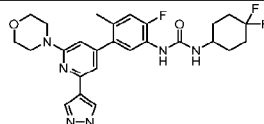
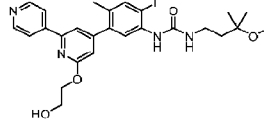
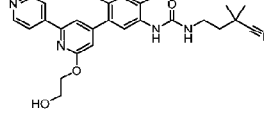
					4.77 (t, J = 5.6 Hz, 1H), 4.23 (t, J = 5.3 Hz, 2H), 3.69 (m, 6H), 3.45 (brm, 4H), 2.95 (m, 1H), 2.89 (m, 1H), 2.49 (m, 1H), 2.15 (s, 3H), 1.78 (m, 1H).	
16	H3 		P	48	8.60 (s, 1H), 8.42 (brs, 1H), 8.18 (d, J = 5.0 Hz, 1H), 7.75 (s, 1H), 6.77 (s, 1H), 6.88 (d, J = 5.0 Hz, 1H), 6.1 (t, J = 5.5 Hz, 1H), 3.69 (m, 4H), 3.48 (m, 4H), 3.08 (m, 2H), 2.33 (s, 3H), 1.35 (m, 2H), 0.89 (s, 9H).	398.2
17	H24 		P	62	8.62 (s, 1H), 8.43 (d, J = 2.5 Hz, 1H), 7.86 (d, J = 2.5 Hz, 1H), 6.62 (s, 1H), 6.16 (t, J = 5.6 Hz, 1H), 3.70 (t, J = 4.6 Hz, 4H), 3.67 (s, 3H), 3.47 (t, J = 4.6 Hz, 4H), 3.08 (m, 2H), 2.40 (s, 3H), 1.33 (m, 2H), 0.89 (s, 9H).	429.2
18	H2 		P	47	8.38 (s, 1H), 8.14 (d, J = 5.1 Hz, 1H), 7.26 (m, 2H), 7.11 (d, J = 8.1 Hz, 1H), 6.69 (s, 1H), 6.62 (d, J = 5.1 Hz, 1H), 5.98 (t, J = 5.6 Hz, 1H), 3.69 (t, J = 4.8 Hz, 4H), 3.46 (t, J = 4.7 Hz, 4H), 3.06 (m, 2H), 2.13 (s, 3H), 1.32 (m, 2H), 0.89 (s, 9H).	397.2
19	H10 		P	26	8.56 (s, 1H), 8.40 (m, 1H), 7.69 (m, 1H), 6.13 (t, J = 5.8 Hz, 1H), 6.04 (s, 2H), 3.67 (m, 8H), 3.40 (m, 8H), 3.07 (m, 2H), 2.32 (s, 3H), 1.33 (m, 2H), 0.89 (s, 9H).	483.2
20	H1 		P	40	8.30 (s, 1H), 7.24 (m, 6H), 7.13 (d, J = 8.0 Hz, 1H), 6.4 (d, J = 8.1 Hz, 1H), 6.21 (s, 1H), 5.99 (s, 1H), 5.15 (m, 1H), 4.80 (t, J = 5.5 Hz, 1H), 4.24 (t, J = 5.0 Hz, 2H), 3.69 (brm, 6H), 3.44 (brm, 4H), 2.91 (m, 1H), 2.79 (m, 1H), 2.46 (m,	489.2

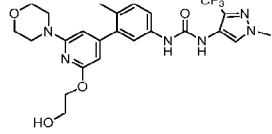
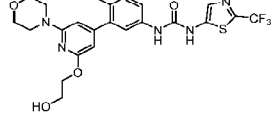
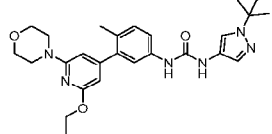
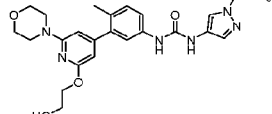
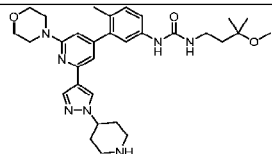
					1H), 2.15 (s, 3H), 1.75 (m, 1H).	
21	H9 		P	44	9.30 (s, 1H), 9.14 (s, 1H), 8.22 (m, 1H), 7.95 (m, 1H), 7.60 (s, 1H), 7.54 (d, J = 8.3 Hz, 1H), 7.12 (d, J = 8.4 Hz, 1H), 6.89 (s, 1H), 6.47 (s, 1H), 3.85 (s, 3H), 3.71 (t, J = 4.7 Hz, 4H), 3.51 (t, J = 4.7 Hz, 4H), 3.39 (t, J = 6.9 Hz, 2H), 2.17 (s, 3H), 1.77 (t, J = 6.9 Hz, 2H), 1.14 (s, 6H).	488.3
22	H6 		P	17	8.27 (s, 1H), 7.91 (d, J = 8.6 Hz, 1H), 7.09 (m, 1H), 6.63 (t, J = 5.7 Hz, 1H), 5.96 (s, 2H), 3.66 (t, J = 4.6 Hz, 8H), 3.39 (t, J = 4.6 Hz, 8H), 3.20 (m, 2H), 2.13 (s, 3H), 1.68 (m, 2H), 1.31 (s, 6H).	511.2
23	H6 		P	52	8.31 (d, J = 2.3 Hz, 1H), 7.90 (d, J = 8.6 Hz, 1H), 7.08 (d, J = 12.3 Hz, 1H), 6.59 (t, J = 5.7 Hz, 1H), 5.95 (s, 2H), 3.66 (t, J = 4.6 Hz, 8H), 3.38 (t, J = 4.6 Hz, 8H), 3.16 (m, 2H), 2.13 (s, 3H), 1.69 (t, J = 7.7 Hz, 2H), 0.89 (t, J = 5.5 Hz, 2H), 0.75 (s, 2H).	552.2
24	H15 		P	38	8.37 (d, J = 2.3 Hz, 1H), 7.97 (d, J = 8.5 Hz, 1H), 7.14 (m, 1H), 6.76 (d, J = 1.2 Hz, 1H), 6.62 (t, J = 5.8 Hz, 1H), 6.50 (d, J = 1.2 Hz, 1H), 4.83 (t, J = 5.6 Hz, 1H), 4.31 (t, J = 5.2 Hz, 2H), 3.92 (m, 2H), 3.72 (m, 2H), 3.41 (m, 2H), 3.16 (m, 2H), 2.87 (m, 1H), 2.15 (s, 3H), 1.76 (m, 4H), 1.69 (m, 2H), 0.89 (m, 2H), 0.74 (m, 2H).	526.2
25	H17 		P & R	40	8.68 (s, 1H), 8.87 (s, 1H), 8.38 (s, 1H), 8.09 (m, 3H), 7.67 (s, 1H), 7.20 (d, J = 12.3 Hz, 1H), 6.80 (s, 1H),	471.2

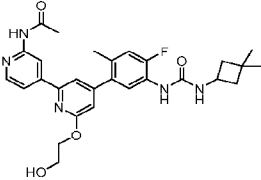
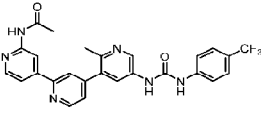
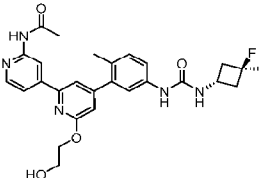
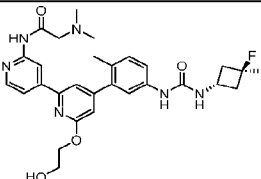
					6.57 (t, J = 5.6 Hz, 1H), 4.89 (brm, 1H), 4.47 (m, 2H), 3.79 (m, 2H), 3.17 (m, 2H), 2.21 (s, 3H), 1.75 (m, 2H), 1.34 (d, J = 21.6 Hz, 6H).	
26	H25 	P	37	8.29 (d, J = 2.3 Hz, 1H), 7.90 (d, J = 8.6 Hz, 1H), 7.07 (d, J = 12.4 Hz, 1H), 6.57 (t, J = 5.7 Hz, 1H), 5.80 (s, 1H), 5.61 (s, 1H), 3.65 (m, 4H), 3.58 (m, 2H), 3.38 (t, J = 4.7 Hz, 4H), 3.28 (m, 1H), 3.16 (m, 2H), 3.05 (m, 1H), 2.72 (s, 1H), 2.18 (s, 6H), 2.10 (s, 3H), 2.08 (m, 1H), 1.76 (m, 1H), 1.67 (m, 2H), 0.89 (m, 2H), 0.75 (brm, 2H).	579.4	
27	H26 	P and deprotection with HCl	48	8.34 (s, 1H), 8.05 (m, 2H), 7.43 (d, J = 1.2 Hz, 1H), 7.14 (m, 3H), 6.74 (d, J = 1.1 Hz, 1H), 6.55 (m, 1H), 6.52 (m, 1H), 4.89 (t, J = 5.6 Hz, 1H), 4.43 (t, J = 5.1 Hz, 2H), 3.78 (q, J = 5.2 Hz, 2H), 3.14 (m, 2H), 2.80 (d, J = 4.8 Hz, 3H), 2.19 (s, 3H), 1.34 (t, J = 7.5 Hz, 2H), 1.00 (s, 3H), 0.23 (m, 2H) 0.21 (m, 2H).	494.2	
28	H26 	O and deprotection with HCl	30	8.41 (s, 1H), 8.05 (m, 2H), 7.42 (d, J = 1.2 Hz, 1H), 7.15 (m, 3H), 6.73 (d, J = 1.1 Hz, 1H), 6.63 (m, 1H), 6.60 (m, 1H), 4.89 (t, J = 5.5 Hz, 1H), 4.43 (m, 2H), 3.78 (m, 2H), 3.17 (m, 2H), 2.80 (d, J = 5.0 Hz, 3H), 2.19 (s, 3H), 1.69 (m, 2H), 0.89 (m, 2H), 0.75 (brm, 2H).	548.2	
29	G26 	Q	19	8.69 (s, 1H), 8.48 (s, 1H), 7.98 (d, J = 8.5 Hz, 1H), 7.79 (d, J = 0.7 Hz, 1H), 7.37 (s, 1H), 6.94 (m, 1H), 6.21 (s, 1H), 5.97 (s, 1H), 4.37 (t, J = 5.7 Hz, 2H), 3.69 (m, 4H), 3.44 (m, 4H).	540.4	

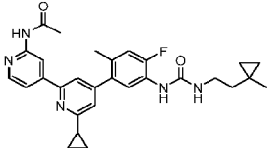
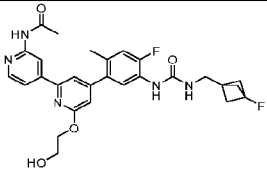
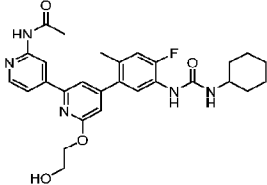
					2.80 (brm, 2H), 2.35 (brs, 6H), 2.16 (s, 3H), 1.47 (s, 9H).	
30	H20 		S	46	8.29 (d, J = 2.2 Hz, 1H), 8.00 (d, J = 8.6 Hz, 1H), 7.06 (d, J = 12.3 Hz, 1H), 6.56 (t, J = 5.8 Hz, 1H), 6.06 (s, 1H), 3.96 (t, J = 7.9 Hz, 2H), 3.72 (dd, J = 5.2 and 8.9 Hz, 2H), 3.63 (t, J = 4.7 Hz, 4H), 3.54 (d, J = 5.0 Hz, 4H), 3.17 (q, J = 7.1 Hz, 2H), 3.05 (s, 1H), 2.22 (s, 3H), 2.08 (s, 6H), 1.70 (t, J = 7.7 Hz, 2H), 0.90 (t, J = 5.5 Hz, 2H), 0.76 (s, 2H).	566.2
31	H27 		P	20	8.03 (m, 2H), 7.02 (d, J = 12.3 Hz, 1H), 6.37 (t, J = 5.6 Hz, 1H), 6.24 (s, 1H), 5.98 (s, 1H), 4.46 (s, 1H), 3.65 (m, 4H), 3.54 (m, 6H), 3.34 (q, J = 6.0 Hz, 2H), 3.15 (m, 2H), 2.25 (s, 3H), 1.38 (m, 2H), 1.03 (s, 3H), 0.28 (m, 2H), 0.22 (m, 2H).	473.2
32	H17 		P & R	44	8.68 (m, 2H), 8.34 (d, J = 2.3 Hz, 1H), 8.08 (m, 3H), 7.67 (d, J = 1.1 Hz, 1H), 7.19 (d, J = 12.4 Hz, 1H), 6.79 (d, J = 1.1 Hz, 1H), 6.51 (t, J = 5.6 Hz, 1H), 4.88 (m, 1H), 4.47 (t, J = 5.1 Hz, 2H), 3.79 (m, 2H), 3.14 (m, 2H), 2.20 (s, 3H), 1.34 (t, J = 7.5 Hz, 2H), 1.00 (s, 3H), 0.25 (m, 2H), 0.19 (m, 2H).	465.2
33	A3 I14		T & R	62	10.6 (s, 1H), 8.79 (s, 1H), 8.38 (d, J = 5.3 Hz, 1H), 8.33 (s, 1H), 8.08 (d, J = 8.4 Hz, 1H), 7.75 (dd, J = 1.6 and 5.3 Hz, 1H), 7.48 (s, 1H), 7.19 (d, J = 12.3 Hz, 1H), 6.80 (s, 1H), 6.50 (t, J = 5.6 Hz, 1H), 4.88 (t, J = 5.6 Hz, 1H), 4.44 (t, J = 5.1 Hz, 2H), 3.79 (q, J = 5.2	522.2

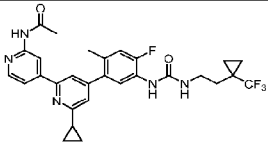
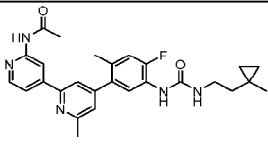
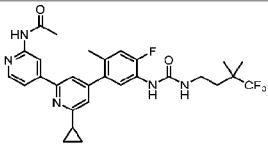
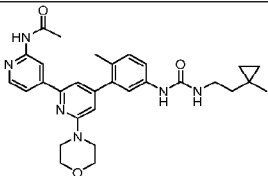
					H _z , 2H), 3.14 (m, 2H), 1.00 (s, 3H), 0.267 (m, 2H), 0.21 (m, 2H).	
34	H29 	P	37	8.68 (d, J = 5.2 Hz, 2H), 8.32 (s, 1H), 8.08 (m, 3H), 7.66 (s, 1H), 7.19 (d, J = 12.3 Hz, 1H), 6.79 (s, 1H), 6.50 (t, J = 5.6 Hz, 1H), 4.67 (s, 1H), 4.23 (s, 2H), 3.14 (m, 2H), 2.21 (s, 3H), 1.35 (t, J = 7.5 Hz, 2H), 1.23 (s, 6H), 1.00 (s, 3H), 0.25 (m, 2H), 0.20 (m 2H).	493.2	
35	H35 	P	20	8.30 (brs, 1H), 8.23 (s, 1H), 7.99 (d, J = 8.0 Hz, 1H), 7.95 (s, 1H), 7.13 (d, J = 12.4 Hz, 1H), 6.87 (s, 1H), 6.50 (brs, 1H), 6.45 (s, 1H), 3.85 (s, 3H), 3.71 (s, 4H), 3.52 (brs, 4H), 3.19 (d, J = 6.0 Hz, 2H), 3.15 (s, 3H), 2.17 (s, 3H), 1.67 (t, J = 6.8 Hz, 2H), 0.64 (s, 2H), 0.40 (s,2H).	509.4	
36	H30 	P	38	8.68 (d, J = 5.4 Hz, 2H), 8.33 (s, 1H), 8.06 (m, 3H), 7.64 (s, 1H), 7.18 (d, J = 12.3 Hz, 1H), 6.75 (s, 1H), 6.51 (t, J = 5.6 Hz, 1H), 5.21 (s, 1H), 3.14 (q, J = 7.0 Hz, 2H), 2.72 (brm, 2H), 2.23(m, 5H), 2.20 (s, 3H), 2.08 (brm, 2H), 1.77 (d, J = 11.7 Hz, 2H), 1.34 (t, J = 7.5 Hz, 2H), 1.00 (s, 3H), 0.26 (t, J = 0.7 Hz, 2H), 0.20 (t, J = 0.7 Hz, 2H).	518.2	
37	H9 	P	31	8.50 (s, 1H), 8.22 (s, 1H), 7.95 (s, 1H), 7.29 (m, 2H), 7.12 (d, J = 8.2 Hz, 1H), 6.89 (s, 1H), 6.47 (s, 1H), 6.03 (t, J = 5.7 Hz, 1H), 3.85 (s, 3H), 3.71 (t, J = 4.7 Hz, 4H), 3.52 (t, J = 4.7 Hz, 4H), 3.14 (m, 2H), 2.15 (s, 3H), 1.35 (t, J = 7.5 Hz, 2H), 1.01 (s, 3H), 0.26	475.2	

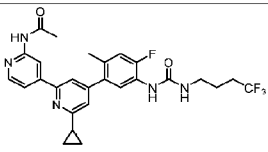
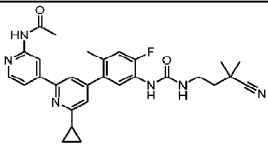
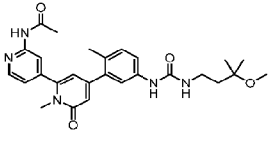
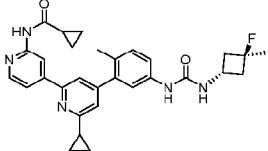
					(m, 2H), 0.21 (m, 2H).	
38	H9 		P	50	8.48 (s, 1H), 8.22 (s, 1H), 7.95 (s, 1H), 7.28 (m, 2H), 7.12 (d, J = 8.2 Hz, 1H), 6.89 (s, 1H), 6.47 (s, 1H), 6.03 (t, J = 5.6 Hz, 1H), 3.85 (s, 3H), 3.71 (t, J = 4.7 Hz, 4H), 3.52 (t, J = 4.7 Hz, 4H), 3.08 (m, 5H), 2.15 (s, 3H), 1.58 (t, J = 7.7 Hz, 2H), 1.09 (s, 6H).	493.2
39	H17 		P	11	8.23 (s, 1H), 8.1 (brs, 1H), 8.00 (d, J = 8.4 Hz, 1H), 7.95 (s, 1H), 7.15 (d, J = 12.0 Hz, 1H), 6.87 (s, 1H), 6.69 (d, J = 7.6 Hz, 1H), 6.4 (s, 1H), 3.85 (s, 3H), 3.71 (brs, 4H), 3.66 (s, 1H), 3.52 (brs, 4H), 2.17 (s, 3H), 1.96 (s, 4H), 1.86 (d, J = 12.4 Hz, 2H), 1.47 (s, 2H).	529.3
40	H36 		P	44	8.67 (m, 2H), 8.33 (s, 1H), 8.08 (m, 3H), 7.66 (d, J = 1.1 Hz, 1H), 7.19 (d, J = 12.3 Hz, 1H), 6.79 (d, J = 1.1 Hz, 1H), 6.51 (t, J = 5.6 Hz, 1H), 4.87 (t, J = 5.6 Hz, 1H), 4.47 (t, J = 5.2 Hz, 2H), 3.79 (q, J = 5.3 Hz, 2H), 3.07 (m, 5H), 2.21 (s, 3H), 1.57 (m, 2H), 1.08 (s, 6H).	483.2
41	H36 		P	44	8.67 (m, 2H), 8.37 (s, 1H), 8.09 (dd, J = 1.6 and 4.7 Hz, 2H), 8.06 (d, J = 8.4 Hz, 1H), 7.66 (d, J = 1.1 Hz, 1H), 7.20 (d, J = 12.3 Hz, 1H), 6.79 (d, J = 1.1 Hz, 1H), 6.66 (t, J = 5.8 Hz, 1H), 4.88 (t, J = 5.6 Hz, 1H), 4.47 (t, J = 5.2 Hz, 2H), 3.79 (q, J = 5.2 Hz, 2H), 3.22 (m, 2H), 2.21 (s, 3H), 1.68 (m, 2H), 1.30 (s, 6H).	478.2

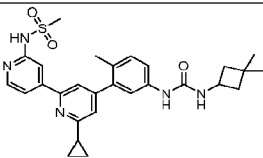
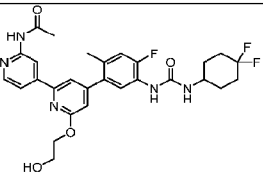
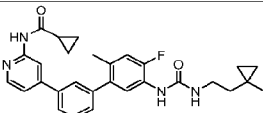
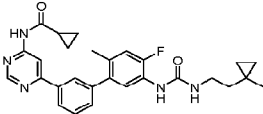
42	G1 		Q & R	53	9.04 (s, 1H), 8.15 (d, J = 5.7 Hz, 2H), 7.34 (d, J = 2.3 Hz, 1H), 7.28 (dd, J = 2.3 and 8.2 Hz, 1H), 7.17 (d, J = 8.3 Hz, 1H), 6.22 (s, 1H), 5.99 (s, 1H), 4.78 (t, J = 5.5 Hz, 1H), 4.24 (t, J = 5.3 Hz, 2H), 3.86 (s, 3H), 3.68(m, 6H), 3.44 (t, J = 4.7 Hz, 4H), 2.16 (s, 3H).	521.2
43	G1 		Q & R	25	10.5 (s, 1H), 9.20 (s, 1H), 7.68 (s, 1H), 7.36 (m, 2H), 7.21 (d, J = 8.3 Hz, 1H), 6.22 (s, 1H), 5.99 (s, 1H), 4.78 (t, J = 5.5 Hz, 1H), 4.24 (t, J = 5.3 Hz, 2H), 3.69 (m, 6H), 3.44 (t, J = 4.7 Hz, 4H), 2.16 (s, 3H).	524.2
44	G1 		Q & R	32	8.57 (m, 1H), 8.26 (s, 1H), 7.79 (s, 1H), 7.37 (s, 1H), 7.34 (d, J = 2.3 Hz, 1H), 7.29 (dd, J = 2.4 and 8.2 Hz, 1H), 7.14 (d, J = 8.3 Hz, 1H), 6.20 (s, 1H), 5.98 (s, 1H), 4.78 (t, J = 5.6 Hz, 1H), 4.24 (t, J = 5.3 Hz, 2H), 3.69 (m, 6H), 3.44 (t, J = 4.7 Hz, 4H), 2.15 (s, 3H), 1.47 (s, 9H).	495.2
45	G1 		Q & R	9	8.63 (s, 1H), 8.47 (m, 1H), 7.90 (s, 1H), 7.51 (s, 1H), 7.31 (m, 2H), 7.15 (d, J = 8.9 Hz, 1H), 6.21 (s, 1H), 5.98 (s, 1H), 5.04 (q, J = 9.0 Hz, 2H), 4.78 (t, J = 5.5 Hz, 1H), 4.24 (t, J = 5.3 Hz, 2H), 3.68 (m, 6H), 3.44 (t, J = 4.7 Hz, 4H), 2.15 (s, 3H).	521.2
46	H38 		P & deprotection with HCl	10	8.50 (s, 1H), 8.30 (s, 1H), 7.98 (s, 1H), 7.31 (m, 2H), 7.14 (d, J = 8.4 Hz, 1H), 6.93 (s, 1H), 6.47 (s, 1H), 6.0 (t, J = 5.6 Hz, 1H), 4.22 (t, J = 11.6 Hz, 1H), 3.72 (m, 4H), 3.52 (brm, 4H), 3.09 (m, 7H), 2.62 (m, 2H),	562.5

					2.16 (s, 3H), 1.99 (m, 2H), 1.80 (m, 2H), 1.59 (t, J = 8 Hz, 2H), 1.10 (s, 6H). NH missing	
47	A3 I15		T & R	16	10.6 (s, 1H), 8.78 (s, 1H), 8.38 (d, J = 5.3 Hz, 1H), 8.19 (s, 1H), 8.04 (d, J = 8.3 Hz, 1H), 7.75 (m, 1H), 7.47 (s, 1H), 7.19 (d, J = 12.2 Hz, 1H), 6.84 (d, J = 7.6 Hz, 1H), 6.80 (s, 1H), 4.88 (t, J = 5.6 Hz, 1H), 4.44 (t, J = 5.1 Hz, 2H), 4.06 (m, 1H), 3.79 (q, J = 5.2 Hz, 2H), 2.20 (s, 3H), 2.11 (s, 3H), 2.06 (m, 2H), 1.60 (m, 2H), 1.09 (s, 3H), 1.08 (s, 3H).	522.2
48 9603	G40 		U	18	10.5 (s, 1H), 9.2 (brs, 1H), 9.0 (brs, 1H), 8.85 (s, 2H), 8.61 (s, 1H), 8.42 (brs, 1H), 8.05 (s, 1H), 7.92 (s, 1H), 7.80 (brs, 1H), 7.65 (m, 4H), 7.57 (brs, 1H), 2.43 (s, 3H), 2.12 (s, 3H).	506.9
49	A3 I2		T & R	42	10.6 (s, 1H), 8.79 (s, 1H), 8.42 (s, 1H), 8.38 (d, J = 5.3 Hz, 1H), 7.76 (dd, J = 1.6 and 5.3 Hz, 1H), 7.50 (s, 1H), 7.38 (d, J = 2.3 Hz, 1H), 7.32 (dd, J = 2.4 and 8.3 Hz, 1H), 7.18 (d, J = 8.4 Hz, 1H), 6.81 (s, 1H), 6.50 (d, J = 7.0 Hz, 1H), 4.88 (t, J = 5.5 Hz, 1H), 4.44 (t, J = 5.1 Hz, 2H), 4.20 (m, 1H), 3.80 (m, 2H), 2.53 (m, 2H), 2.19 (s, 3H), 2.11 (s, 3H), 2.02-2.09 (m, 2H), 1.45 (d, J = 22.2 Hz, 3H).	508.2
50	A9 I2		T	25	8.82 (s, 1H), 8.44 (s, 1H), 8.40 (d, J = 5.3 Hz, 1H), 7.81 (d, J = 5.3 Hz, 1H), 7.53 (s, 1H), 7.39 (d, J = 2.2 Hz, 1H), 7.31 (d, J = 8.5 Hz, 1H), 7.18 (d, J = 8.4 Hz, 1H), 6.82 (s, 1H),	551.2

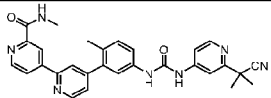
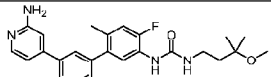
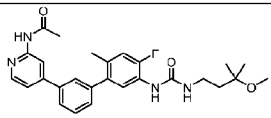
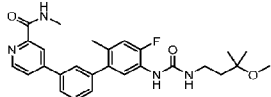
					6.52 (d, J = 7.0 Hz, 1H), 4.89 (t, J = 5.5 Hz, 1H), 4.45 (t, J = 5.0 Hz, 2H), 4.20 (m, 1H), 3.80 (m, 2H), 3.17 (brs, 1H), 2.95 (brs, 1H), 2.53 (m, 2H), 2.36 (brs, 6H), 2.19 (s, 3H), 2.05 (m, 2H), 1.57 (brs, 1H), 1.45 (d, J = 22.2 Hz, 3H).	
51	A3 I5		T	69	10.5 (s, 1H), 8.75 (s, 1H), 8.37 (d, J = 5.3 Hz, 1H), 8.32 (s, 1H), 8.07 (d, J = 8.4 Hz, 1H), 7.71 (d, J = 5.3 Hz, 1H), 7.59 (s, 1H), 7.33 (s, 1H), 7.19 (d, J = 12.3 Hz, 1H), 6.50 (t, J = 5.6 Hz, 1H), 3.14 (m, 2H), 2.23 (m, 1H), 2.19 (s, 3H), 2.11 (s, 3H), 1.35 (m, 2H), 1.08 (m, 2H), 1.03 (m, 2H), 1.01 (s, 3H), 0.26 (m, 2H), 0.20 (m, 2H).	502.2
52	A3 I6		T & R	47	10.6 (s, 1H), 8.78 (s, 1H), 8.38 (d, J = 5.3 Hz, 1H), 8.35 (s, 1H), 8.06 (d, J = 8.4 Hz, 1H), 7.75 (d, J = 5.3 Hz, 1H), 7.48 (s, 1H), 7.20 (d, J = 12.3 Hz, 1H), 6.80 (s, 1H), 6.62 (t, J = 5.7 Hz, 1H), 4.88 (t, J = 5.0 Hz, 1H), 4.44 (t, J = 5.0 Hz, 2H), 3.79 (d, J = 5.4 Hz, 2H), 3.38 (d, J = 5.6 Hz, 2H), 2.20 (s, 3H), 2.11 (s, 3H), 1.92 (d, J = 2.6 Hz, 6H).	538.2
53	A3 I7		T & R	52	10.5 (s, 1H), 8.73 (s, 1H), 8.33 (d, J = 5.3 Hz, 1H), 8.16 (s, 1H), 8.04 (d, J = 8.4 Hz, 1H), 7.69 (d, J = 5.3 Hz, 1H), 7.42 (s, 1H), 7.13 (d, J = 12.3 Hz, 1H), 6.74 (s, 1H), 6.53 (d, J = 7.7 Hz, 1H), 4.82 (t, J = 5.6 Hz, 1H), 4.39 (t, J = 5.0 Hz, 2H), 3.74 (m, 2H), 3.37 (m, 1H), 2.14 (s, 3H), 2.05 (s, 3H), 1.71 (d, J =	522.2

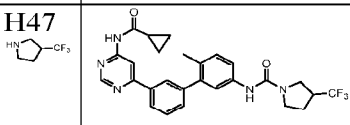
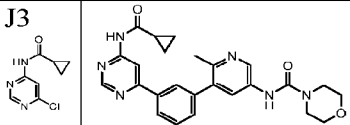
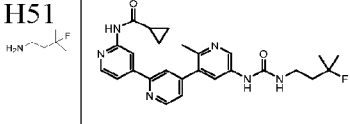
					11.6 Hz, 2H), 1.57 (m, 2H), 1.44 (brs, 1H), 1.04-1.25 (m, 5H).	
54	A3 I18		T	50	10.5 (s, 1H), 8.75 (s, 1H), 8.36 (m, 2H), 8.05 (d, J = 8.4 Hz, 1H), 7.71 (d, J = 5.3 Hz, 1H), 7.58 (s, 1H), 7.32 (s, 1H), 7.19 (d, J = 12.3 Hz, 1H), 6.61 (t, J = 5.8 Hz, 1H), 3.18 (q, J = 7.1 Hz, 2H), 2.24 (m, 1H), 2.19 (s, 3H), 2.11 (s, 3H), 1.70 (m, 2H), 1.08 (s, 2H), 1.02 (m, 2H), 0.89 (m, 2H), 0.75 (m, 2H).	556.2
55	A3 I19		T	58	10.6 (s, 1H), 8.75 (s, 1H), 8.38 (d, J = 5.3 Hz, 1H), 8.33 (s, 1H), 8.07 (d, J = 8.4 Hz, 1H), 7.74 (d, J = 5.3 Hz, 1H), 7.66 (s, 1H), 7.29 (s, 1H), 7.19 (d, J = 12.3 Hz, 1H), 6.51 (t, J = 5.6 Hz, 1H), 3.14 (q, J = 6.9 Hz, 2H), 2.61 (s, 3H), 2.19 (s, 3H), 2.11 (s, 3H), 1.34 (t, J = 7.5 Hz, 2H), 1.00 (s, 3H), 0.26 (m, 2H), 0.20 (m, 2H).	476.2
56	A3 I10		T	43	10.5 (s, 1H), 8.75 (s, 1H), 8.36 (m, 2H), 8.05 (d, J = 8.4 Hz, 1H), 7.72 (d, J = 5.3 Hz, 1H), 7.59 (s, 1H), 7.33 (s, 1H), 7.20 (d, J = 12.3 Hz, 1H), 6.60 (t, J = 5.7 Hz, 1H), 3.15 (m, 2H), 2.23 (m, 1H), 2.19 (s, 3H), 2.10 (s, 3H), 1.61 (t, J = 8.0 Hz, 2H), 1.09 (s, 6H), 1.09 (m, 2H), 1.02 (m, 2H).	558.2
57	A3 I11		T	63	10.5 (s, 1H), 8.76 (s, 1H), 8.50 (s, 1H), 8.35 (d, J = 5.3 Hz, 1H), 7.72 (d, J = 5.3 Hz, 1H), 7.33 (m, 2H), 7.16 (m, 2H), 6.82 (s, 1H), 6.02 (t, J = 5.7 Hz, 1H), 3.74 (t, J = 4.6 Hz, 4H), 3.60 (t, J = 4.6 Hz, 4H), 3.14 (m, 2H), 2.17 (s, 3H),	529.2

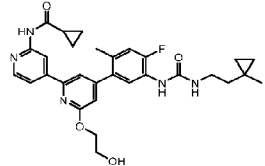
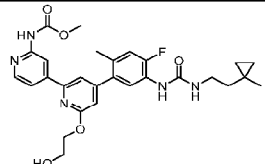
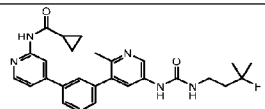
					2.10 (s, 3H), 1.35 (t, J = 7.5 Hz, 2H), 1.01 (s, 3H), 0.26 (t, J = 0.7 Hz, 2H), 0.20 (t, J = 0.8 Hz, 2H).	
58	A3 I12		T	54	10.5 (s, 1H), 8.75 (s, 1H), 8.37 (d, J = 5.2 Hz, 1H), 8.32 (s, 1H), 8.05 (d, J = 8.4 Hz, 1H), 7.71 (d, J = 5.3 Hz, 1H), 7.59 (s, 1H), 7.33 (s, 1H), 7.20 (d, J = 12.3 Hz, 1H), 6.69 (t, J = 5.8 Hz, 1H), 3.12 (m, 2H), 2.24 (m, 3H), 2.21 (s, 3H), 2.11 (s, 3H), 1.63 (m, 2H), 1.08 (s, 2H), 1.02 (m, 2H).	530.2
59	A3 I13		T	32	10.5 (s, 1H), 8.75 (s, 1H), 8.37 (d, J = 4.2 Hz, 2H), 8.05 (d, J = 8.4 Hz, 1H), 7.72 (d, J = 5.3 Hz, 1H), 7.59 (s, 1H), 7.33 (s, 1H), 7.20 (d, J = 12.2 Hz, 1H), 6.66 (t, J = 5.8 Hz, 1H), 3.22 (m, 2H), 2.24 (m, 1H), 2.20 (s, 3H), 2.10 (s, 3H), 1.69 (m, 2H), 1.30 (s, 6H), 1.08 (s, 2H), 1.02 (m, 2H).	515.2
60	A3 I14		T	27	10.7 (s, 1H), 8.5 (s, 1H), 8.44 (d, J = 4.8 Hz, 1H), 8.16 (s, 1H), 7.35 (s, 1H), 7.30 (m, 2H), 7.12 (d, J = 8.4 Hz, 1H), 6.38 (s, 1H), 6.15 (s, 1H), 6.0 (t, J = 5.2 Hz, 1H), 3.28 (s, 3H), 3.06 (brs, 5H), 2.21 (s, 3H), 2.11 (s, 3H), 1.59 (t, J = 7.6 Hz, 2H), 1.09 (s, 6H).	492.2
61	G39 		Q	7	10.8 (s, 1H), 8.75 (s, 1H), 8.41 (s, 1H), 8.38 (d, J = 5.2 Hz, 1H), 7.73 (dd, J = 1.6 Hz & 1.6 Hz, 1H), 7.59 (d, J = 1.2 Hz, 1H), 7.36 (d, J = 2.0 Hz, 1H), 7.33 (m, 2H), 7.19 (d, J = 8.4 Hz, 1H), 6.49 (d, J = 6.8 Hz, 1H), 4.22 (m, 1H), 2.57 (m, 1H), 2.50 (m, 1H), 2.26 (m, 1H), 2.24 (s, 3H), 2.10 (m, 3H), 1.45 (brs, 3H), 1.08	514.2

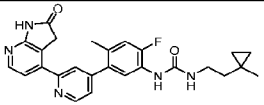
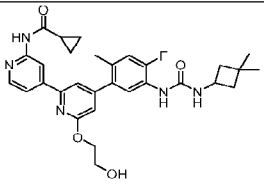
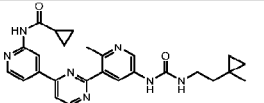
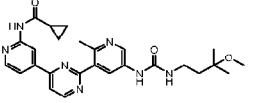
					(m, 2H), 1.03 (m, 2H), 0.81 (m, 4H).	
62	H44 	P	19	10.6 (brs, 1H), 8.30 (brs, 2H), 7.74 (brs, 1H), 7.66 (brs, 2H), 7.38 (d, J = 2.0, Hz, 1H), 7.36 (s, 1H), 7.29 (m, 1H), 7.18 (d, J = 8.4 Hz, 1H), 6.36 (d, J = 7.6 Hz, 1H), 4.10 (m, 1H), 3.31 (s, 3H), 2.28 (m, 1H), 2.19 (s, 3H), 2.06 (m, 2H), 1.64 (m, 2H), 1.11 (m, 8H), 1.05 (m, 2H).	520.2	
63	A3 I16 	T & R	69	10.6 (s, 1H), 8.78 (s, 1H), 8.38 (d, J = 5.3 Hz, 1H), 8.24 (d, J = 2.4 Hz, 1H), 8.08 (d, J = 8.4 Hz, 1H), 7.75 (dd, J = 1.6 and 5.3 Hz, 1H), 7.48 (s, 1H), 7.20 (d, J = 12.3 Hz, 1H), 6.80 (s, 1H), 6.77 (d, J = 7.4 Hz, 1H), 4.88 (t, J = 5.6 Hz, 1H), 4.44 (t, J = 5.0 Hz, 2H), 3.79 (m, 2H), 3.65 (brs, 1H), 2.20 (s, 3H), 2.11 (s, 3H), 1.84-1.98 (m, 6H), 1.43-1.50 (m, 2H).	558.2	
64	A2 I16 	T	18	10.9 (s, 1H), 8.42 (s, 1H), 8.36 (d, J = 5.2 Hz, 1H), 8.30 (s, 1H), 8.03 (d, J = 8.5 Hz, 1H), 7.70 (d, J = 7.9 Hz, 1H), 7.58 (t, J = 7.7 Hz, 1H), 7.54 (s, 1H), 7.44 (dd, J = 1.6 and 5.3 Hz, 1H), 7.39 (d, J = 7.7 Hz, 1H), 7.14 (d, J = 12.3 Hz, 1H), 6.55 (t, J = 5.6 Hz, 1H), 3.13 (m, 2H), 2.16 (s, 3H), 2.02 (m, 1H), 1.34 (t, J = 7.5 Hz, 2H), 1.00 (s, 3H), 0.78-0.83 (m, 4H), 0.18-0.27 (m, 4H).	487.2	
65	J1 	T	37	11.3 (s, 1H), 8.94 (d, J = 1.1 Hz, 1H), 8.59 (s, 1H), 8.30 (s, 1H), 8.03 (t, J = 7.3 Hz, 2H), 7.91 (s, 1H), 7.60 (t, J = 7.7 Hz, 1H), 7.48 (d, J = 7.7 Hz,	488.2	

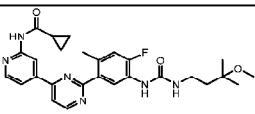
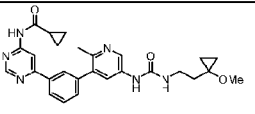
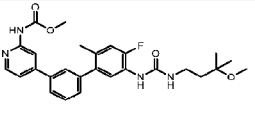
					1H), 7.15 (d, J = 12.3 Hz, 1H), 6.53 (t, J = 5.6 Hz, 1H), 3.13 (q, J = 7.0 Hz, 2H), 2.15 (s, 3H), 2.07 (p, J = 6.2 Hz, 1H), 1.34 (t, J = 7.5 Hz, 2H), 1.00 (s, 3H), 0.84-0.91 (m, 4H), 0.19-0.27 (m, 4H).	
66	A2 I17		T	23	10.9 (s, 1H), 8.41 (s, 1H), 8.38 (s, 1H), 8.36 (d, J = 5.2 Hz, 1H), 8.01 (d, J = 8.5 Hz, 1H), 7.70 (d, J = 7.9 Hz, 1H), 7.58 (t, J = 7.7 Hz, 1H), 7.54 (s, 1H), 7.44 (dd, J = 1.7 and 5.3 Hz, 1H), 7.40 (d, J = 7.7 Hz, 1H), 7.15 (d, J = 12.3 Hz, 1H), 6.79 (t, J = 5.7 Hz, 1H), 3.20 (m, 2H), 2.16 (s, 3H), 2.02 (m, 1H), 1.67 (m, 2H), 1.30 (s, 6H), 0.78-0.83 (m, 4H).	500.2
67	J2 	T	54	11.3 (s, 1H), 8.94 (d, J = 1.1 Hz, 1H), 8.59 (d, J = 1.2 Hz, 1H), 8.36 (s, 1H), 8.02 (m, 2H), 7.91 (s, 1H), 7.60 (t, J = 7.7 Hz, 1H), 7.48 (d, J = 7.7 Hz, 1H), 7.16 (d, J = 12.3 Hz, 1H), 6.73 (t, J = 5.7 Hz, 1H), 3.21 (m, 2H), 2.15 (s, 3H), 2.07 (m, 1H), 1.67 (m, 2H), 1.30 (s, 6H), 0.84-0.91 (m, 4H).	501.2	
68	A5 I18		T	8	10.9 (s, 1H), 9.70 (s, 1H), 9.29 (s, 1H), 8.84 (s, 1H), 8.78 (d, J = 5.0 Hz, 1H), 8.41 (d, J = 5.3 Hz, 1H), 8.34 (d, J = 5.6 Hz, 1H), 7.93 (s, 1H), 7.80 (dd, J = 1.6 and 5.3 Hz, 1H), 7.72 (d, J = 1.9 Hz, 1H), 7.46 (m, 3H), 7.38 (dd, J = 2.0 and 5.6 Hz, 1H), 7.29 (d, J = 8.1 Hz, 1H), 2.22 (s, 3H), 2.03 (m, 1H), 1.65 (s, 6H), 0.82 (m, 4H).	532.2

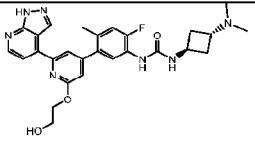
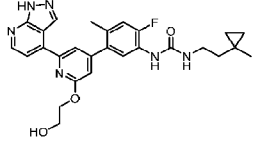
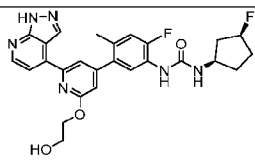
69	A4 I18		T	25	9.35 (s, 1H), 8.94 (s, 1H), 8.83 (d, J = 5.0 Hz, 2H), 8.77 (d, J = 1.7 Hz, 1H), 8.74 (d, J = 5.1 Hz, 1H), 8.36 (d, J = 5.6 Hz, 1H), 8.32 (dd, J = 1.8 and 5.1 Hz, 1H), 8.17 (s, 1H), 7.70 (d, J = 1.9 Hz, 1H), 7.52 (dd, J = 1.5 and 5.0 Hz, 1H), 7.48 (d, J = 2.3 Hz, 1H), 7.45 (dd, J = 2.3 and 8.3 Hz, 1H), 7.37 (dd, J = 2.0 and 5.6 Hz, 1H), 7.30 (d, J = 8.3 Hz, 1H), 2.85 (d, J = 4.8 Hz, 3H), 2.24 (s, 3H), 1.65 (s, 6H).	506.2
70	A3 I19	 Side product	T	29	8.30 (s, 1H), 8.01 (d, J = 8.5 Hz, 1H), 7.96 (d, J = 5.4 Hz, 1H), 7.62 (d, J = 7.8 Hz, 1H), 7.53 (t, J = 7.7 Hz, 1H), 7.48 (s, 1H), 7.34 (d, J = 7.6 Hz, 1H), 7.14 (d, J = 12.3 Hz, 1H), 6.81 (dd, J = 1.6 and 5.4 Hz, 1H), 6.74 (s, 1H), 6.56 (t, J = 5.6 Hz, 1H), 5.96 (s, 2H), 3.03-3.11 (m, 5H), 2.16 (s, 3H), 1.57 (t, J = 7.8 Hz, 2H), 1.08 (s, 6H).	437.2
71	A3 I19		T	17	10.6 (s, 1H), 8.40 (s, 1H), 8.35 (d, J = 5.2 Hz, 1H), 8.29 (s, 1H), 8.02 (d, J = 8.5 Hz, 1H), 7.70 (d, J = 7.9 Hz, 1H), 7.59 (t, J = 7.7 Hz, 1H), 7.55 (s, 1H), 7.43 (dd, J = 5.3, 1.6 Hz, 1H), 7.40 (d, J = 7.6 Hz, 1H), 7.15 (d, J = 12.3 Hz, 1H), 6.54 (t, J = 5.6 Hz, 1H), 3.04-3.11 (m, 5H), 2.17 (s, 3H), 2.10 (s, 3H), 1.56 (m, 2H), 1.08 (s, 6H).	479.2
72	A4 I19		T	57	8.82 (m, 1H), 8.68 (d, J = 5.1 Hz, 1H), 8.32 (s, 1H), 8.28 (d, J = 1.8 Hz, 1H), 8.04 (d, J = 8.5 Hz, 1H), 7.95 (dd, J = 1.9 and 5.1 Hz, 1H), 7.84 (d, J = 7.9 Hz, 1H), 7.70 (s, 1H), 7.61	

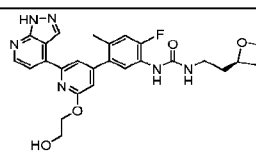
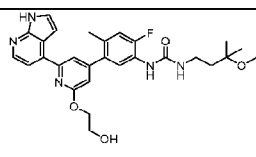
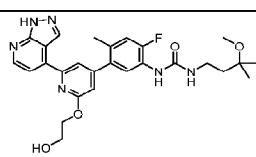
					(t, J = 7.7 Hz, 1H), 7.43 (d, J = 7.7 Hz, 1H), 7.15 (d, J = 12.3 Hz, 1H), 6.59 (t, J = 5.6 Hz, 1H), 3.08 (m, 5H), 2.84 (d, J = 4.8 Hz, 3H), 2.18 (s, 3H), 1.56 (m, 2H), 1.08 (s, 6 H).	
73	H47 	P	39	11.33 (s, 1H), 8.95 (s, 1H), 8.60 (s, 1H), 8.29 (s, 1H), 8.04 (d, J = 8.0 Hz, 1H), 7.95 (s, 1H), 7.61 (t, J = 8.0 Hz, 1H), 7.52 (br d, J = 8.0 Hz, 1H), 7.49 (dd, J = 6.0, 2.0 Hz, 1H), 7.44 (d, J = 2.0 Hz, 1H), 7.18 (d, J = 8.4 Hz, 1H), 3.66 (m, 1H), 3.54 (m, 1H), 3.42-3.51 (m, 2H), 3.26 (br m, 1H), 2.18 (s, 3H), 2.11-2.21 (m, 1H), 2.06 (m, 1H), 2.02 (m, 1H), 0.89 (m, 4H).	510.4	
74	J3 	T	15	11.4 (s, 1H), 8.97 (d, J = 1.2 Hz, 1H), 8.76 (s, 1H), 8.59-8.64 (m, 2H), 8.08 (dt, J = 1.5 and 7.7 Hz, 1H), 8.01 (t, J = 1.9 Hz, 1H), 7.82 (d, J = 2.5 Hz, 1H), 7.66 (t, J = 7.7 Hz, 1H), 7.60 (dt, J = 1.4 and 7.7 Hz, 1H), 3.62 (dd, J = 4.0 and 5.6 Hz, 4H), 3.45 (dd, J = 4.0 and 5.7 Hz, 4H), 2.39 (s, 3H), 2.07 (m, 1H), 0.87-0.94 (m, 4H).	459.2	
75	H51 	P	39	10.9 (s, 1H), 8.86 (m, 1H), 8.81 (m, 2H), 8.52 (d, J = 2.5 Hz, 1H), 8.43 (dd, J = 0.8 and 5.3 Hz, 1H), 8.00 (m, 1H), 7.88 (d, J = 2.6 Hz, 1H), 7.81 (dd, J = 5.3, 1.6 Hz, 1H), 7.54 (dd, J = 1.6 and 4.9 Hz, 1H), 6.30 (t, J = 5.7 Hz, 1H), 3.21 (m, 2H), 2.39 (s, 3H), 2.05 (m, 1H), 1.79 (m, 2H), 1.34 (d, J = 20.0 Hz, 6H), 0.85 (m, 4H).	477.2	

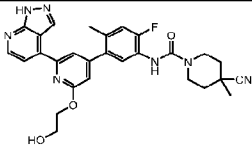
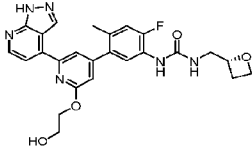
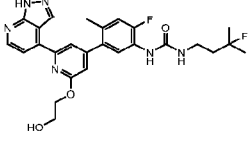
76	A2 I15		T & R	73	10.9 (s, 1H), 8.76 (m, 1H), 8.40 (d, J = 5.2 Hz, 1H), 8.33 (d, J = 2.4 Hz, 1H), 8.07 (d, J = 8.5 Hz, 1H), 7.76 (dd, J = 1.6 and 5.3 Hz, 1H), 7.45 (d, J = 1.1 Hz, 1H), 7.18 (d, J = 12.3 Hz, 1H), 6.80 (d, J = 1.1 Hz, 1H), 6.50 (t, J = 5.6 Hz, 1H), 4.87 (t, J = 5.6 Hz, 1H), 4.40-4.46 (m, 2H), 3.79 (q, J = 5.3 Hz, 2H), 3.15-3.12 (m, 2H), 2.19 (s, 3H), 2.03 (m, 1H), 1.31-1.38 (m, 2H), 1.00 (s, 3H), 0.76-0.87 (m, 4H), 0.24-0.30 (m, 2H), 0.17-0.23 (m, 2H).	548.2
77	A6 I14		T & R	10	10.3 (s, 1H), 8.55 (t, J = 1.1 Hz, 1H), 8.38 (d, J = 2.3 Hz, 1H), 8.34 (d, J = 5.2 Hz, 1H), 8.08 (d, J = 8.4 Hz, 1H), 7.72 (dd, J = 1.6 and 5.3 Hz, 1H), 7.50 (d, J = 1.2 Hz, 1H), 7.19 (d, J = 12.3 Hz, 1H), 6.80 (d, J = 1.1 Hz, 1H), 6.60 (t, J = 5.6 Hz, 1H), 4.89 (t, J = 5.6 Hz, 1H), 4.45 (t, J = 5.1 Hz, 2H), 3.80 (q, J = 5.3 Hz, 2H), 3.69 (s, 3H), 3.10-3.15 (m, 2H), 2.20 (s, 3H), 1.31-1.38 (m, 2H), 1.00 (s, 3H), 0.26 (q, J = 3.8 Hz, 2H), 0.16-0.23 (m, 2H).	538.2
78	A2 I28		T	50	10.8 (s, 1H), 8.65 (s, 1H), 8.35-8.40 (m, 2H), 8.31 (d, J = 5.2 Hz, 1H), 7.75 (d, J = 2.5 Hz, 1H), 7.68 (m, 1H), 7.51-7.61 (m, 2H), 7.42 (dt, J = 1.3 and 7.6 Hz, 1H), 7.40 (dd, J = 1.7 and 5.2 Hz, 1H), 6.19 (t, J = 5.7 Hz, 1H), 3.09-3.17 (m, 2H), 2.29 (s, 3H), 1.92-2.03 (m, 1H), 1.65-1.77 (m, 2H), 1.26 (d, J = 20.0 Hz, 6H), 0.76 (m, 4H).	496.2

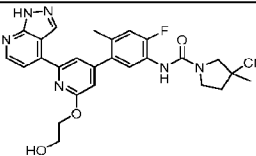
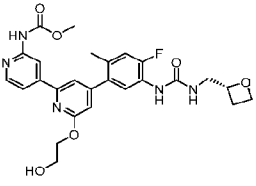
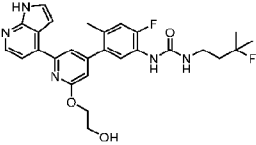
79	A7 I1		T	18	10.9 (s, 1H), 8.58 (m, 1H), 8.13 (d, J = 2.3 Hz, 1H), 7.96 (d, J = 5.6 Hz, 1H), 7.89 (d, J = 8.5 Hz, 1H), 7.68 (t, J = 1.2 Hz, 1H), 7.32 (d, J = 5.6 Hz, 1H), 7.21 (dd, J = 1.6 and 5.0 Hz, 1H), 7.01 (d, J = 12.3 Hz, 1H), 6.30 (t, J = 5.7 Hz, 1H), 3.70 (s, 2H), 2.94 (m, 2H), 2.02 (s, 3H), 1.11-1.17 (m, 2H), 0.80 (s, 3H), 0.03-0.09 (m, 4H).	460.2
80	A2 I15		T	44	10.9 (s, 1H), 8.76 (s, 1H), 8.40 (d, J = 5.2 Hz, 1H), 8.18 (d, J = 2.5 Hz, 1H), 8.04 (d, J = 8.3 Hz, 1H), 7.76 (dd, J = 5.3, 1.7 Hz, 1H), 7.45 (s, 1H), 7.19 (d, J = 12.3 Hz, 1H), 6.78-6.86 (m, 2H), 4.88 (t, J = 5.5 Hz, 1H), 4.43 (t, J = 5.1 Hz, 2H), 4.00-4.12 (m, 1H), 3.79 (q, J = 5.3 Hz, 2H), 2.19 (s, 3H), 1.99-2.13 (m, 3H), 1.56-1.64 (m, 2H), 1.09 (d, J = 4.7 Hz, 6H), 0.77-0.90 (m, 4H).	548.2
81	H50 		P	15	11.0 (s, 1H), 9.10 (d, J = 5.2 Hz, 1H), 8.94 (s, 1H), 8.75 (s, 1H), 8.56 (d, J = 2.4 Hz, 1H), 8.53 (d, J = 5.2 Hz, 1H), 8.42 (d, J = 2.4 Hz, 1H), 8.06 (d, J = 5.2 Hz, 1H), 7.86 (dd, J = 1.2 and 5.2 Hz, 1H), 6.16 (t, J = 5.6 Hz, 1H), 3.18 (dd, J = 6.0 and 14.8 Hz, 2H), 2.69 (s, 3H), 2.05 (m, 1H), 1.38 (m, 2H), 1.03 (s, 3H), 0.80-0.86 (m, 4H), 0.26-0.31 (m, 2H), 0.19-0.24 (m, 2H).	472.4
82	H50 		P	20	11.0 (s, 1H), 9.10 (d, J = 5.2 Hz, 1H), 8.94 (s, 1H), 8.80 (s, 1H), 8.56 (d, J = 2.8 Hz, 1H), 8.53 (d, J = 5.2 Hz, 1H), 8.42 (d, J = 2.4	490.4

					Hz, 1H), 8.06 (d, J = 5.2 Hz, 1H), 7.86 (dd, J = 1.2 and 5.2 Hz, 1H), 6.20 (t, J = 5.6 Hz, 1H), 3.11-3.16 (m, 2H), 3.10 (s, 3H), 2.71 (s, 3H), 2.06 (m, 1H), 1.61 (m, 2H), 1.11 (s, 6H), 0.81-0.89 (m, 4H).	
83	H53 	P	26	11.0 (s, 1H), 9.06 (d, J = 4.4 Hz, 1H), 8.92 (s, 1H), 8.66 (d, J = 8.8 Hz, 1H), 8.51 (d, J = 5.2 Hz, 1H), 8.30 (d, J = 1.6 Hz, 1H), 8.02 (d, J = 5.6 Hz, 1H), 7.85 (dd, J = 5.2, 1.6 Hz, 1H), 7.21 (d, J = 12.4 Hz, 1H), 6.50 (t, J = 5.2 Hz, 1H), 3.10-3.15 (m, 2H), 3.09 (s, 3H), 2.40-2.60 (m, 3H: under solvent DMSO) 2.04 (m, 1H), 1.60 (m, 2H), 1.10 (s, 6H), 0.82-0.89 (m, 4H).	507.4	
84	H54 	P	35	11.3 (s, 1H), 8.96 (s, 1H), 8.75 (s, 1H), 8.60 (s, 1H), 8.42 (d, J = 2.4 Hz, 1H), 8.07 (d, J = 7.6 Hz, 1H), 8.02 (s, 1H), 7.84 (d, J = 2.4 Hz, 1H), 7.65 (t, J = 7.6 Hz, 1H), 7.57 (d, J = 7.6 Hz, 1H), 6.23 (t, J = 5.6 Hz, 1H), 3.21 (q, J = 6.4 Hz, 2H), 3.16 (s, 3H), 2.35 (s, 3H), 2.07 (m, 1H), 1.69 (t, J = 7.2 Hz, 2H), 0.85-0.90 (m, 4H), 0.62-0.68 (t, J = 5.2 Hz, 2H), 0.37-0.44 (t, J = 6.4 Hz, 2H).	487.4	
85	H55 	P	10	10.3 (s, 1H), 8.33 (d, J = 5.3 Hz, 1H), 8.28 (d, J = 2.3 Hz, 1H), 8.16 (d, J = 1.5 Hz, 1H), 8.03 (d, J = 8.5 Hz, 1H), 7.76-7.68 (m, 1H), 7.55-7.63 (m, 2H), 7.37-7.44 (m, 2H), 7.16 (d, J = 12.4 Hz, 1H), 3.69 (s, 3H), 3.03-3.13 (m, 6H), 2.18 (s, 3H), 1.55-1.63 (m,	495.2	

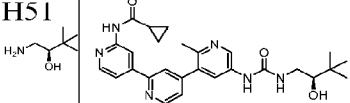
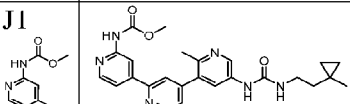
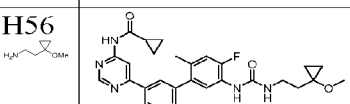
86	H49 		P & deprotection with HCl	53	2H), 1.09 (s, 6H). 10.2 (s, 1H), 8.71 (s, 1H), 8.61 (d, J = 4.9 Hz, 1H), 8.38 (d, J = 6.1 Hz, 1H), 8.05 (s, 1H), 7.83 (d, J = 4.9 Hz, 1H), 7.77 (d, J = 1.1 Hz, 1H), 7.23 (d, J = 12.2 Hz, 1H), 7.13 (d, J = 6.1 Hz, 1H), 6.87 (d, J = 1.1 Hz, 1H), 4.54 (t, J = 5.1 Hz, 2H), 4.04-4.12 (m, 3H), 3.84 (t, J = 5.1 Hz, 2H), 3.78 (p, J = 7.5 Hz, 1H), 2.68 (s, 3H), 2.67 (s, 3H), 2.57 (m, 1H), 2.26 (s, 3H), 2.20-2.25 (m, 2H).	520.2
87	H49 		P & deprotection with HCl	61	13.8 (s, 1H), 8.70 (s, 1H), 8.60 (d, J = 4.8 Hz, 1H), 8.34 (d, J = 2.4 Hz, 1H), 8.12 (d, J = 8.4 Hz, 1H), 7.82 (d, J = 4.9 Hz, 1H), 7.76 (d, J = 1.2 Hz, 1H), 7.20 (d, J = 12.4 Hz, 1H), 6.86 (d, J = 1.1 Hz, 1H), 6.51 (t, J = 5.7 Hz, 1H), 4.53 (t, J = 5.1 Hz, 2H), 3.83 (t, J = 5.2 Hz, 2H), 3.19-3.11 (m, 2H), 2.24 (s, 3H), 1.31-1.38 (m, 2H), 1.00 (s, 3H), 0.23-0.28 (m, 2H), 0.18-0.23 (m, 2H). OH peak is under water	505.2
88	H49 		P & deprotection with HCl	30	13.7 (s, 1H), 8.64 (s, 1H), 8.54 (d, J = 4.9 Hz, 1H), 8.27 (d, J = 2.4 Hz, 1H), 8.08 (d, J = 8.4 Hz, 1H), 7.77 (d, J = 4.9 Hz, 1H), 7.71 (d, J = 1.1 Hz, 1H), 7.15 (d, J = 12.3 Hz, 1H), 6.80 (d, J = 1.1 Hz, 1H), 6.72 (d, J = 7.6 Hz, 1H), 5.13 (td, J = 4.9, 2.5 Hz, 1H), 5.02 (td, J = 4.9, 2.4 Hz, 1H), 4.86 (t, J = 5.5 Hz, 1H), 4.48 (t, J = 5.1 Hz, 2H), 3.99 (m, 1H), 3.78 (q, J = 5.3 Hz, 2H), 2.19 (s, 3H), 2.02-2.25 (m, 1H), 1.50-1.96 (m, 4H),	509.2

					1.42-1.52 (m, 1H).	
89	H49 	P & deprotection with HCl	31	13.8 (s, 1H), 8.72 (s, 1H), 8.60 (d, J = 4.9 Hz, 1H), 7.85 (d, J = 4.9 Hz, 1H), 7.76 (d, J = 1.2 Hz, 1H), 7.05 (d, J = 11.9 Hz, 1H), 6.91 (s, 1H), 6.87 (d, J = 1.1 Hz, 1H), 4.92 (t, J = 5.5 Hz, 1H), 4.54 (t, J = 5.2 Hz, 2H), 4.49 (t, J = 5.2 Hz, 1H), 4.26-4.35 (m, 1H), 3.85 (q, J = 5.3 Hz, 2H), 3.47 (s, 2H), 3.21-3.27 (m, 2H), 2.24 (s, 3H), 1.96 (d, J = 13.6 Hz, 1H), 1.70 (qt, J = 13.3, 7.6 Hz, 2H). 2Hs are missing	507.2	
90	D4 I24 	P & deprotection with HCl	10	11.8 (s, 1H), 8.34 (s, 1H), 8.30 (d, J = 5.0 Hz, 1H), 8.11 (d, J = 8.4 Hz, 1H), 7.62 (d, J = 5.0 Hz, 1H), 7.58 (t, J = 3.0 Hz, 1H), 7.56 (d, J = 1.2 Hz, 1H), 7.19 (d, J = 12.3 Hz, 1H), 7.02 (dd, J = 3.5, 1.9 Hz, 1H), 6.78 (d, J = 1.1 Hz, 1H), 6.52 (t, J = 5.7 Hz, 1H), 4.89 (t, J = 5.5 Hz, 1H), 4.49 (t, J = 5.1 Hz, 2H), 3.81 (q, J = 5.4 Hz, 2H), 3.06-3.13 (m, 5H), 2.25 (s, 3H), 1.55-1.61 (m, 2H), 1.08 (s, 6H).	522.2	
91	H49 	P & deprotection with HCl	49	13.8 (s, 1H), 8.70 (d, J = 1.4 Hz, 1H), 8.59 (d, J = 4.8 Hz, 1H), 8.34 (d, J = 2.3 Hz, 1H), 8.11 (d, J = 8.4 Hz, 1H), 7.82 (d, J = 4.9 Hz, 1H), 7.76 (d, J = 1.2 Hz, 1H), 7.20 (d, J = 12.3 Hz, 1H), 6.86 (d, J = 1.1 Hz, 1H), 6.52 (t, J = 5.7 Hz, 1H), 4.91 (t, J = 5.5 Hz, 1H), 4.53 (t, J = 5.1 Hz, 2H), 3.83 (td, J = 5.5, 5.1 Hz, 2H), 3.07-3.12 (m, 2H), 3.07 (s, 3H), 2.24 (s, 3H), 1.54-1.61 (m, 2H),	523.2	

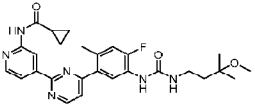
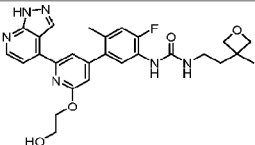
					1.08 (s, 6H).	
92	D3 I21		T & deprote ction with HCl	26	13.8 (s, 1H), 8.71 (d, J = 1.5 Hz, 1H), 8.60 (d, J = 4.8 Hz, 1H), 8.43 (s, 1H), 7.84 (d, J = 4.9 Hz, 1H), 7.78 (d, J = 1.2 Hz, 1H), 7.42 (d, J = 8.1 Hz, 1H), 7.22 (d, J = 11.6 Hz, 1H), 6.88 (d, J = 1.1 Hz, 1H), 4.91 (t, J = 5.5 Hz, 1H), 4.53 (t, J = 5.2 Hz, 2H), 4.08 (m, 2H), 3.83 (td, J = 5.5 and 5.2 Hz, 2H), 2.96 (m, 2H), 2.29 (s, 3H), 1.85-1.92 (m, 2H), 1.48 (td, J = 4.0 and 13.0 Hz, 2H), 1.36 (s, 3H).	530.2
93	H49 		P & deprote ction with HCl	45	13.6 (s, 1H), 8.62 (s, 1H), 8.53 (d, J = 4.8 Hz, 1H), 7.74 (d, J = 5.0 Hz, 1H), 7.67 (d, J = 1.2 Hz, 1H), 7.00 (d, J = 11.7 Hz, 1H), 6.79 (s, 1H), 4.73 (m, 1H), 4.64 (p, J = 7.1 Hz, 1H), 4.47 (t, J = 5.2 Hz, 2H), 4.38 (m, 1H), 3.77 (m, 2H), 3.55 (t, J = 8.6 Hz, 1H), 3.43 (m, 2H), 2.18 (s, 3H), 1.74-1.83 (m, 1H), 1.69 (m, 1H). 3Hs are missing	493.2
94	H49 		P & deprote ction with HCl	46	13.8 (s, 1H), 8.70 (d, J = 1.4 Hz, 1H), 8.60 (d, J = 4.9 Hz, 1H), 8.38 (d, J = 2.3 Hz, 1H), 8.12 (d, J = 8.1 Hz, 1H), 7.82 (d, J = 4.9 Hz, 1H), 7.76 (d, J = 1.2 Hz, 1H), 7.21 (d, J = 12.3 Hz, 1H), 6.86 (d, J = 1.1 Hz, 1H), 6.57 (t, J = 5.7 Hz, 1H), 4.92 (t, J = 5.5 Hz, 1H), 4.53 (t, J = 5.2 Hz, 2H), 3.83 (td, J = 5.5, 5.2 Hz, 2H), 3.13-3.23 (m, 2H), 2.25 (s, 3H), 1.71-1.83 (m, 2H), 1.31 (d, J = 21.5 Hz, 6H).	511.2

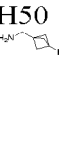
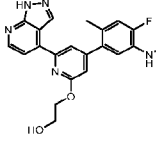
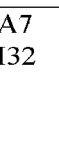
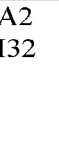
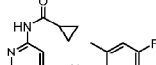
95	D3 I22		T & deprotection with HCl	43	13.8 (s, 1H), 8.71 (d, J = 1.4 Hz, 1H), 8.60 (d, J = 4.9 Hz, 1H), 8.14 (s, 1H), 7.84 (d, J = 4.9 Hz, 1H), 7.78 (d, J = 1.3 Hz, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.24 (d, J = 11.5 Hz, 1H), 6.89 (d, J = 1.2 Hz, 1H), 4.91 (t, J = 5.5 Hz, 1H), 4.53 (t, J = 5.1 Hz, 2H), 3.80-3.88 (m, 3H), 3.64 – 3.49 (m, 2H), 3.33 (d, J = 10.6 Hz, 1H), 2.36 (m, 1H), 2.30 (s, 3H), 2.04 (dt, J = 12.7, 8.2 Hz, 1H), 1.45 (s, 3H).	516.2
96	H52 		P & R	13	10.3 (s, 1H), 8.57 (d, J = 1.6 Hz, 1H), 8.51 (d, J = 2.4 Hz, 1H), 8.36 (d, J = 5.2 Hz, 1H), 8.10 (d, J = 8.4 Hz, 1H), 7.74 (dd, J = 1.6 and 5.2 Hz, 1H), 7.52 (d, J = 1.2 Hz, 1H), 7.22 (d, J = 12.3 Hz, 1H), 6.90 (t, J = 5.8 Hz, 1H), 6.83 (d, J = 1.1 Hz, 1H), 4.90 (t, J = 5.5 Hz, 1H), 4.76 (m, 1H), 4.39-4.55 (m, 4H), 3.82 (q, J = 5.3 Hz, 2H), 3.71 (s, 3H), 3.36 (dt, J = 5.8 and 14.8 Hz, 1H), 3.27 (m, 1H), 2.58 (m, 1H), 2.36 (m, 1H), 2.22 (s, 3H).	526.2
97	D4 I23		T & deprotection with HCl	17	11.8 (s, 1H), 8.44 (d, J = 2.3 Hz, 1H), 8.30 (d, J = 5.0 Hz, 1H), 8.11 (d, J = 8.4 Hz, 1H), 7.62 (d, J = 5.0 Hz, 1H), 7.61 – 7.57 (m, 1H), 7.56 (d, J = 1.2 Hz, 1H), 7.19 (d, J = 12.3 Hz, 1H), 7.04 (m, 1H), 6.78 (d, J = 1.1 Hz, 1H), 6.66 (t, J = 5.7 Hz, 1H), 4.90 (t, J = 5.6 Hz, 1H), 4.49 (t, J = 5.2 Hz, 2H), 3.81 (q, J = 5.1 Hz, 2H), 3.14-3.22 (m, 2H), 2.25 (s, 3H), 1.72-1.80 (m, 2H), 1.31 (d, J = 20.0 Hz, 6H).	510.2

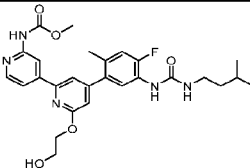
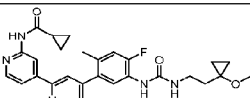
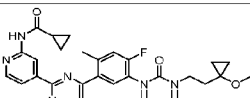
98	A2 I25		T & R	53	10.9 (s, 1H), 8.76 (s, 1H), 8.40 (d, J = 5.2 Hz, 1H), 8.28 (s, 1H), 8.06 (d, J = 8.4 Hz, 1H), 7.76 (dd, J = 1.6 and 5.2 Hz, 1H), 7.45 (s, 1H), 7.18 (d, J = 12.3 Hz, 1H), 6.80 (s, 1H), 6.57 (t, J = 5.5 Hz, 1H), 4.88 (t, J = 5.6 Hz, 1H), 4.43 (t, J = 5.1 Hz, 2H), 3.79 (q, J = 5.3 Hz, 2H), 3.03-3.12 (m, 2H), 2.19 (s, 3H), 2.03 (m, 1H), 1.02 (t, J = 7.2 Hz, 3H), 0.77-0.87 (m, 4H).	494.2
99	A2 I26		T & R	53	10.9 (s, 1H), 8.76 (s, 1H), 8.40 (d, J = 5.3 Hz, 1H), 8.31 (d, J = 2.5 Hz, 1H), 8.08 (d, J = 8.4 Hz, 1H), 7.75 (dd, J = 1.7 and 5.3 Hz, 1H), 7.45 (s, 1H), 7.19 (d, J = 12.3 Hz, 1H), 6.80 (s, 1H), 6.65 (t, J = 5.8 Hz, 1H), 4.88 (t, J = 5.6 Hz, 1H), 4.43 (t, J = 5.1 Hz, 2H), 3.78 (q, J = 5.3 Hz, 2H), 2.89 (t, J = 6.2 Hz, 2H), 2.19 (s, 3H), 2.03 (m, 1H), 1.60-1.71 (m, 1H), 0.77-0.88 (m, 10H).	522.2
100	H75 		P & deprote ction with HCl	30	13.8 (s, 1H), 8.58 (d, J = 4.8 Hz, 1H), 8.32 (d, J = 1.8 Hz, 1H), 8.28 (s, 1H), 8.08 (d, J = 8.5 Hz, 1H), 7.87 (d, J = 7.8 Hz, 1H), 7.71 (t, J = 1.8 Hz, 1H), 7.48 (d, J = 7.8 Hz, 1H), 7.40 (d, J = 4.8 Hz, 1H), 7.16 (d, J = 12.4 Hz, 1H), 6.56 (t, J = 5.6 Hz, 1H), 3.17 (q, J = 6.6 Hz, 2H), 2.23 (s, 3H), 1.70-1.80 (m, 2H), 1.33 (s, 3H), 1.29 (s, 3H). (NH proton is missing)	450.2
101	I29 		T & deprote ction with	30	13.8 (s, 1H), 8.70 (d, J = 1.4 Hz, 1H), 8.60 (d, J = 4.8 Hz, 1H), 8.22 (d, J = 2.3 Hz, 1H), 8.06 (d, J = 8.3 Hz, 1H), 7.82 (d, J =	519.2

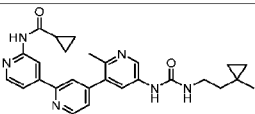
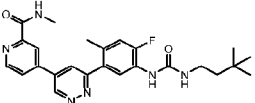
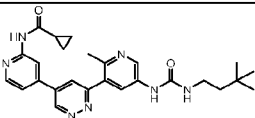
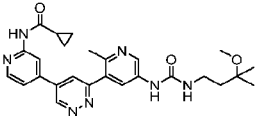
			HCl		4.9 Hz, 1H), 7.75 (d, J = 1.2 Hz, 1H), 7.20 (d, J = 12.3 Hz, 1H), 6.85 (d, J = 1.1 Hz, 1H), 6.79 (d, J = 7.4 Hz, 1H), 4.91 (s, 1H), 4.57 (s, 2H), 4.53 (t, J = 5.1 Hz, 2H), 4.47 (s, 2H), 3.80-3.92 (m, 3H), 2.50-2.55 (m, 2H), 2.24 (s, 3H), 1.95-2.03 (m, 2H).	
102	H51 		P	37	10.9 (s, 1H), 8.93 (d, J = 5.9 Hz, 1H), 8.85 (s, 1H), 8.80 (d, J = 5.0 Hz, 1H), 8.47 (d, J = 2.5 Hz, 1H), 8.41 (d, J = 5.2 Hz, 1H), 7.98 (s, 1H), 7.86 (d, J = 2.6 Hz, 1H), 7.80 (d, J = 5.0 Hz, 1H), 7.52 (d, J = 4.9 Hz, 1H), 6.23 (s, 1H), 4.78 (d, J = 5.8 Hz, 1H), 3.45 (m, 1H), 3.10 (m, 1H), 2.71 (m, 1H), 2.37 (s, 3H), 2.03 (m, 1H), 0.78-0.90 (m, 13H).	489.2
103	J1 		T	6	10.3 (s, 1H), 8.80 (d, J = 4.9 Hz, 1H), 8.69 (s, 1H), 8.61 (d, J = 1.5 Hz, 1H), 8.48 (d, J = 2.5 Hz, 1H), 8.36 (d, J = 5.2 Hz, 1H), 8.00 (m, 1H), 7.85 (d, J = 2.5 Hz, 1H), 7.75 (dd, J = 1.6 and 5.3 Hz, 1H), 7.52 (dd, J = 1.6 and 5.0 Hz, 1H), 6.19 (d, J = 5.7 Hz, 1H), 3.68 (s, 3H), 3.15 (m, 2H), 2.37 (s, 3H), 1.35 (m, 2H), 1.00 (s, 3H), 0.26 (m, 2H), 0.20 (m, 2H).	461.2
104	H56 		P	29	11.3 (s, 1H), 8.89 (d, J = 1.2 Hz, 1H), 8.53 (d, J = 1.2 Hz, 1H), 8.30 (d, J = 2.3 Hz, 1H), 7.98 (m, 2H), 7.85 (m, 1H), 7.55 (t, J = 7.7 Hz, 1H), 7.42 (dt, J = 1.5 and 7.6 Hz, 1H), 7.09 (d, J = 12.3 Hz, 1H), 6.51 (t, J = 5.7 Hz, 1H), 3.13 (q, J = 6.5 Hz, 2H), 3.09 (s, 3H), 2.09 (s, 3H), 2.05 –	504.2

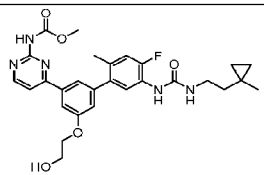
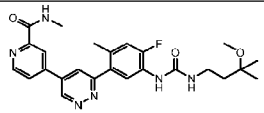
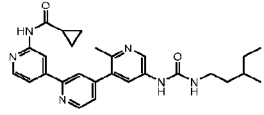
					1.97 (m, 1H), 1.61 (t, J = 7.2 Hz, 2H), 0.78-0.87 (m, 4H), 0.53-0.65 (m, 2H), 0.29-0.40 (m, 2H).	
105	A2 I31		T	32	10.9 (s, 1H), 8.76 (d, J = 1.6 Hz, 1H), 8.37-8.44 (m, 2H), 8.04 (d, J = 8.4 Hz, 1H), 7.76 (dd, J = 1.6 and 5.2 Hz, 1H), 7.45 (s, 1H), 7.19 (d, J = 12.2 Hz, 1H), 6.80 (s, 1H), 6.69 (t, J = 5.8 Hz, 1H), 6.06 (tt, J = 4.4 and 56.8 Hz, 1H), 4.88 (t, J = 5.6 Hz, 1H), 4.43 (t, J = 5.1 Hz, 2H), 3.79 (q, J = 5.3 Hz, 2H), 3.22 (q, J = 6.5 Hz, 2H), 2.19 (s, 3H), 1.90-2.07 (m, 3H), 0.76-0.87 (m, 4H).	544.2
106	H57 		P	20	11.0 (s, 1H), 8.77 (s, 1H), 8.41 (d, J = 5.2 Hz, 1H), 8.27 (brd, J = 2.0 Hz, 1H), 8.08 (d, J = 8.4 Hz, 1H), 7.76 (dd, J = 1.2 and 5.2 Hz, 1H), 7.45 (s, 1H), 7.18 (d, J = 12.8 Hz, 1H), 6.80 (s, 1H), 6.55 (t, J = 5.6 Hz, 1H), 4.88 (t, J = 5.6 Hz, 1H), 4.44 (m, 2H), 3.78 (q, J = 5.6 Hz, 2H), 3.07 (q, J = 6.8 Hz, 2H), 2.21 (s, 3H), 2.04 (m, 1H), 1.58 (m, 1H), 1.30 (q, J = 7.2 Hz, 2H), 0.87 (d, J = 6.4 Hz, 6H), 0.78- 0.84 (m, 4H).	536.2
107	H69 		P	11	11.0 (s, 1H), 9.11 (d, J = 5.2 Hz, 1H), 8.94 (s, 1H), 8.75 (s, 1H), 8.55 (d, J = 2.8 Hz, 1H), 8.53 (d, J = 5.2 Hz, 1H), 8.42 (d, J = 2.4 Hz, 1H), 8.07 (d, J = 5.6 Hz, 1H), 7.87 (dd, J = 1.2 and 5.2 Hz, 1H), 6.16 (t, J = 5.6 Hz, 1H), 3.18 (q, J = 6.0 Hz, 2H), 2.69 (s, 3H), 2.06 (m, 1H), 1.38 (m, 2H), 1.03 (s, 3H), 0.81-0.86 (m, 4H), 0.28 (m, 2H).	472.5

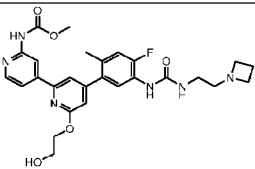
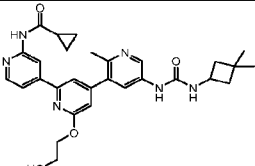
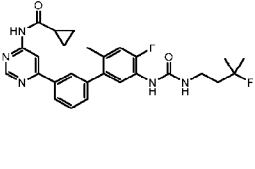
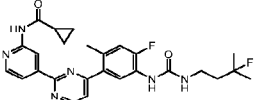
					0.22 (m, 2H).	
108	H58 	P	26	10.9 (s, 1H), 9.10 (s, 1H), 9.12 (d, J = 5.2 Hz, 1H), 8.48 (d, J = 5.2 Hz, 1H), 8.38 (s, 1H), 8.34 (d, J = 8.4 Hz, 1H), 7.98 (d, J = 5.2 Hz, 1H), 7.66 (d, J = 5.2 Hz, 1H), 7.25 (d, J = 12.3 Hz, 1H), 6.53 (t, J = 5.5 Hz, 1H), 3.09 (m, 2H), 3.08 (s, 3H), 2.40 (s, 3H), 2.04 (m, 1H), 1.60 (m, 2H), 1.09 (s, 6H), 0.81-0.86 (m, 4H).	507.5	
109	A6 I30 Side product (cyclopropyl ring open under Suzuki conditions)	T	18	10.3 (s, 1H), 8.83 (dd, J = 0.7 and 5.0 Hz, 1H), 8.68 (s, 1H), 8.64 (t, J = 1.1 Hz, 1H), 8.51 (d, J = 2.5 Hz, 1H), 8.39 (dd, J = 0.8 and 5.3 Hz, 1H), 8.03 (t, J = 1.1 Hz, 1H), 7.89 (d, J = 2.5 Hz, 1H), 7.78 (dd, J = 1.6 and 5.3 Hz, 1H), 7.54 (dd, J = 1.6 and 5.0 Hz, 1H), 6.23 (t, J = 5.6 Hz, 1H), 3.71 (s, 3H), 3.10 (m, 2H), 2.40 (s, 3H), 1.37 (m, 2H), 0.90 (s, 9H).	463.2	
110	H49 	P & deprotection with HCl	30	13.8 (s, 1H), 8.71 (d, J = 1.5 Hz, 1H), 8.60 (d, J = 4.8 Hz, 1H), 7.84 (d, J = 4.9 Hz, 1H), 7.82 (s, 1H), 7.78 (d, J = 1.2 Hz, 1H), 7.55 (d, J = 8.1 Hz, 1H), 7.21 (d, J = 11.6 Hz, 1H), 6.88 (d, J = 1.1 Hz, 1H), 4.91 (br s, 1H), 4.79 (br s, 1H), 4.53 (t, J = 5.2 Hz, 2H), 3.83 (t, J = 5.2 Hz, 2H), 3.43 (t, J = 7.1 Hz, 2H), 3.25 (s, 2H), 3.03 (d, J = 10.2 Hz, 1H), 2.29 (s, 3H), 1.82 (dt, J = 13.7, 7.3 Hz, 1H), 1.53 (dt, J = 13.1, 7.0 Hz, 1H), 1.01 (s, 3H).	521.2	

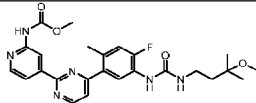
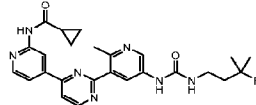
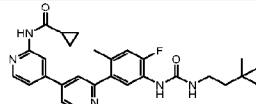
111	H50 		P & deprotection with HCl	44	13.8 (s, 1H), 8.70 (d, J = 1.4 Hz, 1H), 8.60 (d, J = 4.9 Hz, 1H), 8.36 (d, J = 2.4 Hz, 1H), 8.11 (d, J = 8.3 Hz, 1H), 7.82 (d, J = 4.9 Hz, 1H), 7.76 (d, J = 1.2 Hz, 1H), 7.22 (d, J = 12.3 Hz, 1H), 6.86 (d, J = 1.1 Hz, 1H), 6.62 (t, J = 5.7 Hz, 1H), 4.91 (t, J = 5.5 Hz, 1H), 4.53 (t, J = 5.2 Hz, 2H), 3.83 (q, J = 5.3 Hz, 2H), 3.38 (d, J = 5.5 Hz, 2H), 2.25 (s, 3H), 1.93 (d, J = 2.6 Hz, 6H).	521.2
112	A7 I32		T	10	11.1 (s, 1H), 8.77 (s, 1H), 8.47 (d, J = 2.5 Hz, 1H), 8.14 (d, J = 5.6 Hz, 1H), 7.84 (d, J = 2.5 Hz, 1H), 7.63 (s, 1H), 7.55 (d, J = 5.7 Hz, 1H), 6.88 (s, 1H), 6.25 (t, J = 5.7 Hz, 1H), 4.90 (t, J = 5.5 Hz, 1H), 4.43 (t, J = 5.1 Hz, 2H), 3.98 (s, 2H), 3.79 (q, J = 5.3 Hz, 2H), 3.12-3.19 (m, 2H), 2.39 (s, 3H), 1.33-1.39 (m, 2H), 1.01 (s, 3H), 0.19-0.29 (m, 4H).	503.2
113	A2 I32		T	54	10.9 (s, 1H), 8.78 (s, 1H), 8.69 (s, 1H), 8.47 (d, J = 2.5 Hz, 1H), 8.40 (d, J = 5.2 Hz, 1H), 7.83 (d, J = 2.5 Hz, 1H), 7.77 (dd, J = 1.6 and 5.3 Hz, 1H), 7.55 (s, 1H), 6.90 (s, 1H), 6.20 (t, J = 5.7 Hz, 1H), 4.88 (t, J = 5.5 Hz, 1H), 4.44 (t, J = 5.0 Hz, 2H), 3.79 (q, J = 5.3 Hz, 2H), 3.12-3.20 (m, 2H), 2.36 (s, 3H), 2.03 (m, 1H), 1.33-1.39 (m, 2H), 1.01 (s, 3H), 0.77-0.87 (m, 4H), 0.18-0.29 (m, 4H).	531.2
114	H53 		P	23	11.0 (s, 1H), 9.06 (d, J = 5.2 Hz, 1H), 8.93 (s, 1H), 8.67 (d, J = 8.8 Hz, 1H), 8.52 (d, J = 4.8 Hz, 1H), 8.37 (s, 1H), 8.02 (d, J =	495.5

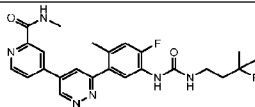
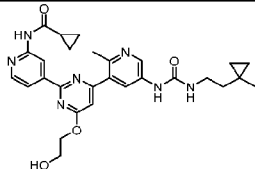
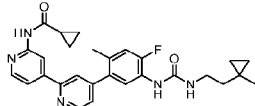
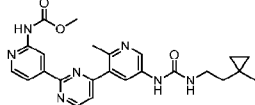
					5.2 Hz, 1H), 7.85 (d, J = 4.4 Hz, 1H), 7.22 (d, J = 12.4 Hz, 1H), 6.57 (brt, J = 5.2 Hz, 1H), 3.20 (m, 2H), 2.04 (m, 1H), 1.78 (dt, J = 7.6 and 20.0 Hz, 2H), 1.33 (d, J = 21.6 Hz, 6H), 0.81-0.86 (m, 4H). 3Hs are under solvents	
115	H61 	P & R	76	10.3 (s, 1H), 8.56 (s, 1H), 8.35 (d, J = 5.2 Hz, 1H), 8.29 (s, 1H), 8.09 (d, J = 8.4 Hz, 1H), 7.73 (d, J = 4.4 Hz, 1H), 7.50 (s, 1H), 7.20 (d, J = 12.4 Hz, 1H), 6.81 (s, 1H), 6.56 (brt, J = 5.6 Hz, 1H), 4.90 (t, J = 5.6 Hz, 1H), 4.45 (t, J = 4.8 Hz, 2H), 3.80 (q, J = 4.8 Hz, 2H), 3.69 (s, 3H), 3.08 (q, J = 6.8 Hz, 2H), 2.21 (s, 3H), 1.58 (m, 1H), 1.30 (q, J = 7.2 Hz, 2H), 0.87 (d, J = 6.4 Hz, 6H).	526.5	
116	H59 	P	20	10.9 (s, 1H), 8.83 (s, 1H), 8.76 (d, J = 4.8 Hz, 1H), 8.42 (m, 2H), 8.09 (d, J = 8.4 Hz, 1H), 7.88 (s, 1H), 7.78 (d, J = 4.8 Hz, 1H), 7.44 (d, J = 4.4 Hz, 1H), 7.22 (d, J = 12.4 Hz, 1H), 6.58 (brt, J = 5.6 Hz, 1H), 3.20 (q, J = 6.8 Hz, 2H), 3.14 (s, 3H), 2.19 (s, 3H), 2.03 (m, 1H), 1.67 (t, J = 7.2 Hz, 2H), 0.81-0.86 (m, 4H), 0.64 (m, 2H), 0.39 (m, 2H).	504.5	
117	H58 	P	18	10.9 (s, 1H), 9.10 (brs, 1H), 9.02 (d, J = 5.2 Hz, 1H), 8.48 (d, J = 5.2 Hz, 1H), 8.46 (br s, 1H), 8.35 (d, J = 8.4 Hz, 1H), 7.99 (dd, J = 4.0 and 6.4 Hz, 1H), 7.66 (d, J = 5.2 Hz, 1H), 7.26 (d, J = 12.4 Hz, 1H), 6.60 (brt, J = 5.6 Hz, 1H), 3.21 (q, J = 6.8 Hz, 2H), 3.16 (s 3H), 2.40 (s,	505.5	

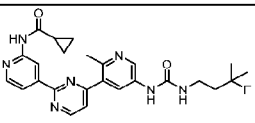
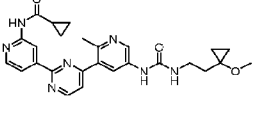
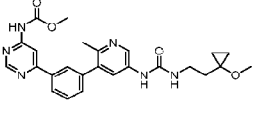
					3H), 2.03 (m, 1H), 1.69 (t, J = 7.2 Hz, 2H), 0.81-0.85 (m, 4H), 0.64 (m, 2H), 0.41 (m, 2H).	
118	G48 		Q	19	10.9 (s, 1H), 8.85 (s, 1H), 8.80 (d, J = 4.8 Hz, 1H), 8.71 (s, 1H), 8.49 (d, J = 2.0 Hz, 1H), 8.41 (d, J = 5.2 Hz, 1H), 7.99 (s, 1H), 7.86 (d, J = 2.4 Hz, 1H), 7.80 (d, J = 5.2 Hz, 1H), 7.52 (d, J = 4.8 Hz, 1H), 6.22 (brt, J = 5.2 Hz, 1H), 3.16 (m, 2H), 2.38 (s, 3H), 2.03 (m, 1H), 1.36 (m, 2H), 1.01 (s, 3H), 0.81- 0.86 (m, 4H), 0.24 (m, 2H), 0.19 (m, 2H).	471.5
119	H62 		P	9	9.75 (d, J = 2.2 Hz, 1H), 8.89 (q, J = 4.8 Hz, 1H), 8.83 (d, J = 5.0 Hz, 1H), 8.52 (d, J = 1.8 Hz, 1H), 8.31 (m, 2H), 8.27 (d, J = 2.2 Hz, 1H), 8.19 (dd, J = 1.9 and 5.2 Hz, 1H), 7.25 (d, J = 12.2 Hz, 1H), 6.50 (t, J = 5.6 Hz, 1H), 3.09 (m, 2H), 2.86 (d, J = 4.7 Hz, 3H), 2.28 (s, 3H), 1.34 (m, 2H), 0.89 (s, 9H).	465.2
120	H63 		P	19	11.0 (s, 1H), 9.61 (d, J = 2.2 Hz, 1H), 8.75 (s, 1H), 8.56 (d, J = 2.6 Hz, 1H), 8.54 (d, J = 1.5 Hz, 1H), 8.51 (d, J = 5.2 Hz, 1H), 8.17 (d, J = 2.2 Hz, 1H), 8.06 (d, J = 2.5 Hz, 1H), 7.67 (dd, J = 1.7 and 5.2 Hz, 1H), 6.27 (t, J = 5.7 Hz, 1H), 3.05-3.13 (m, 2H), 2.43 (s, 3H), 2.05 (m, 1H), 1.32-1.39 (m, 2H), 0.89 (s, 9H), 0.82-0.87 (m, 4H).	474.2
121	H63 		P	20	11.0 (s, 1H), 9.61 (d, J = 2.2 Hz, 1H), 8.77 (s, 1H), 8.56 (d, J = 2.6 Hz, 1H), 8.54 (d, J = 1.6 Hz, 1H),	490.2

					8.51 (d, J = 5.2 Hz, 1H), 8.17 (d, J = 2.2 Hz, 1H), 8.06 (d, J = 2.6 Hz, 1H), 7.66 (dd, J = 1.7 and 5.3 Hz, 1H), 6.24 (t, J = 5.6 Hz, 1H), 3.05-3.16 (m, 5H), 2.43 (s, 3H), 2.06-2.01 (m, 1H), 1.57-1.69 (m, 2H), 1.10 (s, 6H), 0.81-0.88 (m, 4H).	
122	J4 		T	18	10.4 (s, 1H), 8.66 (d, J = 5.2 Hz, 1H), 8.29 (d, J = 2.3 Hz, 1H), 8.04 (d, J = 8.5 Hz, 1H), 7.75-7.82 (m, 2H), 7.72 (t, J = 1.6 Hz, 1H), 7.16 (d, J = 12.4 Hz, 1H), 7.00 (m, 1H), 6.50 (t, J = 5.7 Hz, 1H), 4.92 (t, J = 5.5 Hz, 1H), 4.13 (t, J = 5.0 Hz, 2H), 3.76 (q, J = 5.2 Hz, 2H), 3.68 (s, 3H), 3.11-3.19 (m, 2H), 2.18 (s, 3H), 1.35 (dd, J = 8.3, 6.6 Hz, 2H), 1.01 (s, 3H), 0.27 (m, 2H), 0.21 (m, 2H).	538.2
123	H62 		P	4	9.76 (d, J = 2.2 Hz, 1H), 8.89 (q, J = 4.8 Hz, 1H), 8.83 (d, J = 5.1 Hz, 1H), 8.52 (d, J = 1.8 Hz, 1H), 8.38 (d, J = 2.3 Hz, 1H), 8.29 (m, 2H), 8.20 (dd, J = 1.9 and 5.1 Hz, 1H), 7.26 (d, J = 12.3 Hz, 1H), 6.54 (t, J = 5.6 Hz, 1H), 3.11 (m, 2H), 3.09 (s, 3H), 2.87 (d, J = 4.8 Hz, 3H), 2.29 (s, 3H), 1.60 (m, 2H), 1.10 (s, 6H).	481.2
124	H51 		P	4	10.9 (s, 1H), 8.85 (s, 1H), 8.80 (d, J = 4.8 Hz, 1H), 8.64 (s, 1H), 8.50 (d, J = 2.4 Hz, 1H), 8.41 (d, J = 5.2 Hz, 1H), 7.99 (s, 1H), 7.56 (d, J = 2.4 Hz, 1H), 7.80 (dd, J = 1.6 and 5.2 Hz, 1H), 7.52 (dd, J = 1.6 and 5.2 Hz, 1H), 6.27 (t, J = 5.6 Hz, 1H), 3.02-3.16 (m, 2H), 2.38 (s, 3H), 2.03 (m,	473.5

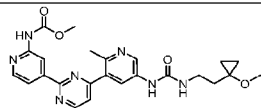
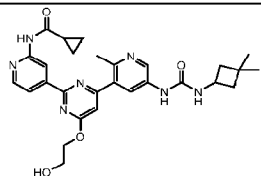
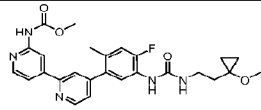
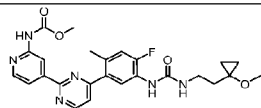
					1H), 1.10-1.50 (m, 5H), 0.81-0.88 (m, 10H).	
125	H61 	P & R	76	10.2 (s, 1H), 8.55 (s, 1H), 8.45 (brs, 1H), 8.35 (d, J = 5.2 Hz, 1H), 8.07 (d, J = 8.4 Hz, 1H), 7.72 (d, J = 5.2 Hz, 1H), 7.50 (s, 1H), 7.19 (d, J = 12.4 Hz, 1H), 6.80 (s, 1H), 6.61 (brt, J = 5.2 Hz, 1H), 4.88 (t, J = 5.6 Hz, 1H), 4.45 (t, J = 4.8 Hz, 2H), 3.80 (q, J = 5.2 Hz, 2H), 3.69 (s, 3H), 3.10 (t, J = 6.8 Hz, 4H), 3.04 (q, J = 5.6 Hz, 2H), 2.39 (t, J = 6.2 Hz, 2H), 2.21 (s, 3H), 1.96 (m, 2H).	539.5	
126	H66 	P	6	10.9 (s, 1H), 8.78 (s, 1H), 8.50 (s, 1H), 8.48 (d, J = 2.4 Hz, 1H), 8.41 (d, J = 5.2 Hz, 1H), 7.80 (d, J = 2.0 Hz, 1H), 7.77 (d, J = 5.2 Hz, 1H), 7.55 (s, 1H), 6.90 (s, 1H), 6.55 (d, J = 7.6 Hz, 1H), 4.88 (t, J = 5.6 Hz, 1H), 4.44 (t, J = 4.8 Hz, 2H), 4.10 (m, 1H), 3.79 (q, J = 4.8 Hz, 2H), 2.37 (s, 3H), 2.06 (m, 3H), 1.66 (dd, J = 9.2 and 11.2 Hz, 2H), 1.14 (s, 3H), 1.11 (s, 3H), 0.80-0.87 (m, 4H).	531.6	
127	H56 	P	27	11.3 (s, 1H), 8.95 (s, 1H), 8.59 (s, 1H), 8.32 (brs, 1H), 8.05 (s, 1H), 8.03 (s, 1H), 7.92 (s, 1H), 7.61 (t, J = 7.6 Hz, 1H), 7.49 (d, J = 7.6 Hz, 1H), 7.16 (d, J = 12.4 Hz, 1H), 6.56 (brt, J = 5.2 Hz, 1H), 3.17 (q, J = 8.4 Hz, 2H), 2.16 (s, 3H), 2.08 (m, 1H), 1.76 (dt, J = 7.6 and 20.0 Hz, 2H), 1.31 (d, J = 21.6 Hz, 6H), 0.86 (m, 4H).	494.5	
128	H58 	P	20	10.9 (s, 1H), 9.10 (s, 1H), 9.01 (d, J = 5.2 Hz, 1H), 8.48 (d, J = 5.2 Hz, 1H),	495.5	

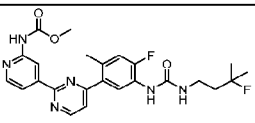
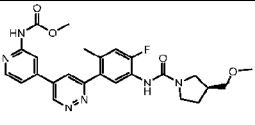
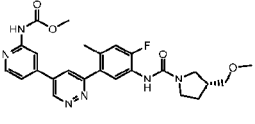
					8.42 (s, 1H), 8.34 (d, J = 8.4 Hz, 1H), 7.98 (d, J = 4.4 Hz, 1H), 7.65 (d, J = 5.2 Hz, 1H), 7.25 (d, J = 12.0 Hz, 1H), 6.59 (brt, J = 5.2 Hz, 1H), 3.20 (dd, J = 14.4, 6.4 Hz, 2H), 2.40 (s, 3H), 2.02 (m, 1H), 1.77 (dt, J = 7.6 and 20.0 Hz, 2H), 1.27 (d, J = 21.6 Hz, 6H), 0.81-0.86 (m, 4H).	
129	H67 	P	26	10.4 (s, 1H), 9.03 (d, J = 5.2 Hz, 1H), 8.89 (s, 1H), 8.43 (d, J = 8.4 Hz, 1H), 8.40 (d, J = 1.2 Hz, 1H), 8.35 (d, J = 8.4 Hz, 1H), 7.95 (dd, J = 1.2 and 5.2 Hz, 1H), 7.67 (d, J = 5.2 Hz, 1H), 7.26 (d, J = 12.4 Hz, 1H), 6.54 (brt, J = 5.2 Hz, 1H), 3.70 (s, 3H), 3.10-3.15 (m, 2H), 3.08 (s, 3H), 2.42 (s, 3H), 1.60 (m, 2H), 1.10 (s, 6H).	497.5	
130	H50 	P	20	11.0 (s, 1H), 9.10 (d, J = 5.2 Hz, 1H), 8.94 (s, 1H), 8.81 (s, 1H), 8.56 (d, J = 2.4 Hz, 1H), 8.53 (d, J = 5.2 Hz, 1H), 8.42 (d, J = 2.0 Hz, 1H), 8.06 (d, J = 5.2 Hz, 1H), 7.86 (d, J = 4.8 Hz, 1H), 6.24 (brt, J = 5.2 Hz, 1H), 3.21 (dd, J = 6.4 and 14.8 Hz, 2H), 2.69 (s, 3H), 2.05 (m, 1H), 1.78 (dt, J = 20.4, 7.6 Hz, 2H), 1.34 (d, J = 22.0 Hz, 6H), 0.81-0.86 (m, 4H).	478.5	
131	H64 	P	67	11.0 (s, 1H), 9.59 (d, J = 2.2 Hz, 1H), 8.55 (t, J = 1.2 Hz, 1H), 8.52 (d, J = 5.2 Hz, 1H), 8.32 (d, J = 2.3 Hz, 1H), 8.28 (d, J = 8.5 Hz, 1H), 8.04 (d, J = 2.2 Hz, 1H), 7.68 (dd, J = 1.7 and 5.2 Hz, 1H), 7.25 (d, J = 12.3 Hz, 1H), 6.51 (t, J = 5.6 Hz, 1H), 3.10-3.06 (m, 2H), 2.27 (s, 3H), 2.16 (m,	491.2	

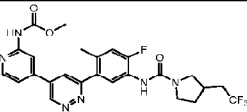
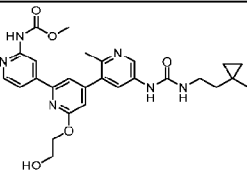
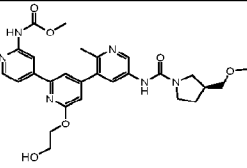
					1H), 1.32-1.38 (m, 2H), 0.90 (s, 9H), 0.78-0.89 (m, 4H).	
132	H62 	P	34	9.76 (d, J = 2.2 Hz, 1H), 8.89 (q, J = 4.8 Hz, 1H), 8.83 (d, J = 5.1 Hz, 1H), 8.52 (d, J = 1.8 Hz, 1H), 8.42 (d, J = 2.3 Hz, 1H), 8.29 (m, 2H), 8.20 (dd, J = 1.9 and 5.1 Hz, 1H), 7.26 (d, J = 12.3 Hz, 1H), 6.59 (t, J = 5.7 Hz, 1H), 3.20 (m, 2H), 2.87 (d, J = 4.8 Hz, 3H), 2.29 (s, 3H), 1.78 (m, 2H), 1.33 (d, J = 22.0 Hz, 6H).	469.2	
133	G61 	Q	20	10.9 (s, 1H), 9.06 (s, 1H), 8.73 (s, 1H), 8.53 (d, J = 2.4 Hz, 1H), 8.48 (d, J = 4.8 Hz, 1H), 8.04 (d, J = 2.4 Hz, 1H), 7.98 (d, J = 5.2 Hz, 1H), 7.13 (s, 1H), 6.21 (brt, J = 5.6 Hz, 1H), 4.97 (t, J = 5.6 Hz, 1H), 4.55 (brt, J = 4.8 Hz, 2H), 3.81 (q, J = 5.2 Hz, 2H), 3.17 (m, 2H), 2.52 (s, 3H), 2.04 (m, 1H), 1.37 (m, 2H), 1.02 (s, 3H), 0.83 (m, 4H), 0.27 (m, 2H), 0.22 (m, 2H).	532.1	
134	H59 	P	6	10.9 (s, 1H), 8.83 (brs, 1H), 8.76 (d, J = 4.8 Hz, 1H), 8.41 (d, J = 5.2 Hz, 1H), 8.35 (brs, 1H), 8.09 (d, J = 8.4 Hz, 1H), 7.87 (s, 1H), 7.78 (dd, J = 1.6 and 5.2 Hz, 1H), 7.43 (dd, J = 1.2 and 4.8 Hz, 1H), 7.21 (d, J = 12.4 Hz, 1H), 6.51 (brt, J = 5.6 Hz, 1H), 3.15 (m, 2H), 2.19 (s, 3H), 2.03 (m, 1H), 1.35 (m, 2H), 1.01 (s, 3H), 0.83 (m, 4H), 0.26 (m, 2H), 0.22 (m, 2H).	488.1	
135	G65 	Q	4	10.4 (s, 1H), 9.08 (d, J = 5.2 Hz, 1H), 8.90 (s, 1H), 8.79 (s, 1H), 8.57 (d, J = 2.4 Hz, 1H), 8.45 (d, J =	462.4	

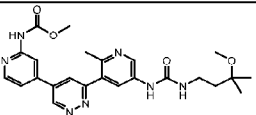
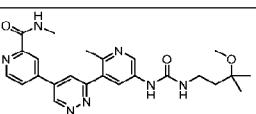
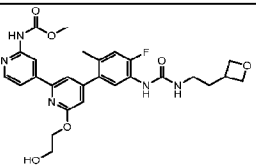
					5.2 Hz, 1H), 8.12 (d, J = 2.4 Hz, 1H), 7.97 (dd, J = 1.2 and 4.8 Hz, 1H), 7.79 (d, J = 5.2 Hz, 1H), 6.24 (brt, J = 5.2 Hz, 1H), 3.70 (s, 3H), 3.18 (m, 2H), 2.58 (s, 3H), 1.38 (m, 2H), 1.02 (s, 3H), 0.27 (m, 2H), 0.22 (m, 2H).	
136	H69 	P	14	11.0 (s, 1H), 9.12 (s, 1H), 9.07 (d, J = 4.8 Hz, 1H), 8.85 (s, 1H), 8.57 (s, 1H), 8.49 (d, J = 4.0 Hz, 1H), 8.11 (s, 1H), 8.00 (d, J = 4.0 Hz, 1H), 7.78 (d, J = 4.4 Hz, 1H), 6.31 (brm, 1H), 3.21 (m, 2H), 2.56 (s, 3H), 2.04 (m, 1H), 1.75-1.83 (m, 2H), 1.33 (d, J = 21.6 Hz, 6H), 0.79-0.87 (m, 4H).	478.1	
137	H69 	P	11	11.0 (s, 1H), 9.71 (brs, 1H), 9.18 (d, J = 5.2 Hz, 1H), 8.96, (brm, 2H), 8.83 (brs, 1H), 8.55 (d, J = 5.2 Hz, 1H), 8.20 (d, J = 5.2 Hz, 1H), 7.90 (d, J = 4.4 Hz, 1H), 6.65 (b t, J = 5.2 Hz, 1H), 3.28 (q, J = 6.4 Hz, 2H), 3.18 (s, 3H), 2.93 (s, 3H), 2.06 (m, 1H), 1.73 (m, 2H), 0.83 (m, 4H), 0.67 (m, 2H), 0.42 ((m, 2H).	488.1	
138	H70 	P	10	10.9 (s, 1H), 8.90 (s, 1H), 8.76, (s, 1H), 8.43 (d, J = 2.4 Hz, 1H), 8.38 (s, 1H), 8.08 (d, J = 8.0 Hz, 1H), 8.01 (s, 1H), 7.86 (d, J = 2.4 Hz, 1H), 7.66 (t, J = 7.6 Hz, 1H), 7.58 (brd, J = 7.6 Hz, 1H), 6.23 (brt, J = 5.6 Hz, 1H), 3.74 (s, 3H), 3.21 (q, J = 6.8 Hz, 2H), 3.16 (s, 3H), 2.36 (s, 3H), 1.69 (t, J = 7.2 Hz, 2H), 0.65 (m, 2H), 0.40 (m, 2H).	477.1	

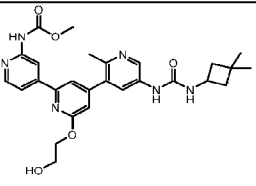
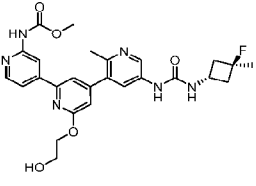
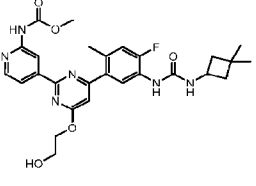
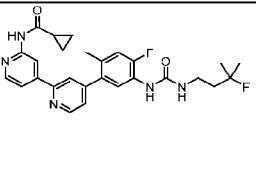
139	H64 	P	27	11.0 (s, 1H), 9.57 (d, J = 2.2 Hz, 1H), 8.53 (d, J = 1.6 Hz, 1H), 8.50 (d, J = 5.2 Hz, 1H), 8.40 (d, J = 2.2 Hz, 1H), 8.25 (d, J = 8.4 Hz, 1H), 8.02 (d, J = 2.2 Hz, 1H), 7.66 (dd, J = 1.7 and 5.2 Hz, 1H), 7.24 (d, J = 12.2 Hz, 1H), 6.58 (t, J = 5.7 Hz, 1H), 3.14-3.22 (m, 2H), 2.25 (s, 3H), 2.08-2.01 (m, 1H), 1.71-1.81 (m, 2H), 1.33 (s, 3H), 1.29 (s, 3H), 0.79-0.89 (m, 4H).	495.2
140	H71 	P	12	10.4 (s, 1H), 9.59 (d, J = 2.2 Hz, 1H), 8.45 (d, J = 5.2 Hz, 1H), 8.36 (m, 1H), 8.24-8.29 (m, 2H), 8.05 (d, J = 2.3 Hz, 1H), 7.62 (dd, J = 1.7 and 5.2 Hz, 1H), 7.24 (d, J = 12.3 Hz, 1H), 6.52 (t, J = 5.7 Hz, 1H), 3.70 (s, 3H), 3.04-3.13 (m, 5H), 2.26 (s, 3H), 1.55-1.62 (m, 2H), 1.08 (s, 6H).	497.2
141	H71 	P	15	10.4 (s, 1H), 9.59 (d, J = 2.2 Hz, 1H), 8.45 (d, J = 5.2 Hz, 1H), 8.42 (m, 1H), 8.24-8.29 (m, 2H), 8.05 (d, J = 2.2 Hz, 1H), 7.62 (dd, J = 1.7 and 5.2 Hz, 1H), 7.25 (d, J = 12.3 Hz, 1H), 6.61 (t, J = 5.7 Hz, 1H), 3.70 (s, 3H), 3.14-3.22 (m, 2H), 2.27 (s, 3H), 1.71-1.82 (m, 2H), 1.26-1.38 (m, 6H).	485.2
142	H64 	P	30	11.0 (s, 1H), 9.57 (d, J = 2.2 Hz, 1H), 8.53 (d, J = 1.6 Hz, 1H), 8.50 (d, J = 5.2 Hz, 1H), 8.37 (d, J = 2.3 Hz, 1H), 8.25 (d, J = 8.4 Hz, 1H), 8.02 (d, J = 2.2 Hz, 1H), 7.66 (dd, J = 1.7 and 5.2 Hz, 1H), 7.24 (d, J = 12.3 Hz, 1H), 6.53 (t, J = 5.6 Hz, 1H), 3.03-3.14 (m, 5H), 2.25 (s, 3H), 2.08-2.02 (m, 1H), 1.55-	507.2

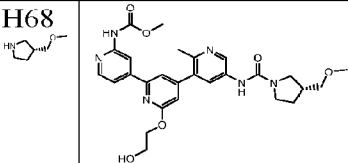
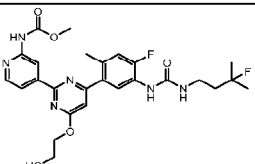
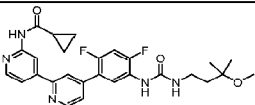
					1.62 (m, 2H), 1.08 (s, 6H), 0.80-0.86 (m, 4H)	
143	H72 	P	4	10.4 (s, 1H), 9.08 (d, J = 4.8 Hz, 1H), 8.90, (d, J = 4.0 Hz, 2H), 8.57 (d, J = 2.4 Hz, 1H), 8.45 (d, J = 5.2 Hz, 1H), 8.13 (d, J = 2.4 Hz, 1H), 7.97 (d, J = 4.8 Hz, 1H), 7.79 (d, J = 5.2 Hz, 1H), 6.31 (brt, J = 5.6 Hz, 1H), 3.70 (s, 3H), 3.23 (q, J = 6.8 Hz, 2H), 3.17 (s, 3H), 2.58 (s, 3H), 1.71 (t, J = 7.2 Hz, 2H), 0.66 (m, 2H), 0.43 (m, 2H).	478.2	
144	H73 	P & R	20	10.9 (s, 1H), 9.06 (s, 1H), 8.55 (s, 1H), 8.53 (d, J = 2.4 Hz, 1H), 8.48 (d, J = 5.2 Hz, 1H), 8.01 (d, J = 2.4 Hz, 1H), 7.98 (dd, J = 3.6 and 6.8 Hz, 1H), 7.13 (s, 1H), 6.56 (d, J = 7.6 Hz, 1H), 4.97 (t, J = 5.6, 1H), 4.55 (m, 2H), 4.11 (m, 1H), 3.82 (q, J = 5.6 Hz, 2H), 2.02-2.09 (m, 3H), 1.67 (m, 2H), 1.09 (s, 3H), 1.11 (s, 3H), 0.78-0.87 (m, 4H). 3Hs are under solvent	532.2	
145	H74 	P	16	10.3 (s, 1H), 8.78 (d, J = 4.8 Hz, 1H), 8.60, (s, 1H), 8.41 (d, J = 1.6 Hz, 1H), 8.36 (d, J = 5.2 Hz, 1H), 8.09 (d, J = 8.4 Hz, 1H), 7.90 (s, 1H), 7.75 (dd, J = 1.6 and 5.6 Hz, 1H), 7.44 (dd, J = 1.2 and 4.8 Hz, 1H), 7.21 (d, J = 12.4 Hz, 1H), 6.58 (brt, J = 5.6 Hz, 1H), 3.69 (s, 3H), 3.20 (q, J = 6.4 Hz, 2H), 3.15 (s, 3H), 2.21 (s, 3H), 1.68 (t, J = 7.2 Hz, 2H), 0.64 (m, 2H), 0.39 (m, 2H).	494.2	
146	H67 	P	14	10.4 (s, 1H), 9.03 (d, J = 5.2 Hz, 1H), 8.88, (s, 1H), 8.46 (brs, 1H), 8.44 (d, J = 5.2 Hz, 1H), 8.36 (d, J =	495.2	

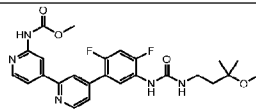
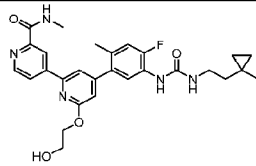
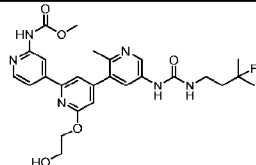
					8.4 Hz, 1H), 7.96 (dd, J = 1.2 and 5.2 Hz, 1H), 7.67 (d, J = 5.2 Hz, 1H), 7.26 (d, J = 12.4 Hz, 1H), 6.60 (t, J = 5.6 Hz, 1H), 3.70 (s, 3H), 3.22 (q, J = 6.4 Hz, 2H), 3.16 (s, 3H), 2.42 (s, 3H), 1.69 (m, 2H), 0.65 (m, 2H), 0.40 (m, 2H).	
147	H67 	P	8	10.4 (s, 1H), 9.03 (d, J = 5.2 Hz, 1H), 8.88 (s, 1H), 8.44, (m, 2H), 8.36 (d, J = 8.4 Hz, 1H), 7.96 (dd, J = 1.2 and 5.2 Hz, 1H), 7.67 (d, J = 5.2 Hz, 1H), 7.26 (d, J = 12.4 Hz, 1H), 6.60 (brt, J = 5.6 Hz, 1H), 3.70 (s, 3H), 3.20 (q, J = 6.0 Hz, 2H), 2.42 (s, 3H), 1.78 (dt, J = 7.6 and 20.0 Hz, 2H), 1.33 (d, J = 21.6 Hz, 6H).	485.1	
148	H71 	P	16	10.4 (s, 1H), 9.59 (d, J = 2.2 Hz, 1H), 8.45 (d, J = 5.1 Hz, 1H), 8.27 (s, 1H), 8.08 (d, J = 2.2 Hz, 1H), 7.95 (s, 1H), 7.69 (d, J = 8.1 Hz, 1H), 7.64 (dd, J = 1.7 and 5.2 Hz, 1H), 7.25 (d, J = 11.5 Hz, 1H), 3.70 (s, 3H), 3.42-3.55 (m, 2H), 3.28-3.36 (m, 2H), 3.25 (s, 3H), 3.10 (m, 1H), 2.42-2.48 (m, 2H), 2.33 (s, 3H), 1.90-1.99 (m, 1H), 1.56-1.67 (m, 1H).	495.2	
149	H71 	P	15	10.4 (s, 1H), 9.59 (d, J = 2.2 Hz, 1H), 8.45 (d, J = 5.2 Hz, 1H), 8.27 (s, 1H), 8.08 (d, J = 2.2 Hz, 1H), 7.95 (s, 1H), 7.69 (d, J = 8.1 Hz, 1H), 7.64 (dd, J = 1.7 and 5.3 Hz, 1H), 7.25 (d, J = 11.5 Hz, 1H), 3.70 (s, 3H), 3.42-3.55 (m, 2H), 3.27-3.36 (m, 2H), 3.25 (s, 3H), 3.10 (m, 1H), 2.42-2.48 (m, 2H), 2.33 (s, 3H), 1.88-1.99 (m, 1H), 1.61	495.2	

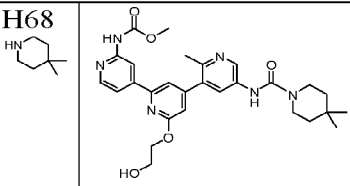
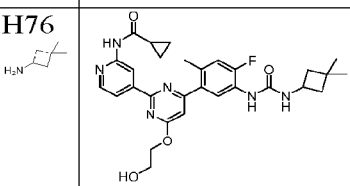
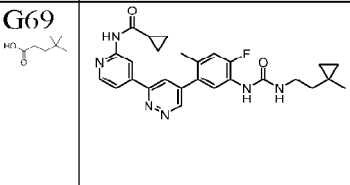
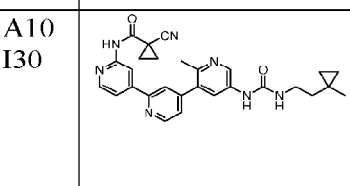
					(m, 1H).	
150	H71 	P	21	10.4 (s, 1H), 9.59 (d, J = 2.2 Hz, 1H), 8.45 (d, J = 5.1 Hz, 1H), 8.27 (s, 1H), 8.08 (d, J = 2.1 Hz, 1H), 8.01 (s, 1H), 7.68 (d, J = 8.1 Hz, 1H), 7.64 (dd, J = 1.6 and 5.2 Hz, 1H), 7.26 (d, J = 11.5 Hz, 1H), 3.63-3.73 (m, 4H), 3.52 (m, 1H), 3.03 (m, 1H), 2.37-2.47 (m, 2H), 2.33 (s, 3H), 2.07 (m, 1H), 1.60-1.72 (m, 1H), 0.93 (d, J = 6.5 Hz, 2H).	533.2	
151	H68 	P	23	10.3 (s, 1H), 8.69 (s, 1H), 8.57 (d, J = 1.5 Hz, 1H), 8.48 (d, J = 2.5 Hz, 1H), 8.35 (d, J = 5.2 Hz, 1H), 7.84 (d, J = 2.5 Hz, 1H), 7.73 (m, 1H), 7.60 (d, J = 1.1 Hz, 1H), 6.91 (d, J = 1.1 Hz, 1H), 6.20 (t, J = 5.7 Hz, 1H), 4.89 (t, J = 5.5 Hz, 1H), 4.46 (t, J = 5.1 Hz, 2H), 3.80 (q, J = 5.2 Hz, 2H), 3.69 (s, 3H), 3.13-3.19 (m, 2H), 2.38 (s, 3H), 1.33-1.40 (m, 2H), 1.01 (s, 3H), 0.25-1.29 (m, 2H), 0.18-0.24 (m, 2H).	521.2	
152	H68 	P	38	10.3 (s, 1H), 8.68 (d, J = 2.5 Hz, 1H), 8.59 (m, 1H), 8.39 (s, 1H), 8.35 (d, J = 5.2 Hz, 1H), 7.90 (d, J = 2.5 Hz, 1H), 7.74 (dd, J = 1.7 and 5.4 Hz, 1H), 7.59 (d, J = 1.1 Hz, 1H), 6.91 (d, J = 1.1 Hz, 1H), 4.89 (t, J = 5.6 Hz, 1H), 4.46 (t, J = 5.1 Hz, 2H), 3.80 (q, J = 5.1 Hz, 2H), 3.69 (s, 3H), 3.44-3.54 (m, 2H), 3.35 (m, 1H), 3.29-3.21 (m, 5H), 3.12 (dd, J = 7.2 and 10.2 Hz, 1H), 2.47 (m, 1H), 2.40 (s, 3H), 1.95 (m, 1H), 1.63 (m, 1H).	537.2	

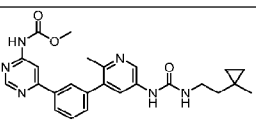
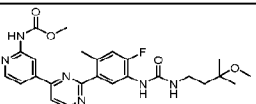
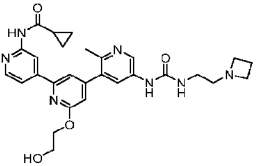
153	A6 	T	31	10.4 (s, 1H), 9.57 (d, J = 2.2 Hz, 1H), 8.84 (s, 1H), 8.51 (d, J = 2.5 Hz, 1H), 8.40 (d, J = 5.2 Hz, 1H), 8.22 (s, 1H), 8.14 (d, J = 2.2 Hz, 1H), 8.02 (d, J = 2.5 Hz, 1H), 7.57 (dd, J = 1.7 and 5.1 Hz, 1H), 6.32 (t, J = 5.6 Hz, 1H), 3.64 (s, 3H), 3.04-3.08 (m, 2H), 3.03 (s, 3H), 2.38 (s, 3H), 1.52-1.58 (m, 2H), 1.04 (s, 6H).	480.2
154	A4 	T	24	9.72 (d, J = 2.2 Hz, 1H), 8.82 (q, J = 4.8 Hz, 1H), 8.77 (d, J = 5.1 Hz, 1H), 8.73 (s, 1H), 8.50 (d, J = 2.5 Hz, 1H), 8.47 (d, J = 1.8 Hz, 1H), 8.34 (d, J = 2.2 Hz, 1H), 8.14 (dd, J = 1.9 and 5.1 Hz, 1H), 8.03 (d, J = 2.5 Hz, 1H), 6.21 (t, J = 5.7 Hz, 1H), 3.06 (dt, J = 5.5 and 7.9 Hz, 2H), 3.03 (s, 3H), 2.79 (d, J = 4.8 Hz, 3H), 2.39 (s, 3H), 1.52-1.58 (m, 2H), 1.04 (s, 6H).	464.2
155	H61 	P	4	10.3 (s, 1H), 8.56 (s, 1H), 8.35 (d, J = 5.2 Hz, 1H), 8.30 (d, J = 2.0 Hz, 1H), 8.05 (d, J = 8.4 Hz, 1H), 7.72 (dd, J = 1.6 and 5.2 Hz, 1H), 7.50 (d, J = 0.8 Hz, 1H), 7.20 (d, J = 12.4 Hz, 1H), 6.81 (d, J = 0.8 Hz, 1H), 6.55 (brt, J = 5.6 Hz, 1H), 4.89 (t, J = 5.6 Hz, 1H), 4.62 (dd, J = 6.0 and 8.0 Hz, 2H), 4.45 (m, 2H), 4.25 (t, J = 6.4 Hz, 2H), 3.80 (q, J = 5.2 Hz, 2H), 3.69 (s, 3H), 3.01 (q, J = 6.8 Hz, 2H), 2.94 (m, 1H), 2.21 (s, 3H), 1.76 (q, J = 6.8 Hz, 2H).	540.2

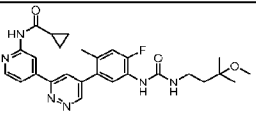
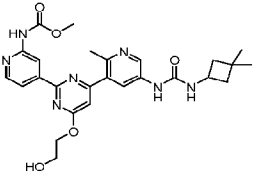
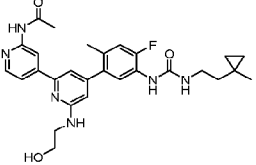
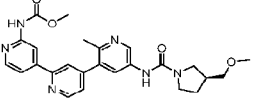
156	H58 	P	22	10.3 (s, 1H), 8.57 (s, 1H), 8.50 (s, 1H), 8.48 (d, J = 2.4 Hz, 1H), 8.35 (d, J = 5.2 Hz, 1H), 7.81 (d, J = 2.4 Hz, 1H), 7.74 (dd, J = 1.6 and 5.2 Hz, 1H), 7.60 (s, 1H), 6.91 (s, 1H), 6.56 (d, J = 7.6 Hz, 1H), 4.90 (t, J = 5.6 Hz, 1H), 4.46 (m, 2H), 4.10 (m, 1H), 3.81 (q, J = 5.6 Hz, 2H), 3.71 (s, 3H), 2.38 (s, 3H), 2.06 (m, 2H), 1.66 (m, 2H), 1.1 (s, 3H), 1.09 (s, 3H).	521.2
157	A6 	T	14	10.3 (s, 1H), 8.64 (s, 1H), 8.57 (s, 1H), 8.50 (d, J = 2.4 Hz, 1H), 8.35 (d, J = 5.2 Hz, 1H), 7.83 (d, J = 2.4 Hz, 1H), 7.74 (dd, J = 1.2 and 5.2 Hz, 1H), 7.60 (s, 1H), 6.91 (s, 1H), 6.71 (d, J = 6.8 Hz, 1H), 4.90 (t, J = 5.6 Hz, 1H), 4.46 (m, 2H), 4.22 (m, 1H), 3.81 (q, J = 5.6 Hz, 2H), 3.69 (s, 3H), 2.58 (m, 2H), 2.38 (s, 3H), 2.13 (m, 1H), 2.07 (m, 1H), 1.45 (d, J = 22.4 Hz, 3H).	525.2
158	H65 	P	25	10.3 (s, 1H), 8.83 (s, 1H), 8.43 (d, J = 4.8 Hz, 1H), 8.27 (d, J = 8.4 Hz, 1H), 8.20 (d, J = 1.2 Hz, 1H), 7.93 (dd, J = 1.2 and 5.2 Hz, 1H), 7.22 (d, J = 12.4 Hz, 1H), 6.99 (s, 1H), 6.82 (d, J = 7.6 Hz, 1H), 4.96 (t, J = 5.6 Hz, 1H), 4.55 (m, 2H), 4.09 (m, 1H), 3.82 (q, J = 5.6 Hz, 2H), 3.70 (s, 3H), 2.39 (s, 3H), 2.08 (m, 2H), 1.61 (m, 2H), 1.11 (s, 3H), 1.10 (s, 3H).	539.1
159	H59 	P	22	10.9 (s, 1H), 8.83 (s, 1H), 8.76 (d, J = 4.8 Hz, 1H), 8.41 (d, J = 5.2 Hz, 1H), 8.39 (d, J = 1.6 Hz, 1H), 8.08 (d, J = 8.4 Hz, 1H), 7.87 (s, 1H), 7.78 (dd, J =	494.2

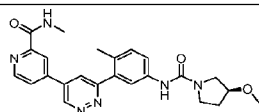
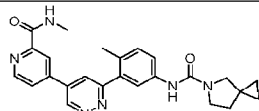
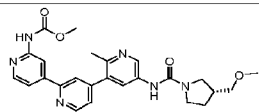
					1.6 and 5.6 Hz, 1H), 7.43 (dd, J = 1.6 and 5.2 Hz, 1H), 7.21 (d, J = 12.4 Hz, 1H), 6.58 (brt, J = 5.6 Hz, 1H), 3.18 (q, J = 6.0 Hz, 1H), 2.20 (s, 3H), 2.03 (m, 1H), 1.76 (dt, J = 7.6 and 20.0 Hz, 2H), 1.31 (d, J = 21.6 Hz, 6H), 0.79-0.86 (m, 4H).	
160	H68 	P	44	10.3 (s, 1H), 8.68 (d, J = 2.4 Hz, 1H), 8.57 (t, J = 1.0 Hz, 1H), 8.39 (s, 1H), 8.35 (d, J = 5.2 Hz, 1H), 7.90 (d, J = 2.6 Hz, 1H), 7.74 (dd, J = 1.6 and 5.2 Hz, 1H), 7.59 (d, J = 1.1 Hz, 1H), 6.91 (t, J = 0.9 Hz, 1H), 4.89 (t, J = 5.5 Hz, 1H), 4.46 (t, J = 5.1 Hz, 2H), 3.80 (q, J = 5.2 Hz, 2H), 3.66-3.72 (m, 3H), 3.42-3.58 (m, 3H), 3.36 (m, 1H), 3.23-3.28 (m, 5H), 3.12 (m, 1H), 2.40 (s, 3H), 2.00 (m, 1H), 1.56 (m, 1H).	537.2	
161	H65 	P	23	10.3 (s, 1H), 8.84 (s, 1H), 8.43 (d, J = 4.8 Hz, 1H), 8.40 (s, 1H), 8.29 (d, J = 8.4 Hz, 1H), 7.93 (dd, J = 3.6 and 6.8 Hz, 1H), 7.23 (d, J = 12.0 Hz, 1H), 7.00 (s, 1H), 6.58 (brt, J = 5.6 Hz, 1H), 4.97 (t, J = 5.6 Hz, 1H), 4.55 (m, 2H), 3.82 (m, 2H), 3.70 (s, 3H), 3.20 (m, 2H), 2.49 (s, 3H), 1.78 (dt, J = 7.6 and 20.0 Hz, 2H), 1.31 (d, J = 21.6 Hz, 6H).	545.2	
162	A2 	T	21	10.9 (s, 1H), 8.81 (m, 2H), 8.41 (m, 2H), 8.36 (t, J = 8.4 Hz, 1H), 8.04 (s, 1H), 7.78 (brd, J = 4.4 Hz, 1H), 7.59 (brd, J = 4.8 Hz, 1H), 7.49 (t, J = 10.8 Hz, 1H), 6.54 (brt, J = 5.2 Hz, 1H), 3.13 (m, 2H), 3.08 (s, 3H), 2.03 (brm, 1H), 1.60 (m,	510.2	

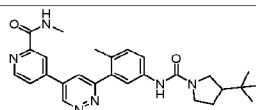
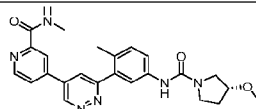
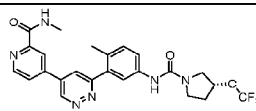
					2H), 1.10 (s, 6H), 0.80-0.88 (m, 4H).	
163	A6 	T	36	10.3 (s, 1H), 8.83 (brd, J = 4.8 Hz, 1H), 8.59 (s, 1H), 8.51 (s, 1H), 8.37 (m, 2H), 8.06 (s, 1H), 7.75 (brd, J = 4.4 Hz, 1H), 7.60 (brd, J = 4.8 Hz, 1H), 7.49 (t, J = 11.2 Hz, 1H), 6.54 (brt, J = 5.2 Hz, 1H), 3.70 (s, 3H), 3.13 (m, 2H), 3.08 (s, 3H), 1.60 (m, 2H), 1.01 (s, 6H).	500.1	
164	A4 114 	T	14	8.82 (q, J = 4.8 Hz, 1H), 8.72 (m, 1H), 8.67 (d, J = 1.7 Hz, 1H), 8.33 (d, J = 2.3 Hz, 1H), 8.27 (dd, J = 1.9 and 5.2 Hz, 1H), 8.09 (d, J = 8.5 Hz, 1H), 7.71 (d, J = 1.2 Hz, 1H), 7.19 (d, J = 12.4 Hz, 1H), 6.84 (d, J = 1.1 Hz, 1H), 6.50 (t, J = 5.6 Hz, 1H), 4.90 (t, J = 5.6 Hz, 1H), 4.47 (t, J = 5.1 Hz, 2H), 3.80 (q, J = 5.4 Hz, 2H), 3.10-3.19 (m, 2H), 2.84 (d, J = 4.8 Hz, 3H), 2.21 (s, 3H), 1.39 – 1.30 (m, 2H), 1.00 (s, 3H), 0.24-0.29 (m, 2H), 0.17-0.23 (m, 2H).	522.2	
165	H68 	P	19	10.3 (s, 1H), 8.86 (s, 1H), 8.58 (s, 1H), 8.49 (d, J = 2.4 Hz, 1H), 8.36 (d, J = 5.2 Hz, 1H), 7.84 (d, J = 2.8, Hz, 1H), 7.74 (dd, J = 4.0 and 6.4 Hz, 1H), 7.60 (d, J = 0.8 Hz, 1H), 6.91 (d, J = 0.8 Hz, 1H), 6.38 (brt, J = 5.6 Hz, 1H), 4.90 (t, J = 5.6 Hz, 1H), 4.46 (t, J = 4.8 Hz, 2H), 3.81 (q, J = 5.6 Hz, 2H), 3.70 (s, 3H), 3.19 (m, 2H), 2.38 (s, 3H), 1.78 (dt, J = 7.6 and 20.0 Hz, 2H), 1.33 (d, J = 21.6 Hz, 6H).	527.5	

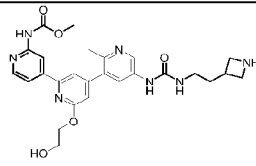
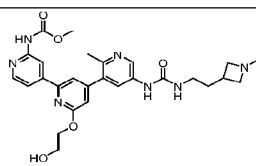
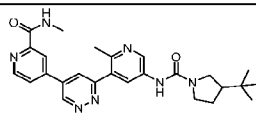
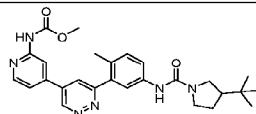
166	H68 	P	4	10.3 (s, 1H), 8.67 (s, 1H), 8.63 (d, J = 2.4 Hz, 1H), 8.58 (s, 1H), 8.36 (d, J = 5.2 Hz, 1H), 7.84 (d, J = 2.4, Hz, 1H), 7.74 (dd, J = 3.6 and 5.2 Hz, 1H), 7.60 (s, 1H), 6.92 (d, J = 1.2 Hz, 1H), 4.89 (t, J = 5.2 Hz, 1H), 4.46 (t, J = 4.8 Hz, 2H), 3.81 (q, J = 5.6 Hz, 2H), 3.70 (s, 3H), 3.44 (m, 4H), 2.40 (s, 3H), 1.30 (m, 4H), 0.95 (s, 6H).	535.3
167	H76 	P	16	10.9 (s, 1H), 9.04 (s, 1H), 8.48 (d, J = 5.2 Hz, 1H), 8.26 (d, J = 8.4 Hz, 1H), 8.20 (brd, J = 1.6 Hz, 1H), 7.97 (dd, J = 1.2 and 6.4 Hz, 1H), 7.22 (d, J = 12.0 Hz, 1H), 6.99 (s, 1H), 6.82 (d, J = 7.6 Hz, 1H), 4.54 (m, 2H), 4.09 (m, 1H), 3.81 (m, 2H), 2.36 (s, 3H), 2.00-2.10 (m, 4H), 1.61 (m, 2H), 1.10 (s, 3H), 1.09 (s, 3H), 0.80-0.86 (m, 4H).	549.2
168	G69 	Q	11	11.0 (s, 1H), 9.34 (d, J = 2.0 Hz, 1H), 8.92 (s, 1H), 8.50 (d, J = 5.2 Hz, 1H), 8.39 (brd, J = 1.6 Hz, 1H), 8.18 (d, J = 4.0, Hz, 1H), 8.15 (d, J = 8.4, Hz, 1H), 7.85 (dd, J = 3.6 and 5.2 Hz, 1H), 7.27 (d, J = 12.4 Hz, 1H), 6.52 (brt, J = 5.6 Hz, 1H), 3.15 (m, 2H), 2.23 (s, 3H), 2.05 (m, 1H), 1.35 (m, 2H), 1.01 (s, 3H), 0.80-0.88 (m, 4H), 0.26 (m, 2H), 0.21 (m, 2H).	489.3
169	A10 I30 	T	20	10.4 (s, 1H), 8.82 (d, J = 4.8 Hz, 1H), 8.70 (s, 2H), 8.49 (m, 2H), 8.06 (s, 1H), 7.92 (d, J = 5.2 Hz, 1H), 7.86 (d, J = 2.4 Hz, 1H), 7.54 (d, J = 4.8 Hz, 1H), 6.21 (t, J = 6.0 Hz, 1H), 3.16 (m, 2H), 2.38 (s, 3H), 1.75 (m, 2H), 1.74 (m, 2H).	496.3

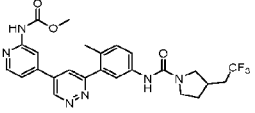
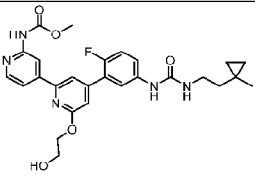
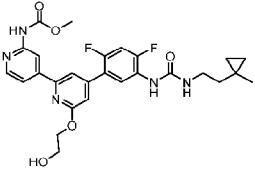
					1.37 (m, 2H), 1.01 (s, 3H), 0.27 (m, 2H), 0.21 (m, 2H).	
170	J5 		T	14	10.9 (s, 1H), 8.90 (d, J = 0.8 Hz, 1H), 8.68 (s, 1H), 8.42 (d, J = 2.4 Hz, 1H), 8.37 (d, J = 1.2 Hz, 1H), 8.06 (d, J = 7.6 Hz, 1H), 8.01 (s, 1H), 7.85 (d, J = 2.4 Hz, 1H), 7.66 (t, J = 7.6 Hz, 1H), 7.58 (d, J = 7.6 Hz, 1H), 6.19 (brt, J = 5.6 Hz, 1H), 3.74 (s, 3H), 3.16 (m, 2H), 2.35 (s, 3H), 1.37 (m, 2H), 1.02 (s, 3H), 0.25 (m, 2H), 0.21 (m, 2H).	461.5
171	H77 		P	8	10.4 (s, 1H), 9.08 (d, J = 5.2 Hz, 1H), 8.71 (s, 1H), 8.69 (d, J = 8.8 Hz, 1H), 8.47 (d, J = 5.2 Hz, 1H), 8.32 (d, J = 1.2 Hz, 1H), 8.04 (d, J = 5.2 Hz, 1H), 7.82 (dd, J = 1.2 and 5.2 Hz, 1H), 7.22 (d, J = 12.4 Hz, 1H), 6.51 (t, J = 5.6 Hz, 1H), 3.70 (s, 3H), 3.12 (m, 2H), 3.09 (s, 3H), 2.54 (s, 3H), 1.60 (m, 2H), 1.10 (s, 6H).	497.3
172	H73 		P	18	10.9 (s, 1H), 8.91 (s, 1H), 8.78 (s, 1H), 8.46 (d, J = 2.5 Hz, 1H), 8.40 (d, J = 0.8 Hz, 1H), 8.23 (s, 1H), 7.82 (d, J = 2.5 Hz, 1H), 7.77 (dd, J = 1.6 and 5.2 Hz, 1H), 7.55 (d, J = 1.2 Hz, 1H), 6.90 (d, J = 1.1 Hz, 1H), 6.31 (m, 1H), 4.44 (t, J = 5.1 Hz, 2H), 3.79 (t, J = 5.1 Hz, 2H), 3.15 (t, J = 7.0 Hz, 4H), 3.02 (q, J = 5.9 Hz, 2H), 2.39-2.48 (m, 4H), 2.36 (s, 3H), 2.03 (m, 1H), 1.91-1.99 (m, 2H), 0.77-0.86 (m, 4H).	532.2

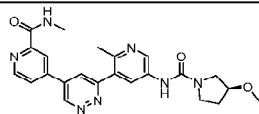
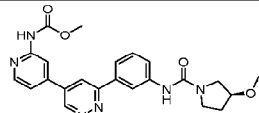
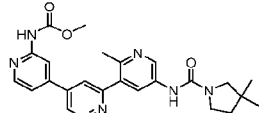
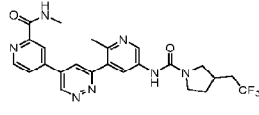
173	G69 		Q	13	11.0 (s, 1H), 9.33 (d, J = 2.0 Hz, 1H), 8.92 (s, 1H), 8.49 (d, J = 5.2 Hz, 1H), 8.40 (d, J = 1.6 Hz, 1H), 8.18 (d, J = 2.0 Hz, 1H), 8.13 (d, J = 8.0 Hz, 1H), 7.85 (dd, J = 1.6 and 5.2 Hz, 1H), 7.26 (d, J = 12.4 Hz, 1H), 6.54 (brt, J = 5.6 Hz, 1H), 3.10 (m, 2H), 3.07 (s, 3H), 2.23 (s, 3H), 2.05 (m, 1H), 1.58 (m, 2H), 1.09 (s, 6H), 0.80-0.88 (m, 4H).	507.4
174	H79 		P	2	10.3 (s, 1H), 8.85 (s, 1H), 8.65 (br m, 1H), 8.54 (d, J = 2.4 Hz, 1H), 8.44 (d, J = 5.2 Hz, 1H), 8.02 (d, J = 2.4 Hz, 1H), 7.95 (dd, J = 1.2 and 4.0 Hz, 1H), 7.14 (s, 1H), 6.65 (brt, J = 6.4 Hz, 1H), 4.96 (t, J = 5.6 Hz, 1H), 4.56 (m, 2H), 4.12 (m, 1H), 3.83 (m, 2H), 3.70 (s, 3H), 2.54 (s, 3H), 2.07 (m, 2H), 1.67 (m, 2H), 1.11 (s, 3H), 1.09 (s, 3H).	522.4
175	A3 I35		T	7	10.5 (s, 1H), 8.70 (s, 1H), 8.34 (d, J = 5.2 Hz, 1H), 8.30 (d, J = 1.6 Hz, 1H), 8.03 (d, J = 8.4 Hz, 1H), 7.67 (dd, J = 1.2 and 5.2 Hz, 1H), 7.15 (d, J = 12.4 Hz, 1H), 6.95 (s, 1H), 6.82 (brt, J = 5.6 Hz, 1H), 6.45-6.53 (m, 2H), 4.73 (t, J = 5.6 Hz, 1H), 3.62 (q, J = 6.0 Hz, 2H), 3.47 (q, J = 5.6 Hz, 2H), 3.15 (m, 2H), 2.19 (s, 3H), 2.11 (s, 3H), 1.35 (m, 2H), 1.01 (s, 3H), 0.26 (m, 2H), 0.21 (m, 2H).	521.4
176	H78 		P	61	10.3 (s, 1H), 8.81 (brd, J = 5.0 Hz, 1H), 8.69 (d, J = 2.4 Hz, 1H), 8.62 (m, 1H), 8.41 (s, 1H), 8.36 (br d, J = 5.3 Hz, 1H), 8.01 (dt, J = 0.8 and 1.6 Hz, 1H), 7.91 (d, J = 2.5 Hz, 1H), 7.76	477.2

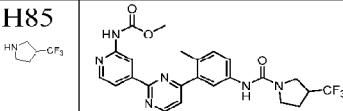
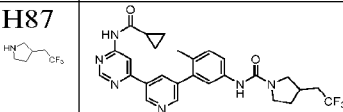
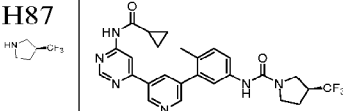
					(dd, J = 0.7 and 5.3 Hz, 1H), 7.52 (dd, J = 0.7 and 5.0 Hz, 1H), 3.69 (d, J = 0.8 Hz, 3H), 3.42-3.57 (m, 2H), 3.32-3.39 (m, 1H), 3.28 (m, 1H), 3.22-3.28 (m, 3H), 3.08-3.17 (m, 1H), 2.48 (m, 2H), 2.40 (s, 3H), 1.94 (m, 1H), 1.61 (m, 1H).	
177	H80 	P	65	9.74 (d, J = 2.2 Hz, 1H), 8.88 (q, J = 4.8 Hz, 1H), 8.82 (dd, J = 0.8 and 5.1 Hz, 1H), 8.51 (dd, J = 0.8 and 1.9 Hz, 1H), 8.27 (d, J = 2.2 Hz, 1H), 8.25 (s, 1H), 8.19 (dd, J = 1.9 and 5.1 Hz, 1H), 7.68 (d, J = 2.3 Hz, 1H), 7.60 (dd, J = 2.3 and 8.3 Hz, 1H), 7.25 (d, J = 8.7 Hz, 1H), 3.97 (m, 1H), 3.32-3.53 (m, 4H), 3.24 (s, 3H), 2.85 (d, J = 4.9 Hz, 3H), 2.29 (s, 3H), 1.87-1.99 (m, 2H).	447.2	
178	H80 	P	54	9.74 (d, J = 2.2 Hz, 1H), 8.88 (q, J = 4.8 Hz, 1H), 8.82 (d, J = 5.1 Hz, 1H), 8.50 (m, 1H), 8.26 (d, J = 2.3 Hz, 1H), 8.16-8.23 (m, 2H), 7.69 (d, J = 2.3 Hz, 1H), 7.60 (dd, J = 2.3 and 8.3 Hz, 1H), 7.24 (d, J = 8.4 Hz, 1H), 3.52 (t, J = 6.8 Hz, 2H), 3.28 (s, 2H), 2.85 (d, J = 4.8 Hz, 3H), 2.29 (s, 3H), 1.79 (t, J = 6.8 Hz, 2H), 0.52-0.62 (m, 4H).	443.2	
179	H78 	P	38	10.3 (s, 1H), 8.81 (m, 1H), 8.69 (t, J = 2.4 Hz, 1H), 8.62 (d, J = 1.7 Hz, 1H), 8.41 (s, 1H), 8.36 (m, 1H), 8.01 (m, 1H), 7.91 (d, J = 2.4 Hz, 1H), 7.76 (dt, J = 1.8 and 5.4 Hz, 1H), 7.52 (dd, J = 1.7 and 4.9 Hz, 1H), 3.69 (d, J = 2.2 Hz, 3H), 3.41-3.58 (m, 2H), 3.25-3.39 (m, 4H), 3.25 (d,	477.2	

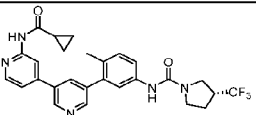
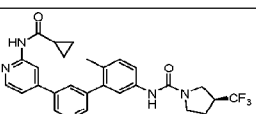
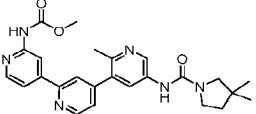
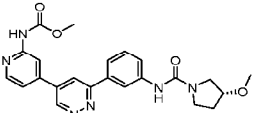
					J = 2.2 Hz, 3H), 3.12 (t, J = 8.8 Hz, 1H), 2.40 (d, J = 2.2 Hz, 3H), 2.00(m, 1H), 1.54-1.69 (m, 1H).	
180	H80 	P	68	9.74 (brd, J = 0.7 Hz, 1H), 8.88 (q, J = 4.7 Hz, 1H), 8.81 (m, 1H), 8.50 (m, 1H), 8.27 (dd, J = 0.7 and 2.3 Hz, 1H), 8.16-8.22 (m, 2H), 7.68 (d, J = 2.3 Hz, 1H), 7.63 (dd, J = 2.4 and 8.3 Hz, 1H), 7.24 (d, J = 8.4 Hz, 1H), 3.56 (t, J = 9.2 Hz, 1H), 3.45 (m, 1H), 3.25 (m, 1H), 3.05 (t, J = 10.2 Hz, 1H), 2.85 (d, J = 0.6 Hz, 3H), 2.29 (s, 3H), 1.98 (m, 1H), 1.81 (m, 1H), 1.60 (m, 1H), 0.90 (s, 9H).	473.2	
181	H80 	P	60	9.74 (d, J = 2.2 Hz, 1H), 8.88 (q, J = 4.8 Hz, 1H), 8.82 (d, J = 0.8 Hz, 1H), 8.50 (m, 1H), 8.27 (d, J = 2.2 Hz, 1H), 8.25 (s, 1H), 8.19 (dd, J = 1.9 amd 5.1 Hz, 1H), 7.68 (d, J = 2.3 Hz, 1H), 7.60 (dd, J = 2.3 and 8.3 Hz, 1H), 7.25 (d, J = 8.4 Hz, 1H), 3.98 (m, 1H), 3.33-3.52 (m, 4H), 3.23 (s, 3H), 2.85 (d, J = 5.0 Hz, 3H), 2.29 (s, 3H), 1.87-2.02 (m, 2H).	447.2	
182	H80 	P	30	9.71 (d, J = 2.3 Hz, 1H), 8.81 (d, J = 5.1 Hz, 1H), 8.76 (m, 1H), 8.50 (s, 1H), 8.32 (s, 1H), 8.23 (d, J = 2.2 Hz, 1H), 8.17 (dd, J = 1.9 and 5.1 Hz, 1H), 7.68 (d, J = 2.3 Hz, 1H), 7.60 (dd, J = 2.4 and 8.4 Hz, 1H), 7.26 (d, J = 8.4 Hz, 1H), 5.13 (m, 1H), 3.72 – 3.55 (m, 3H), 3.47 (m, 1H), 2.87 (d, J = 4.8 Hz, 3H), 2.30 (s, 3H), 2.23 (m, 1H), 2.15 (m, 1H).	501.2	

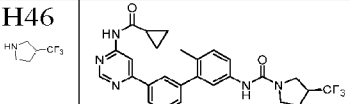
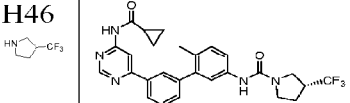
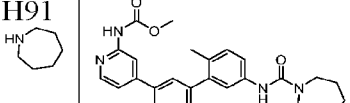
183a	H68 	 P & deprotection with HCl	63	10.6 (s, 1H), 10.2 (s, 1H), 8.99 (br m, 2H), 8.86 (br m, 1H), 8.58 (d, J = 6.0 Hz, 1H), 8.41 (t, J = 5.2 Hz, 1H), 8.18 (br m, 1H), 7.81 (br m, 2H), 7.05 (m, 1H), 4.48 (t, J = 4.4 Hz, 2H), 3.81 (t, J = 5.2 Hz, 2H), 3.72 (s, 3H), 3.67 (m, 2H), 3.09 (br m, 2H), 3.01 (m, 1H), 2.82 (m, 2H), 2.60 (s, 3H), 1.77 (q, J = 6.4 Hz, 2H). OH proton is missing.	522.4
183	183a  reductive alkylation	HCOOH NaBH ₃ (CN)	30	10.3 (s, 1H), 8.66 (brs, 1H), 8.57 (s, 1H), 8.49 (d, J = 2.4 Hz, 1H), 8.36 (d, J = 5.2 Hz, 1H), 8.83 (d, J = 2.8 Hz, 1H), 7.74 (dd, J = 1.2 and 5.2 Hz, 1H), 7.60 (d, J = 0.8 Hz, 1H), 6.91 (d, J = 0.8 Hz, 1H), 6.28 (brt, J = 5.6 Hz, 1H), 4.89 (t, J = 5.2 Hz, 1H), 4.46 (m, 2H), 3.81 (m, 2H), 3.70 (s, 3H), 3.31 (m, 2H), 3.03 (m, 2H), 2.77 (m, 2H), 2.38 (s, 3H), 2.34 (m, 1H), 2.20 (s, 3H), 1.64 (m, 2H).	536.4
184	H81 	P	69	9.78 (d, J = 2.2 Hz, 1H), 8.88 (q, J = 4.8 Hz, 1H), 8.83 (dd, J = 0.8 and 5.1 Hz, 1H), 8.76 (d, J = 2.5 Hz, 1H), 8.53 (m, 1H), 8.43 (s, 1H), 8.39 (d, J = 2.2 Hz, 1H), 8.20 (dd, J = 1.9 and 5.1 Hz, 1H), 8.12 (d, J = 2.5 Hz, 1H), 3.58 (t, J = 9.3 Hz, 1H), 3.48 (m, 1H), 3.25 (m, 1H), 3.07 (t, J = 10.3 Hz, 1H), 2.85 (d, J = 4.8 Hz, 3H), 2.48 (s, 3H), 1.99 (m, 1H), 1.89 – 1.78 (m, 1H), 1.52-1.65 (m, 1H), 0.91 (s, 9H).	474.2
185	H82 	P	43	10.4 (s, 1H), 9.59 (d, J = 2.2 Hz, 1H), 8.46 (d, J = 5.2 Hz, 1H), 8.28 (d, J = 1.5 Hz, 1H), 8.19 (s, 1H), 8.07 (d, J = 2.2 Hz, 1H),	489.2

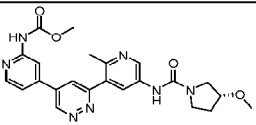
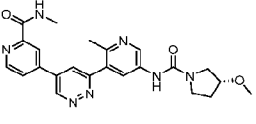
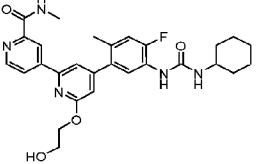
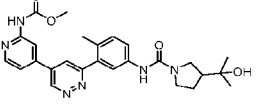
					7.67 (d, J = 2.3 Hz, 1H), 7.61-7.65 (m, 2H), 7.24 (d, J = 8.3 Hz, 1H), 3.70 (s, 3H), 3.56 (t, J = 9.3 Hz, 1H), 3.46 (dd, J = 8.0 and 10.1 Hz, 1H), 3.23 (m, 1H), 3.05 (t, J = 10.3 Hz, 1H), 2.28 (s, 3H), 2.03 (m, 1H), 1.81 (m, 1H), 1.59 (m, 1H), 0.90 (s, 9H).	
186	H82 	P	35	10.4 (s, 1H), 9.59 (d, J = 2.2 Hz, 1H), 8.46 (d, J = 5.2 Hz, 1H), 8.27 (d, J = 2.2 Hz, 2H), 8.06 (d, J = 2.1 Hz, 1H), 7.67 (d, J = 2.3 Hz, 1H), 7.58-7.66 (m, 2H), 7.24 (d, J = 8.4 Hz, 1H), 3.68-3.72 (m, 5H), 3.52 (m, 1H), 3.02 (t, J = 9.4 Hz, 1H), 2.34-2.46 (m, 2H), 2.28 (s, 4H), 2.09 (m, 1H), 1.66 (m, 1H).	515.2	
187	H83 	P	48	10.29 (s, 1H), 9.30 (s, 1H), 8.56 (s, 1H), 8.37 (d, J = 5.2 Hz, 1H), 7.77 – 7.71 (m, 2H), 7.69 (s, 1H), 7.55 – 7.47 (m, 1H), 7.23 (dd, J = 10.4, 9.0 Hz, 1H), 6.99 (s, 1H), 6.73 (t, J = 5.7 Hz, 1H), 4.93 (br s, 1H), 4.46 (t, J = 5.1 Hz, 2H), 3.81 (t, J = 5.1 Hz, 2H), 3.71 (s, 3H), 3.19 – 3.12 (m, 2H), 1.40 – 1.34 (m, 2H), 1.02 (s, 3H), 0.31 – 0.25 (m, 2H), 0.24 – 0.19 (m, 2H)	524.2	
188	H84 	P	51	10.29 (s, 1H), 8.54 (s, 1H), 8.46 (s, 1H), 8.36 (dd, J = 6.8, 4.4 Hz, 2H), 7.71 (d, J = 1.2 Hz, 1H), 7.66 (s, 1H), 7.47 (t, J = 10.7 Hz, 1H), 6.97 (s, 1H), 6.56 (t, J = 5.6 Hz, 1H), 4.90 (t, J = 5.6 Hz, 1H), 4.45 (t, J = 5.1 Hz, 2H), 3.80 (q, J = 5.3 Hz, 2H), 3.70 (s, 3H), 3.21 – 3.13 (m, 2H), 1.40 – 1.33 (m, 2H), 1.01 (s, 3H), 0.32 – 0.26 (m, 2H), 0.23 – 0.19	542.2	

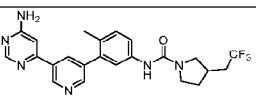
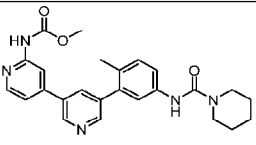
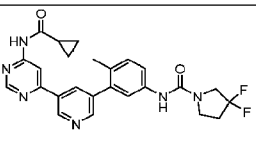
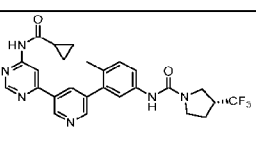
					(m, 2H).	
189	H81 	P	10	9.79 (d, J = 2.0 Hz, 1H), 8.88 (q, J = 5.2 Hz, 1H), 8.83 (d, J = 4.8 Hz, 1H), 8.74 (d, J = 2.4 Hz, 1H), 8.54 (d, J = 1.2 Hz, 1H), 8.49 (s, 1H), 8.40 (d, J = 2.4 Hz, 1H), 8.20 (dd, J = 5.2, 2.0 Hz, 1H), 8.12 (d, J = 2.4 Hz, 1H), 3.99 (br m, 1H), 3.40- 3.53 (m, 3H), 3.38 (m, 1H), 3.24 (s, 3H), 2.85 (d, J = 5.2 Hz, 3H), 1.93- 2.00 (m, 2H). 3Hs are under solvents	448.4	
190	H88 	P	29	10.40 (s, 1H), 9.55 (d, J = 2.0 Hz, 1H), 8.48 (d, J = 5.2 Hz, 1H), 8.40 (d, J = 2.4 Hz, 2H), 8.36 (d, J = 2.0 Hz, 1H), 8.29 (s, 1H), 7.80 (dd, J = 8.0, 1.6 Hz, 1H), 7.67 (dd, J = 5.2, 1.6 Hz, 2H), 7.45 (t, J = 8.0 Hz, 1H), 4.00 (br m, 1H), 3.72 (s, 3H), 3.48- 3.55 (m, 3H), 3.45 (m, 1H), 3.26 (s, 3H), 1.95- 2.00 (m, 2H).	449.3	
191	H86 	P	7	10.4 (s, 1H), 9.63 (d, J = 2.0 Hz, 1H), 8.75 (d, J = 2.0 Hz, 1H), 8.46 (d, J = 5.2 Hz, 1H), 8.41 (s, 1H), 8.29 (s, 1H), 8.19 (d, J = 2.0 Hz, 1H), 8.13 (d, J = 2.0 Hz, 1H), 7.64 (d, J = 5.2 Hz, 1H), 3.71 (s, 3H), 3.47 (t, J = 7.2 Hz, 2H), 3.16 (s, 2H), 1.68 (t, J = 7.2 Hz, 2H), 1.07 (s, 6H). 3Hs are under solvents	462.3	
192	H86 	P	40	9.79 (d, J = 2.0 Hz, 1H), 8.88 (q, J = 4.4 Hz, 1H), 8.83 (d, J = 4.8 Hz, 1H), 8.75 (d, J = 2.4 Hz, 1H), 8.54 (s, 1H), 8.51 (s, 1H), 8.39 (d, J = 2.0 Hz, 1H), 8.20 (dd, J = 5.2, 0.8 Hz, 1H), 7.67 (d, J = 2.0 Hz, 1H), 3.70 (m, 1H), 3.56 (m,	500.3	

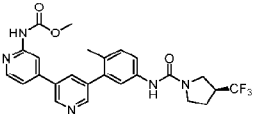
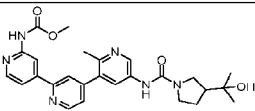
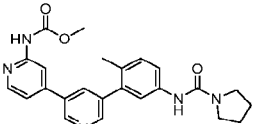
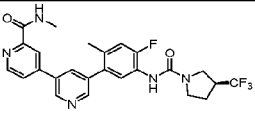
					1H), 3.36 (m, 1H), 3.06 (m, 1H), 2.85 (d, J = 4.8 Hz, 3H), 2.10 (m, 1H), 1.68 (m, 1H). 6Hs are under solvents.	
193	H85 	P	24	10.4 (s, 1H), 9.06 (d, J = 5.1 Hz, 1H), 8.91 (s, 1H), 8.46 (d, J = 5.2 Hz, 1H), 8.42 (s, 1H), 7.99 (d, J = 5.3 Hz, 1H), 7.77 (d, J = 2.2 Hz, 1H), 7.70 (d, J = 5.1 Hz, 1H), 7.62 (dd, J = 2.3 and 8.3 Hz, 1H), 7.28 (d, J = 8.4 Hz, 1H), 3.73 (s, 3H), 3.71 (m, 1H), 3.57 (m, 1H), 3.48 (m, 2H), 3.28 (m, 1H), 2.43 (s, 3H), 2.21 (m, 1H), 2.04 (m, 1H).	501.2	
194	H87 	P	38	11.4 (s, 1H), 9.18 (d, J = 2.3 Hz, 1H), 9.00 (s, 1H), 8.71 (d, J = 2.2 Hz, 1H), 8.63 (s, 1H), 8.27 (m, 1H), 8.23 (s, 1H), 7.54 (dd, J = 2.3 and 8.3 Hz, 1H), 7.48 (d, J = 2.3 Hz, 1H), 7.20 (d, J = 8.4 Hz, 1H), 3.66 (m, 1H), 3.52 (t, J = 9.2 Hz, 1H), 3.28 (m, 1H), 3.02 (t, J = 9.4 Hz, 1H), 2.34-2.47 (m, 3H), 2.19 (s, 3H), 2.04-2.11 (m, 2H), 1.65 (m, 1H), 0.87-0.92 (m, 4H).	525.2	
195	H87 	P	49	11.4 (s, 1H), 9.18 (d, J = 2.1 Hz, 1H), 9.00 (s, 1H), 8.72 (d, J = 2.1 Hz, 1H), 8.63 (s, 1H), 8.34 (s, 1H), 8.27 (m, 1H), 7.53 (dd, J = 2.3 and 8.4 Hz, 1H), 7.48 (d, J = 2.3 Hz, 1H), 7.22 (d, J = 8.3 Hz, 1H), 3.67 (m, 1H), 3.54 (m, 1H), 3.39-3.50 (m, 2H), 3.25 (m, 1H), 2.13-2.23 (m, 4H), 2.09 (m, 1H), 1.98 (m, 1H), 0.87-0.94 (m, 4H).	511.2	

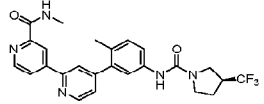
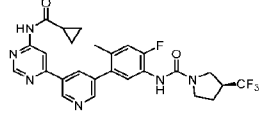
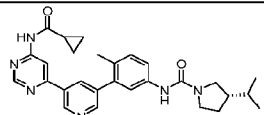
196	H89 		P	30	10.94 (s, 1H), 8.91 (t, J = 1.6 Hz, 1H), 8.66 – 8.60 (m, 1H), 8.44 (s, 1H), 8.42 (d, J = 5.3 Hz, 1H), 8.31 (s, 1H), 8.01 (q, J = 3.4 Hz, 1H), 7.55 – 7.50 (m, 2H), 7.46 (d, J = 2.3 Hz, 1H), 7.22 (d, J = 8.3 Hz, 1H), 3.66 (dd, J = 10.9, 8.3 Hz, 1H), 3.53 (td, J = 9.2, 5.0 Hz, 1H), 3.49 – 3.39 (m, 2H), 2.23-2.13 (m, 4H), 2.10 – 1.94 (m, 2H), 0.86-0.78 (m, 4H).	510.2
197	H89 		P	35	10.94 (s, 1H), 8.93 – 8.88 (m, 1H), 8.64 (t, J = 1.5 Hz, 1H), 8.44 (s, 1H), 8.42 (d, J = 5.2 Hz, 1H), 8.31 (s, 1H), 8.00 (d, J = 2.6 Hz, 1H), 7.56 – 7.48 (m, 2H), 7.46 (d, J = 2.3 Hz, 1H), 7.21 (d, J = 8.5 Hz, 1H), 3.69-3.61 (m, 1H), 3.58-3.48 (m, 1H), 3.49 – 3.40 (m, 2H), 3.30 – 3.21 (m, 1H), 2.23 – 2.13 (m, 4H), 2.10 – 1.94 (m, 2H), 0.85-0.78 (m, 4H).	510.2
198	H78 		P	8	10.3 (br s, 1H), 8.82 (d, J = 4.8 Hz, 1H), 8.63 (d, J = 6.8 Hz, 1H), 8.63 (s, 1H), 8.38 (m, 2H), 8.02 (s, 1H), 7.92 (d, J = 2.4 Hz, 1H), 7.78 (dd, J = 1.2 and 5.2 Hz, 1H), 7.53 (dd, J = 1.6 and 5.2 Hz, 1H), 3.70 (s, 3H), 3.46 (t, J = 6.8 Hz, 2H), 3.15 (s, 2H), 2.41 (s, 3H), 1.67 (t, J = 6.8 Hz, 2H), 1.06 (s, 6H).	461.2
199	H88 		P	32	10.5 (s, 1H), 9.55 (d, J = 2.0 Hz, 1H), 8.48 (d, J = 5.2 Hz, 1H), 8.40 (m, 2H), 8.36 (d, J = 2.0 Hz, 1H), 8.29 (s, 1H), 7.81 (d, J = 2.8 Hz, 1H), 7.79 (d, J = 2.0 Hz, 1H), 7.67 (dd, J = 1.6 and 5.2 Hz, 1H), 7.45 (t, J = 8.0 Hz, 1H), 4.00	449.2

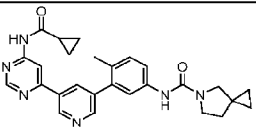
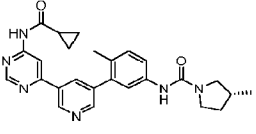
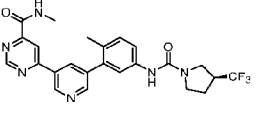
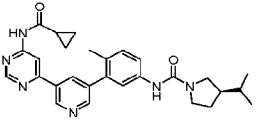
					(brm, 1H), 3.72 (s, 3H), 3.48-3.53 (m, 3H), 3.45 (m, 1H), 3.26 (s, 3H), 1.92-2.00 (m, 2H).	
200	H46 	Pure enantiomer (either R or S)	P & chiral purification	8	11.3 (s, 1H), 8.95 (s, 1H), 8.60 (s, 1H), 8.29 (s, 1H), 8.04 (d, J = 8.0 Hz, 1H), 7.95 (s, 1H), 7.61 (t, J = 7.6 Hz, 1H), 7.53 (brd, J = 7.6 Hz, 1H), 7.49 (dd, J = 2.0 and 8.0 Hz, 1H), 7.43 (d, J = 2.0 Hz, 1H), 7.18 (d, J = 8.4 Hz, 1H), 3.67 (dd, J = 8.4 and 10.8 Hz, 1H), 3.53 (m, 1H), 3.40-3.49 (m, 2H), 3.27 (m, 1H), 2.14-2.22 (m, 1H), 2.18 (s, 3H), 2.05 (m, 1H), 1.98 (m, 1H), 0.82-0.89 (m, 4H).	510.4
201	H46 	Pure enantiomer (either R or S)	P & chiral purification	8	11.3 (s, 1H), 8.95 (s, 1H), 8.60 (s, 1H), 8.29 (s, 1H), 8.04 (d, J = 8.0 Hz, 1H), 7.95 (s, 1H), 7.61 (t, J = 7.6 Hz, 1H), 7.53 (brd, J = 7.6 Hz, 1H), 7.49 (dd, J = 2.0 and 8.0 Hz, 1H), 7.43 (d, J = 2.0 Hz, 1H), 7.18 (d, J = 8.4 Hz, 1H), 3.67 (dd, J = 8.4 and 10.8 Hz, 1H), 3.54 (m, 1H), 3.40-3.49 (m, 2H), 3.27 (m, 1H), 2.14-2.22 (m, 1H), 2.18 (s, 3H), 2.05 (m, 1H), 1.98 (m, 1H), 0.82-0.89 (m, 4H).	510.4
202	H91 		P	17	10.36 (s, 1H), 8.92 (d, J = 2.0 Hz, 1H), 8.65 (d, J = 2.0 Hz, 1H), 8.38 (d, J = 5.2 Hz, 1H), 8.18 (m, 2H), 8.04 (t, J = 2.0 Hz, 1H), 7.52 (m, 2H), 7.46 (d, J = 2.0 Hz, 1H), 7.21 (d, J = 9.4 Hz, 1H), 3.69 (s, 3H), 3.44 (m, 4H), 2.21 (s, 3H), 1.65 (br m, 4H), 1.50 (br m, 4H).	460.2

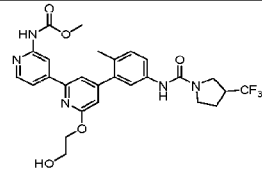
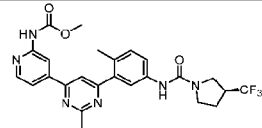
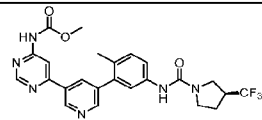
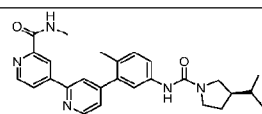
203	H86 		P	12	10.5 (s, 1H), 9.64 (d, J = 2.0 Hz, 1H), 8.75 (d, J = 2.4 Hz, 1H), 8.49 (s, 1H), 8.47 (d, J = 5.2 Hz, 1H), 8.29 (s, 1H), 8.21 (d, J = 2.0 Hz, 1H), 8.11 (d, J = 2.4 Hz, 1H), 7.64 (dd, J = 1.2 and 5.2 Hz, 1H), 3.99 (brm, 1H), 3.71 (s, 3H), 3.48- 3.53 (m, 3H), 3.44 (m, 1H), 3.25 (s, 3H), 2.50 (s, 3H), 1.94- 2.00 (m, 2H).	464.3
204	H81 		P	20	9.79 (d, J = 2.0 Hz, 1H), 8.91 (q, J = 4.4 Hz, 1H), 8.83 (d, J = 5.2 Hz, 1H), 8.74 (d, J = 2.0 Hz, 1H), 8.54 (s, 1H), 8.49 (s, 1H), 8.41 (d, J = 1.6 Hz, 1H), 8.21 (br d, J = 5.2 Hz, 1H), 8.12 (d, J = 2.4 Hz, 1H), 3.99 (br m, 1H), 3.44- 3.53 (m, 3H), 3.38 (m, 1H), 3.25 (s, 3H), 2.85 (d, J = 4.8 Hz, 3H), 1.94-2.00 (m, 2H).	448.2
205	A4 I5		T & R	55	8.81 (q, J = 4.4 Hz, 1H), 8.72 (d, J = 5.1 Hz, 1H), 8.67 (s, 1H), 8.26 (d, J = 4.8 Hz, 1H), 8.23 (s, 1H), 8.11 (d, J = 8.4 Hz, 1H), 7.71 (s, 1H), 7.19 (d, J = 12.3 Hz, 1H), 6.84 (s, 1H), 6.59 (d, J = 7.7 Hz, 1H), 4.90 (t, J = 5.6 Hz, 1H), 4.47 (m, 2H), 3.80 (m, 2H), 3.41 (m, 1H), 2.84 (d, J = 4.8 Hz, 3H), 2.21 (s, 3H), 1.77 (m, 2H), 1.63 (m, 2H), 1.50 (m, 1H), 1.11-1.31 (m, 5H).	522.2
206	H82 		P	6	10.5 (s, 1H), 9.60 (d, J = 2.0 Hz, 1H), 8.46 (d, J = 5.2 Hz, 1H), 8.28 (s, 1H), 8.20 (s, 1H), 8.07 (d, J = 2.4 Hz, 1H), 7.68 (d, J = 2.0 Hz, 1H), 7.61-7.66 (m, 2H), 7.24 (d, J = 8.4 Hz, 1H), 4.36 (s, 1H), 3.70 (s, 3H), 3.55 (m, 1H), 3.46 (m, 1H), 3.26 (m, 2H), 2.32 (s,	491.2

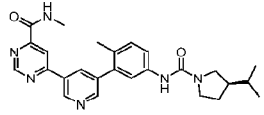
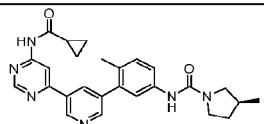
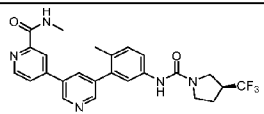
					3H), 2.20 (m, 1H), 1.79 (m, 2H), 1.11 (s, 6H).	
207	H90 		P & deprotection with HCl		9.04 (s, 1H), 8.88 (s, 1H), 8.72 (s, 1H), 8.25 (brs, 2H), 7.50 (brd, J = 2.0 Hz, 1H), 7.44 (dd, J = 2.0 and 8.0 Hz, 1H), 7.23(d, J = 9.4 Hz, 1H), 7.10 (s, 1H), 3.50 (m, 1H), 3.29 (m, 1H), 3.00 (m, 1H), 2.40 (m, 4H), 2.19 (s, 3H), 2.09 (m, 1H), 1.65 (m, 1H). in D ₂ O 3NHs are missing	
208	H91 		P	19	10.4 (s, 1H), 8.92 (d, J = 1.6 Hz, 1H), 8.64 (d, J = 1.6 Hz, 1H), 8.46 (s, 1H), 8.38 (d, J = 5.2 Hz, 1H), 8.19 (s, 1H), 8.04 (br s, 1H), 7.46-7.55 (m, 2H), 7.44 (s, 1H), 7.21 (d, J = 8.4 Hz, 1H), 3.69 (s, 3H), 3.40 (m, 4H), 2.21 (s, 3H), 1.55 (m, 2H), 1.47 (m, 4H).	446.1
209	H87 		P	21	11.4 (s, 1H), 9.18 (d, J = 2.0 Hz, 1H), 9.00 (d, J = 1.1 Hz, 1H), 8.72 (d, J = 2.1 Hz, 1H), 8.63 (d, J = 1.5 Hz, 1H), 8.42 (s, 1H), 8.28 (d, J = 2.3 Hz, 1H), 7.52 (dd, J = 2.3 and 8.5 Hz, 1H), 7.46 (d, J = 2.3 Hz, 1H), 7.24 (d, J = 8.3 Hz, 1H), 3.80 (t, J = 13.3 Hz, 2H), 3.61 (t, J = 7.3 Hz, 2H), 2.43 (m, 2H), 2.20 (s, 3H), 2.08 (m, 1H), 0.87-0.94 (m, 4H).	479.2
210	H87 		P	60	11.4 (s, 1H), 9.18 (s, 1H), 9.00 (s, 1H), 8.71 (d, J = 2.1 Hz, 1H), 8.63 (s, 1H), 8.33 (s, 1H), 8.27 (s, 1H), 7.53 (d, J = 2.3 Hz, 1H), 7.47 (s, 1H), 7.22 (d, J = 8.3 Hz, 1H), 3.67 (m, 1H), 3.53 (m, 1H), 3.39-3.49 (m, 2H), 3.26 (m, 1H), 2.13-2.23 (m, 4H), 2.08 (m, 1H), 1.99 (m, 1H),	511.2

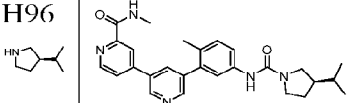
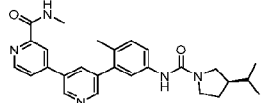
					0.87-0.94 (m, 4H).	
211	H91 	P	10	10.3 (s, 1H), 8.92 (d, J = 2.2 Hz, 1H), 8.64 (s, 1H), 8.37 (d, J = 5.2 Hz, 1H), 8.31 (s, 1H), 8.18 (s, 1H), 8.03 (m, 1H), 7.48-7.55 (m, 2H), 7.46 (m, 1H), 7.22 (d, J = 8.3 Hz, 1H), 3.68 (s, 3H), 3.65 (m, 1H), 3.51 (m, 1H), 3.38-3.49 (m, 2H), 3.26 (m, 1H), 2.21 (s, 3H), 2.17 (m, 1H), 1.99 (m, 1H).	500.2	
212	H78 	P	4	10.3 (br s, 1H), 8.82 (d, J = 4.8 Hz, 1H), 8.71 (d, J = 2.0 Hz, 1H), 8.63 (s, 1H), 8.40 (s, 1H), 8.38 (d, J = 5.2 Hz, 1H), 8.02 (s, 1H), 7.91 (d, J = 2.0 Hz, 1H), 7.77 (dd, J = 1.2 and 5.2 Hz, 1H), 7.54 (dd, J = 1.2 and 4.8 Hz, 1H), 4.38 (br s, 1H), 3.70 (s, 3H), 3.56 (m, 1H), 3.47 (m, 1H), 3.23 (m, 2H), 2.40 (s, 3H), 2.21 (m, 1H), 1.81 (br m, 2H), 1.12 (s, 3H), 1.12 (s, 3H).	491.2	
213	H91 	P	14	10.4 (s, 1H), 8.97 (d, J = 2.0 Hz, 1H), 8.70 (d, J = 2.0 Hz, 1H), 8.39 (d, J = 5.2 Hz, 1H), 8.19 (s, 1H), 8.15 (m, 2H), 7.52 (m, 3H), 7.22 (d, J = 8.4 Hz, 1H), 3.70 (s, 3H), 3.35 (m, 4H), 2.21 (s, 3H), 1.81 (m, 4H).	432.2	
214	G88 	Coupling with triphos gene	13	9.06 (s, 1H), 8.86 (q, J = 4.9 Hz, 1H), 8.75 (d, J = 5.1 Hz, 1H), 8.68 (s, 1H), 8.38 (s, 1H), 8.23 (s, 1H), 8.14 (s, 1H), 8.08 (dt, J = 5.2, 1.6 Hz, 1H), 7.48 (d, J = 7.9 Hz, 1H), 7.25 (d, J = 11.5 Hz, 1H), 3.72 – 3.65 (m, 1H), 3.55 (q, J = 8.5 Hz, 1H), 3.52 – 3.41 (m, 2H), 3.31 – 3.23 (m, 1H), 2.86 (d, J = 4.6 Hz, 3H), 2.27 (s, 3H), 2.21 (td, J = 13.9, 7.8 Hz, 1H), 2.02 (dq,	502.2	

					J = 14.8, 7.7 Hz, 1H).	
215	H92 		P	18	8.86 (d, J = 5.0 Hz, 1H), 8.83 (d, J = 5.2 Hz, 1H), 8.78 (d, J = 4.1 Hz, 1H), 8.76 (d, J = 5.1 Hz, 1H), 8.36 (s, 1H), 8.33 (dd, J = 1.8 and 5.2 Hz, 1H), 8.14 (s, 1H), 7.56 (dd, J = 2.3 and 8.3 Hz, 1H), 7.52 (t, J = 3.1 Hz, 2H), 7.25 (d, J = 8.3 Hz, 1H), 3.69 (m, 1H), 3.58 (m, 1H), 3.37-3.52 (m, 2H), 3.30 (s, 1H), 2.87 (d, J = 5.0 Hz, 3H), 2.24 (d, J = 3.6 Hz, 3H), 2.19 (m, 1H), 2.02 (dp, J = 15.0, 7.4 Hz, 1H).	484.2
216	G90 		Coupling with triphos gene	14	11.41 (s, 1H), 9.20 (s, 1H), 9.01 (s, 1H), 8.73 (s, 1H), 8.64 (s, 1H), 8.28 (s, 1H), 8.14 (s, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.25 (d, J = 11.5 Hz, 1H), 3.68 (dd, J = 10.9, 8.3 Hz, 1H), 3.55 (td, J = 9.1, 5.0 Hz, 1H), 3.51 – 3.41 (m, 2H), 3.32 – 3.18 (m, 1H), 2.25 (s, 3H), 2.23 – 2.15 (m, 1H), 2.09 (p, J = 6.3 Hz, 1H), 2.02 (dq, J = 15.2, 7.8 Hz, 1H), 0.95 – 0.88 (m, 4H).	529.2
217	G90 		Coupling with triphos gene	21	11.4 (s, 1H), 9.18 (s, 1H), 9.00 (s, 1H), 8.71 (s, 1H), 8.63 (s, 1H), 8.27 (s, 1H), 8.14 (s, 1H), 7.54 (dd, J = 2.3 and 8.3 Hz, 1H), 7.48 (d, J = 2.2 Hz, 1H), 7.20 (d, J = 8.3 Hz, 1H), 3.59 (m, 1H), 3.53 (t, J = 9.3 Hz, 1H), 3.25 (m, 1H), 2.91 (t, J = 9.9 Hz, 1H), 2.19 (s, 3H), 2.08 (p, J = 6.2 Hz, 1H), 1.98 (m, 1H), 1.83 (m, 1H), 1.42-1.53 (m, 2H), 0.87-0.93 (m, 10H).	485.2

218	H87 		P	26	11.4 (s, 1H), 9.19 (d, J = 1.6 Hz, 1H), 9.00 (s, 1H), 8.72 (d, J = 2.0 Hz, 1H), 8.64 (s, 1H), 8.28 (t, J = 2.0 Hz, 1H), 8.15 (s, 1H), 7.53 (dd, J = 2.0 and 8.0 Hz, 1H), 7.49 (d, J = 2.0 Hz, 1H), 7.21 (d, J = 8.4 Hz, 1H), 3.51 (t, J = 6.8 Hz, 2H), 3.28 (s, 2H), 2.20 (s, 3H), 2.08 (m, 1H), 1.79 (t, J = 6.8 Hz, 2H), 0.90 (m, 4H), 0.57 (m, 4H).	469.2
219	H87 		P	35	11.4 (s, 1H), 9.18 (d, J = 2.0 Hz, 1H), 9.00 (s, 1H), 8.72 (d, J = 2.0 Hz, 1H), 8.64 (s, 1H), 8.27 (t, J = 2.0 Hz, 1H), 8.14 (s, 1H), 7.54 (dd, J = 2.0 and 8.4 Hz, 1H), 7.49 (d, J = 2.0 Hz, 1H), 7.21 (d, J = 8.4 Hz, 1H), 3.57 (m, 1H), 3.47 (m, 1H), 3.27 (m, 1H), 2.88 (t, J = 8.4 Hz, 1H), 2.23 (m, 1H), 2.19 (s, 3H), 2.10 (m, 1H), 1.97 (m, 1H), 1.47 (m, 1H), 1.02 (d, J = 6.4 Hz, 3H), 0.86- 0.91 (m, 4H).	457.3
220	G91 		Coupling with triphosgene	8	9.41 (s, 2H), 9.06 (q, J = 4.8 Hz, 1H), 8.75 (m, 1H), 8.64 (s, 1H), 8.56 (m, 1H), 8.33 (s, 1H), 7.48-7.56 (m, 2H), 7.23 (d, J = 8.3 Hz, 1H), 3.67 (m, 1H), 3.54 (m, 1H), 3.39-3.50 (m, 2H), 3.26 (m, 1H), 2.86 (d, J = 4.8 Hz, 3H), 2.22 (s, 3H), 2.16 (m, 1H), 1.99 (m, 1H).	485.2
221	H87 		P	27	11.4 (s, 1H), 9.18 (s, 1H), 9.00 (s, 1H), 8.71 (s, 1H), 8.63 (s, 1H), 8.26 (m, 1H), 8.14 (s, 1H), 7.54 (d, J = 1.8 Hz, 1H), 7.47 (s, 1H), 7.20 (d, J = 8.3 Hz, 1H), 3.59 (m, 1H), 3.56 – 3.49 (m, 1H), 3.19-3.28 (m, 1H), 2.91 (t, J = 9.9 Hz, 1H), 2.19 (s, 3H), 2.12 – 2.05 (m, 1H), 1.97 (m, 1H),	485.2

					1.82 (m, 1H), 1.42-1.53 (m, 2H), 0.87-0.94 (m, 10H).	
222	H94 	P	77	10.29 (s, 1H), 8.57 (s, 1H), 8.36 (d, J = 6.0 Hz, 1H), 8.33 (s, 1H), 7.74 (d, J = 4.0 Hz, 1H), 7.52 (m, 2H), 7.48 (d, J = 2.0 Hz, 1H), 7.21 (d, J = 8.4 Hz, 1H), 6.84 (s, 1H), 4.90 (t, J = 5.6 Hz, 1H), 4.45 (t, J = 5.2 Hz, 2H), 3.81 (m, 2H), 3.78 (s, 3H), 3.65-3.76 (m, 1H), 3.49 (m, 1H), 3.44-3.47 (m, 2H), 3.29-3.33 (m, 1H), 2.22 (s, 3H), 2.16-2.19 (m, 1H), 1.98-2.03 (m, 1H).	560.2	
223	H93 	P	12	10.41 (s, 1H), 8.66 (s, 1H), 8.44 (d, J = 5.2 Hz, 1H), 8.40 (s, 1H), 7.97 (s, 1H), 7.83 (d, J = 5.2 Hz, 1H), 7.67 (d, J = 2.0 Hz, 1H), 7.62 (dd, J = 8.4, 2.4 Hz, 1H), 7.23 (d, J = 8.4 Hz, 1H), 3.69 (s, 3H), 3.66 (m, 1H), 3.52 (m, 1H), 3.43-3.55 (m, 2H), 3.27 (m, 1H), 2.77 (s, 3H), 2.34 (s, 3H), 2.18 (m, 1H), 2.00 (m, 1H).	515.2	
224	H95 	P	24	10.95 (s, 1H), 9.20 (d, J = 2.0 Hz, 1H), 8.94 (d, J = 0.8 Hz, 1H), 8.73 (d, J = 2.0 Hz, 1H), 8.41 (d, J = 0.8 Hz, 1H), 8.35 (s, 1H), 8.31 (t, J = 2.0 Hz, 1H), 7.53 (dd, J = 2.4 and 8.4 Hz, 1H), 7.49 (d, J = 2.0 Hz, 1H), 7.23 (d, J = 8.4 Hz, 1H), 3.74 (s, 3H), 3.67 (m, 1H), 3.53 (m, 1H), 3.48-3.49 (m, 2H), 3.30 (m, 1H), 2.21 (s, 3H), 2.17 (m, 1H), 2.01 (m, 1H).	501.1	
225	G89 	Coupling with triphos gene	50	8.84 (q, J = 4.8 Hz, 1H), 8.81 (br d, J = 5.1 Hz, 1H), 8.76 (m, 1H), 8.73 (dd, J = 0.8 and 5.1 Hz, 1H), 8.31	458.2	

					(dd, J = 1.9 and 5.1 Hz, 1H), 8.14 (s, 1H), 8.12 (s, 1H), 7.56 (dd, J = 2.3 and 8.3 Hz, 1H), 7.47-7.51 (m, 2H), 7.20 (d, J = 8.4 Hz, 1H), 3.59 (dd, J = 7.7 and 10.1 Hz, 1H), 3.54 (br t, J = 7.2 Hz, 1H), 3.25 (m, 1H), 2.91 (t, J = 10.0 Hz, 1H), 2.85 (d, J = 4.8 Hz, 3H), 2.22 (s, 3H), 1.98 (m, 1H), 1.82 (m, 1H), 1.41-1.52 (m, 2H), 0.85-0.93 (m, 6H).	
226	G91 		Coupling with triphosgene	28	9.42 (s, 2H), 9.07 (q, J = 4.8 Hz, 1H), 8.75 (s, 1H), 8.66 (s, 1H), 8.56 (s, 1H), 8.14 (s, 1H), 7.55 (br d, J = 2.3 Hz, 1H), 7.51 (s, 1H), 7.21 (d, J = 8.3 Hz, 1H), 3.61 (t, J = 7.7 Hz, 1H), 3.54 (t, J = 9.3 Hz, 1H), 3.25 (m, 1H), 2.93 (t, J = 9.9 Hz, 1H), 2.86 (d, J = 4.7 Hz, 3H), 2.22 (s, 3H), 1.99 (m, 1H), 1.84 (m, 1H), 1.41-1.53 (m, 2H), 0.85-0.94 (m, 6H).	459.2
227	H87 		P	26	11.41 (br s, 1H), 9.18 (d, J = 2.0 Hz, 1H), 9.00 (d, J = 0.8 Hz, 1H), 8.72 (d, J = 2.0 Hz, 1H), 8.64 (d, J = 0.8 Hz, 1H), 8.27 (t, J = 2.0 Hz, 1H), 8.14 (s, 1H), 7.54 (dd, J = 2.0 and 4.0 Hz, 1H), 7.49 (d, J = 2.4 Hz, 1H), 7.20 (d, J = 8.4 Hz, 1H), 3.55 (dd, J = 2.8 and 7.2 Hz, 1H), 3.47 (m, 1H), 3.29 (m, 1H), 2.88 (m, 1H), 2.27 (m, 1H), 2.21 (s, 3H), 2.06 (m, 1H), 1.97 (m, 1H), 1.47 (m, 1H), 1.02 (d, J = 6.4 Hz, 3H), 0.89-0.90 (m, 4H).	457.3
228	H96 		P	60	9.05 (d, J = 2.2 Hz, 1H), 8.86 (br q, J = 4.4 Hz, 1H), 8.74 (d, J = 5.1 Hz, 1H), 8.68 (d, J = 2.0 Hz, 1H),	484.2

					8.37 (d, J = 1.8 Hz, 1H), 8.33 (s, 1H), 8.22 (br t, J = 2.0 Hz, 1H), 8.06 (m, 1H), 7.54 (dd, J = 2.3 and 8.3 Hz, 1H), 7.50 (d, J = 1.6 Hz, 1H), 7.23 (d, J = 8.3 Hz, 1H), 3.68 (m, 1H), 3.55 (m, 1H), 3.40-3.50 (m, 2H), 3.29 (m, 1H), 2.85 (d, J = 4.8 Hz, 3H), 2.24 (s, 3H), 2.20 (m, 1H), 2.01 (m, 1H).	
229	H96 		P	80	9.05 (t, J = 2.2 Hz, 1H), 8.86 (q, J = 4.4 Hz, 1H), 8.74 (dd, J = 1.9 and 5.1 Hz, 1H), 8.68 (t, J = 2.0 Hz, 1H), 8.37 (br m, 1H), 8.21 (br q, J = 4.0 Hz, 1H), 8.12 (br s 1H), 8.06 (m, 1H), 7.55 (dt, J = 1.9 and 8.4 Hz, 1H), 7.49 (br t, J = 1.8 Hz, 1H), 7.21 (br d, J = 8.5 Hz, 1H), 3.61 (br t, J = 7.4 Hz, 1H), 3.54 (br t, J = 6.8 Hz, 1H), 3.25 (m, 1H), 2.92 (br d, J = 8.0 Hz, 1H), 2.85 (d, J = 4.9 Hz, 3H), 2.22 (s, 3H), 1.99 (m, 1H), 1.84 (m, 1H), 1.42-1.53 (m, 2H), 0.88-0.94 (m, 6H).	458.2

Biochemical assay for A-Raf.1

[000311] Activity of A-Raf kinase (SEQ. ID NO. 1) was determined spectroscopically using a coupled pyruvate kinase/lactate dehydrogenase assay that continuously monitors the ATP hydrolysis-dependent oxidation of NADH (e.g., Schindler *et al.*, Science, 2000, 289, 1938-1942). Assays were conducted in 384-well plates (100 μ L final volume) using 5.55 nM A-Raf (Sigma), 1.5 units pyruvate kinase, 2.1 units lactate dehydrogenase, 1 mM phosphoenol pyruvate, 0.28 mM NADH, 30.1 nM MEK (SignalChem), and 1 mM ATP in assay buffer (100 mM Tris, pH 7.5, 15 mM MgCl₂, 0.5 mM DTT, 0.1% octyl-glucoside, 0.002% (w/v) BSA, and 0.002% Triton X-100). Inhibition of A-Raf was measured by adding serial diluted test compound (final assay concentration of 1% DMSO). A decrease in absorption at 340 nm was monitored continuously for 6 h at 30 °C on a multi-mode microplate reader (BioTek). The reaction rate was calculated using the 4 to 5 h time frame.

The reaction rate at each concentration of compound was converted to percent inhibition using controls (*i.e.*, reaction with no test compound and reaction with a known inhibitor) and IC₅₀ values were calculated by fitting a four-parameter sigmoidal curve to the data using Prism (GraphPad software).

Biochemical assay for A-Raf.2

Activity of A-Raf kinase (SEQ. ID No: 1) was determined spectroscopically using a coupled pyruvate kinase/lactate dehydrogenase assay that continuously monitors the ATP hydrolysis-dependent oxidation of NADH (*e.g.*, Schindler *et al.*, Science, 2000, 289, 1938-1942). Assays were conducted in 384-well plates (25 µL final volume) using 20 nM A-Raf (Eurofins), 1.5 units pyruvate kinase, 2.1 units lactate dehydrogenase, 1 mM phosphoenol pyruvate, 0.7 mM NADH, 100 nM MEK (SignalChem), and 1 mM ATP in assay buffer (100 mM Tris, pH 7.5, 15 mM MgCl₂, 0.5 mM DTT, 0.1% octyl-glucoside, 0.002% (w/v) BSA, and 0.002% Triton X-100). Inhibition of A-Raf was measured by adding serial diluted test compound (final assay concentration of 1% DMSO). A decrease in absorption at 340 nm was monitored hourly for 4 h at 30 °C on a multi-mode microplate reader (BioTek). The reaction rate was calculated using the 3 to 4 h time frame. The reaction rate at each concentration of compound was converted to percent inhibition using controls (*i.e.*, reaction with no test compound and reaction with a known inhibitor) and IC₅₀ values were calculated by fitting a four-parameter sigmoidal curve to the data using Prism (GraphPad software).

A-Raf protein sequence residues 273-end containing Y301D and Y302D mutations with N-terminal GST-tag (SEQ. ID NO: 1)

MSPILGYWKIKGLVQPTRLLEYLEEKYEEHLYERDEGDKWRNKKFELGLEFPNLPY
YIDGDVKLTQSMARIYIADKHNMLGGCPKERAIEISMLEGAVLDIRYGVSRIAYSKDF
ETLKVDLFLSKLPEMLKMFEDRLCHKTYLNGDHVTHPDFMLYDALDVVLYMDPMCL
DAFPKLVCFKKRIEAIPIQIDKYLKSSKYIAWPLQGWQATFGGGDHPPKSDLEVLFGQ
PEFKSPAERERKSLADDDKKVKNLGYRDSGDDWEVPPSEVQLLKRIGTGSFGTVFR
GRWHGDVAVKVLKVSQPTAEQAQAFKNEMQVLRKTRHVNILLFMGFMTRPGFAIT
QWCEGSSLYHHLHVADTRFDMVQLIDVARQTAQGMDYLHAKNIIHRDLKSNNIFLH
EGLTVKIGDFGLATVKTRWGAQPLEQPSGSVLWMAAEVIRMQDPNPYSFQSDVYA
YGVVLYELMTGSLPYSHIGCRDQIIFMVGRGYLSPDLSSKISSNCPKAMRRLSDCLKF
QREERPLFPQILATIELLQRSPLKIERASAPSLHRTQADELPACLLSAARLVP

Biochemical assay for B-Raf.1

[000312] Activity of B-Raf kinase (SEQ. ID NO: 2) was determined spectroscopically using a coupled pyruvate kinase/lactate dehydrogenase assay that continuously monitors the ATP hydrolysis-dependent oxidation of NADH (*e.g.*, Schindler *et al.*, Science, 2000, 289,

1938-1942). Assays were conducted in 384-well plates (100 μ L final volume) using 0.13 nM B-Raf (Sigma), 1.5 units pyruvate kinase, 2.1 units lactate dehydrogenase, 1 mM phosphoenol pyruvate, 0.28 mM NADH, 30.1 nM MEK (SignalChem), and 1 mM ATP in assay buffer (100 mM Tris, pH 7.5, 15 mM MgCl₂, 0.5 mM DTT, 0.1% octyl-glucoside, 0.002% (w/v) BSA, and 0.002% Triton X-100). Inhibition of B-Raf was measured by adding serial diluted test compound (final assay concentration of 1% DMSO). A decrease in absorption at 340 nm was monitored continuously for 6 h at 30 °C on a multi-mode microplate reader (BioTek). The reaction rate was calculated using the 4 to 5 h time frame. The reaction rate at each concentration of compound was converted to percent inhibition using controls (*i.e.*, reaction with no test compound and reaction with a known inhibitor) and IC₅₀ values were calculated by fitting a four-parameter sigmoidal curve to the data using Prism (GraphPad software).

Biochemical assay for B-Raf.2

Activity of B-Raf kinase (SEQ. ID NO: 2) was determined spectroscopically using a coupled pyruvate kinase/lactate dehydrogenase assay that continuously monitors the ATP hydrolysis-dependent oxidation of NADH (*e.g.*, Schindler *et al.*, Science, 2000, 289, 1938-1942). Assays were conducted in 384-well plates (25 μ L final volume) using 2 nM B-Raf (Sigma), 1.5 units pyruvate kinase, 2.1 units lactate dehydrogenase, 1 mM phosphoenol pyruvate, 0.7 mM NADH, 50 nM MEK (SignalChem), and 1 mM ATP in assay buffer (100 mM Tris, pH 7.5, 15 mM MgCl₂, 0.5 mM DTT, 0.1% octyl-glucoside, 0.002% (w/v) BSA, and 0.002% Triton X-100). Inhibition of B-Raf was measured by adding serial diluted test compound (final assay concentration of 1% DMSO). A decrease in absorption at 340 nm was monitored hourly for 4 h at 30 °C on a multi-mode microplate reader (BioTek). The reaction rate was calculated using the 2 to 3 h time frame. The reaction rate at each concentration of compound was converted to percent inhibition using controls (*i.e.*, reaction with no test compound and reaction with a known inhibitor) and IC₅₀ values were calculated by fitting a four-parameter sigmoidal curve to the data using Prism (GraphPad software).

B-Raf protein sequence residues 416-766 with N-terminal GST-tag (SEQ ID NO: 2)

LQKSPGPQRERKSSSSSEDNRNRMKTGLRRDSSDDWEIPDGQITVGQRIGSGSFGTVYK
GKWHGADVAVKMLNVTAPTPQQLQAFKNEVGVLKTRHVNILLFMGYSTKQPQLAIV
TQWCEGSSLYHHLHIIETKFEMIKLIDIARQTAQGM DY LHAKSIIHRDLKSNINFLHED
LTVKIGD FGLATVKS RWSGSHQFEQLSGSILWMAPEVIRMQDKNPYSFQSDVYAFGI
VLYELMTGQLPYSNNNRDQIIFMVGRGYLSPDLSKVRSNCPKAMKRLMAECLKKK

RDERPLFPQILASIELLARSLPKIHRSASEPSLNRAGFQTEDFSLYACASPKTPIQAGGY
GAFPVH

Biochemical assay for C-Raf.1

[000313] Activity of C-Raf kinase (SEQ. ID NO: 3) was determined spectroscopically using a coupled pyruvate kinase/lactate dehydrogenase assay that continuously monitors the ATP hydrolysis-dependent oxidation of NADH (*e.g.*, Schindler *et al.*, Science, 2000, 289, 1938-1942). Assays were conducted in 384-well plates (100 μ L final volume) using 0.43 nM C-Raf (Sigma), 1.5 units pyruvate kinase, 2.1 units lactate dehydrogenase, 1 mM phosphoenol pyruvate, 0.28 mM NADH, 30.1 nM MEK (SignalChem), and 1 mM ATP in assay buffer (100 mM Tris, pH 7.5, 15 mM MgCl₂, 0.5 mM DTT, 0.1% octyl-glucoside, 0.002% (w/v) BSA, and 0.002 % Triton X-100). Inhibition of C-Raf was measured by adding serial diluted test compound (final assay concentration of 1% DMSO). A decrease in absorption at 340 nm was monitored continuously for 6 h at 30 °C on a multi-mode microplate reader (BioTek). The reaction rate was calculated using the 4 to 5 h time frame. The reaction rate at each concentration of compound was converted to percent inhibition using controls (*i.e.*, reaction with no test compound and reaction with a known inhibitor) and IC₅₀ values were calculated by fitting a four-parameter sigmoidal curve to the data using Prism (GraphPad software).

Biochemical assay for C-Raf.2

Activity of C-Raf kinase (SEQ. ID NO: 3) was determined spectroscopically using a coupled pyruvate kinase/lactate dehydrogenase assay that continuously monitors the ATP hydrolysis-dependent oxidation of NADH (*e.g.*, Schindler *et al.*, Science, 2000, 289, 1938-1942). Assays were conducted in 384-well plates (25 μ L final volume) using 3.84 nM C-Raf (Eurofins), 1.5 units pyruvate kinase, 2.1 units lactate dehydrogenase, 1 mM phosphoenol pyruvate, 0.7 mM NADH, 50 nM MEK (SignalChem), and 1 mM ATP in assay buffer (100 mM Tris, pH 7.5, 15 mM MgCl₂, 0.5 mM DTT, 0.1% octyl-glucoside, 0.002% (w/v) BSA, and 0.002% Triton X-100). Inhibition of C-Raf was measured by adding serial diluted test compound (final assay concentration of 1% DMSO). A decrease in absorption at 340 nm was monitored hourly for 4 h at 30 °C on a multi-mode microplate reader (BioTek). The reaction rate was calculated using the 2 to 3 h time frame. The reaction rate at each concentration of compound was converted to percent inhibition using controls (*i.e.*, reaction with no test compound and reaction with a known inhibitor) and IC₅₀ values were calculated by fitting a four-parameter sigmoidal curve to the data using Prism (GraphPad software).

Sequence 2: C-Raf residues 306-end; Y340D, Y341D with N-terminal GST-tag (SEQ ID NO: 3)

QPKTPVPAQRERAPVSGTQEK NKIRPRGQRDSSDDWEIEASEV MLSTRIGSGSFGTVY
 KGKWHGDVAVKILKVVDPTPEQFQAFRNEVAVLRKTRHVNILLFMGYMTKDNLA I
 VTQWCEGSSLYKHLHVQETKFQMFQLIDIARQTAQGMDYLHAKNIIHRDMKSNNIF
 LHEGLTVKIGDFGLATVKSRWSGSQQVEQPTGSVLWMAPEVIRMQDNNPFSFQSDV
 YSYGIVLYELMTGELPYSHINN RDQIIFMVGRGYASPDLSKLYKNCPKAMKRLVADC
 VKKVKEERPLFPQILSSI ELLQHSLPKINRSASEPSLHRAAHTEDINACTLT TSPRLPVF

Biochemical assay for B-Raf (V600E).1

[000314] Activity of B-Raf (V600E) (SEQ. ID NO: 4) kinase was determined spectroscopically using a coupled pyruvate kinase/lactate dehydrogenase assay that continuously monitors the ATP hydrolysis-dependent oxidation of NADH (*e.g.*, Schindler *et al.*, Science, 2000, 289, 1938-1942). Assays were conducted in 384-well plates (100 μ L final volume) using 0.03 nM B-Raf (SignalChem), 1.5 units pyruvate kinase, 2.1 units lactate dehydrogenase, 1 mM phosphoenol pyruvate, 0.28 mM NADH, 30.1 nM MEK (SignalChem), and 1 mM ATP in assay buffer (100 mM Tris, pH 7.5, 15 mM MgCl₂, 0.5 mM DTT, 0.1% octyl-glucoside, 0.002% (w/v) BSA, and 0.002% Triton X-100). Inhibition of B-Raf (V600E) was measured by adding serial diluted test compound (final assay concentration of 1% DMSO). A decrease in absorption at 340 nm was monitored continuously for 6 h at 30 °C on a multi-mode microplate reader (BioTek). The reaction rate was calculated using the 3 to 4 h time frame. The reaction rate at each concentration of compound was converted to percent inhibition using controls (*i.e.*, reaction with no test compound and reaction with a known inhibitor) and IC₅₀ values were calculated by fitting a four-parameter sigmoidal curve to the data using Prism (GraphPad software).

Biochemical assay for B-Raf (V600E).2

Activity of B-Raf (V600E) (SEQ. ID NO: 4) kinase was determined spectroscopically using a coupled pyruvate kinase/lactate dehydrogenase assay that continuously monitors the ATP hydrolysis-dependent oxidation of NADH (*e.g.*, Schindler *et al.*, Science, 2000, 289, 1938-1942). Assays were conducted in 384-well plates (25 μ L final volume) using 0.5 nM B-Raf (deCode), 1.5 units pyruvate kinase, 2.1 units lactate dehydrogenase, 1 mM phosphoenol pyruvate, 0.7 mM NADH, 100 nM MEK (SignalChem), and 1 mM ATP in assay buffer (100 mM Tris, pH 7.5, 15 mM MgCl₂, 0.5 mM DTT, 0.1% octyl-glucoside, 0.002% (w/v) BSA, and 0.002% Triton X-100). Inhibition of B-Raf (V600E) was measured by adding serial diluted test compound (final assay concentration of 1% DMSO). A decrease in absorption at

340 nm was monitored hourly for 4 h at 30 °C on a multi-mode microplate reader (BioTek). The reaction rate was calculated using the 3 to 4 h time frame. The reaction rate at each concentration of compound was converted to percent inhibition using controls (*i.e.*, reaction with no test compound and reaction with a known inhibitor) and IC₅₀ values were calculated by fitting a four-parameter sigmoidal curve to the data using Prism (GraphPad software).

B-Raf (V600E) residues 416-766 with a N-terminal GST-tag (SEQ. ID NO: 4)

LQKSPGPQRRERKSSSSSEDNRNRMKTLGRRDSSDDWEIPDGQITVGQRIGSGSFGTVYK
GKWHGDVAVKMLNVTAPTPQQLQAFKNEVGVLKTRHVNILLFMGYSTKPQLAIV
TQWCEGSSLYHHLHIIETKFEMIKLIDIAHQTAQGMDYLHAKSIIHRDLKSNINFLHED
LTVKIGDFGLATEKSRWSGSHQFEQLSGSILWMAPEVIRMQDKNPYSFQSDVYAFGI
VLYELMTGQLPYSNINNRDQIIFMVGRGYLSPDLSKVRSNCPKAMKRLMAECLKKK
RDERPLFPQILASIELLARSLPKIHRSASEPSLNRAGFQTEDFSLYACASPKTPIQAGGY
GAFPVH

Table L. Inhibition of biochemical activity of BRAF, CRAF and BRAF V600E kinases by exemplary compounds shown in Table G.

Example (Compound) Number	ARAF.1 IC ₅₀	BRAF.1 IC ₅₀	CRAF.1 IC ₅₀	BRAF V600E.1 IC ₅₀	ARAF.2 IC ₅₀	BRAF.2 IC ₅₀	CRAF.2 IC ₅₀	BRAF V600E.2 IC ₅₀
1	++++	+	+	+				
2	++++	+++	++	+				
3	++	+	+	+				
4	++++	+	+	+				
5	++++	+	+	+				
6	++++	++	++	+				
7	++++	+	+	+				
8	++++	++++	+++	+				
9	++++	+	+	+				
10	++++	+	+	+				
11	++++	+++	++	+				
12	++++	+++	++	+				
13	++++	++	+	+				
14	++++	++++	++	+				
15	++++	++	+	+				
16	++++	+++	++	+				
17	++++	++++	++++	+				
18	++++	+	+	+				
19	++++	+++	++	+				
20	++++	+++	++	+				
21	++++	+++	++	+				
22	++++	++	+	+				

23	++++	+	+	+				
24	++++	+	+	+				
25	++++	++	+	+				
26	++++	++	++	+				
27	++++	+	+	+				
28	++++	++	+	+				
29								
30	++++	++++	+++	+				
31	++++	++	++	+				
32	++++	+	+	+				
33	++	+	+	+				
34	++++	+	+	+				
35	++++	++	++	+				
36	++++	++	++	+				
37	++++	+	+	+				
38	++++	+	+	+				
39	++++	+	+	+				
40	++++	++	++	+				
41	++++	++	++	+				
42	++++	++++	++++	+				
43	++++	++	+	+				
44	++++	++	++	+				
45	++++	++++	++	+				
46	++++	++	++	+				
47	++	+	+	+				
48	++++	+	+	+				
49	++	+	+	+				
50	++++	+	+	+				
51	++++	+	+	+				
52	++++	+	+	+				
53	++	+	+	+				
54	++++	+	+	+				
55	++	+	+	+				
56	++++	+	+	+				
57	+++	+	+	+				
58	+++	+	+	+				
59	++	+	+	+				
60	++++	++++	++	+				
61	++++	+	+	+				
62	++++	+++	+	+				
63	+++	+	+	+				
64								
65	++++	+	+	+				
66	++++	+	+	+				

67	++	+	+	+				
68	++++	+	+	+				
69	++++	+	+	+				
70	++++	++	++	+				
71	++	+	+	+				
72	++++	++	+	+				
73								
74	++++	++++	++++	++				
75	++++	+	+	+				
76	++	+	+	+				
77	++++	+	+	+				
78	++++	+	+	+				
79	++++	+	+	+				
80	++++	+	+	+				
81	++++	+	+	+				
82	++++	++	+	+				
83	+++	+	+	+				
84	++++	+	+	+				
85	++++	+	+	+				
86	++++	++++	++++	++				
87	+++	+	+	+				
88	++++	+++	++	+				
89	++++	++++	++++	++++				
90	++++	+	+	+				
91	++++	+	+	+				
92	++++	+++	++	+				
93	++++	++++	++++	++++				
94	++++	+	+	+				
95	++++	+++	+++	+				
96	++++	+++	++	+				
97	++++	+	+	+				
98	++++	++	+	+				
99	+++	+	+	+				
100	++++	+	+	+				
101	++++	++	+	+				
102	++++	+	+	+				
103	++++	+	+	+				
104	++	+	+	+				
105	++	+	+	+				
106	++++	+	+	+				
107	+++	+	+	+				
108								
109	++++	+	+	+				
110	++++	++	++	+				

111	++++	+	+	+				
112	++++	+	+	+				
113	+++	+	+	+				
114	++	+	+	+				
115	++++	+	+	+				
116	++	+	+	+				
117								
118	++++	+	+	+				
119	++++	++	++	+				
120	++++	+	+	+				
121	++++	++	+	+				
122	++++	+	+	+				
123	++++	++++	+++	+				
124	++++	+	+	+				
125	++++	++++	++++	++				
126	+++	+	+	+				
127	++	+	+	+				
128	++	+	+	+				
129	++++	+	+	+				
130	++++	++	+	+				
131	++	+	+	+				
132	++++	++	++	+				
133	+++	+	+	+				
134	+++	+	+	+				
135	++++	++	+	+				
136	++++	+	+	+				
137	++++	++	+	+				
138	++++	++	+	+				
139	++++	+	+	+				
140	++++	++	++	+				
141	++++	+	+	+				
142	++++	+	+	+				
143	++++	+++	++	+				
144	++++	+	+	+				
145	++++	+	+	+				
146	++++	+	+	+				
147	++++	+	+	+				
148	++++	+++	+++	+				
149	++++	+++	+++	+				
150	++++	+	+	+				
151	++++	+	+	+				
152								
153	++++	+++	+++	+				
154	++++	++++	++++	+				

155	++++	+	+	+				
156	++++	+	+	+				
157	++++	+	+	+				
158	++++	+	+	+				
159	+++	+	+	+				
160	++++	++	++	+				
161								
162	++++	+	+	+				
163	++++	++	++	+				
164	++++	+	+	+				
165	++++	+	+	+				
166	++++	++	+	+				
167	+++	+	+	+				
168	+++	+	+	+				
169	++++	+	+	+				
170	++++	+	+	+				
171	++++	+	+	+				
172	++++	++++	++++	++				
173	++++	+	+	+				
174	++++	++	+	+				
175	++	+	+	+				
176	++++	++++	++	+				
177	++++	++++	++++	++				
178	++++	++++	+++	+				
179	++++	++++	++	+				
180	++++	+++	++	+				
181	++++	++++	++++	++				
182	++++	+++	++	+				
183	++++	++++	++++	++++				
184	++++	++++	+++	+				
185	++++	++	+	+				
186	++++	+	+	+				
187	++++	+	+	++				
188	++++	+	+	+				
189	++++	++++	++++	++++				
190	++++	++++	++++	++++				
191	++++	++++	++++	++++				
192	++++	++++	+++	++++				
193	++++	+	+	++				
194	++++	+	+	+				
195	+++	+	+	+				
196								
197	+++	+	+	+				
198	++++	+++	++	++++				

199	++++	++++	++++	++++				
200	++++	+	+	+				
201	++++	+	+	+				
202	++++	+++	++	++				
203	++++	++++	++++	++++				
204	++++	++++	++++	++++				
205								
206	++++	+++	++	++++				
207	++++	++	+	+++				
208	++++	++++	++	++++				
209	++++	+	+	++				
210	+++	+	+	+				
211	++++	+	+	+				
212	++++	++++	+++	++++				
213	++++	++++	+++	+++				
214	++++	+++	++	++				
215					++++	++	+	++
216	++	+	+	+				
217	++	+	+	+				
218	++++	+	+	+				
219	++++	+	+	++				
220					++++	++	++	++
221	++	+	+	+				
222	++++	+	+	+				
223	++++	+	++	++++				
224					++	+	+	+
225					++++	++	++	+
226					++++	+++	++	+
227					++	+	+	+
228					++++	++	++	+
229					++++	++	+	+

For Table L, “+” refers to an IC₅₀ less than or equal to 100 nM; “++” refers to an IC₅₀ greater than 100 nM and less than or equal to 500 nM; “+++” refers to an IC₅₀ greater than 500 nM and less than or equal to 1000 nM; and “++++” refers to an IC₅₀ greater than 1000 nM.

A375 Cell Proliferation Assay (1)

[000315] A375 cells (catalog (#CRL-1619) are obtained from the American Type Culture Collect (ATTC, Manassas, VA). Briefly, cells were grown in DMEM High Glucose supplemented with 10% characterized fetal bovine serum (Invitrogen, Carlsbad, CA) and 1%

Penicillin/Streptomycin/L-Glutamine at 37 °C, 5% CO₂, and 95% humidity. Cells are expanded until reaching 70-95% confluency at which point they are sub-cultured or harvested for assay use. A serial dilution of test compound is dispensed into a 96-well black clear bottom plate in triplicate. Two thousand five hundred cells are added per well in 200 µL complete growth medium in the 96-well plate. Plates are incubated for 67-72 hours at 37 °C, 5% CO₂, and 95% humidity. At the end of the incubation, 40 µL of a 440 µM solution of resazurin (Sigma, St. Louis, MO) in PBS is added to each well of the plate and plates are incubated for an additional 5-6 hours at 37 °C, 5% CO₂, and 95% humidity. Plates are read on a Synergy2 or equivalent reader (Biotek, Winooski VT) using an excitation of 540 nm and an emission of 600 nm. Data is analyzed using Prism software (GraphPad, San Diego, CA) to calculate IC₅₀ values.

A375 Cell Proliferation Assay (2)

[000316] A375 cells (catalog (#CRL-1619) are obtained from the American Type Culture Collect (ATTC, Manassas, VA). Briefly, cells were grown in DMEM High Glucose supplemented with 10% characterized fetal bovine serum (Invitrogen, Carlsbad, CA) and 1% Penicillin/Streptomycin/L-Glutamine at 37 °C, 5% CO₂, and 95% humidity. Cells are expanded until reaching 70-95% confluency at which point they are sub-cultured or harvested for assay use. Using the Beckman Coulter Echo 650, a serial dilution of test compound is dispensed into a 384-well black clear bottom plate in triplicate. Six hundred twenty-five cells are added per well in 50 µL complete growth medium in the 384-well plate. Plates are incubated for 67-72 h at 37 °C, 5% CO₂, and 95% humidity. At the end of the incubation, 10 µL of a 440 µM solution of resazurin (Sigma, St. Louis, MO) in PBS is added to each well of the plate and plates are incubated for an additional 3-6 h at 37 °C, 5% CO₂, and 95% humidity. Plates are read on a Synergy2 or equivalent reader (Biotek, Winooski VT) using an excitation of 540 nm and an emission of 600 nm. Data is analyzed using Prism software (GraphPad, San Diego, CA) to calculate IC₅₀ values.

H2405 Cell Proliferation Assay (1)

H2405 cells (catalog #CRL-5944) are obtained from the American Type Culture Collect (ATTC, Manassas, VA). Briefly, cells were grown in RPMI 1640 supplemented with 5% characterized fetal bovine serum (Invitrogen, Carlsbad, CA) and 1%

Penicillin/Streptomycin/L-Glutamine at 37 °C, 5% CO₂, and 95% humidity. Cells are expanded until reaching 70-95% confluency at which point they are subcultured or harvested for assay use. A serial dilution of test compound is dispensed into a 96-well black clear bottom plate in triplicate. Three thousand cells are added per well in 200 µL complete growth medium in the 96-well plate. Plates are incubated for 67- 72 hours at 37 °C, 5% CO₂, and 95% humidity. At the end of the incubation, 40 µL of a 440 µM solution of resazurin (Sigma, St. Louis, MO) in PBS is added to each well of the plate and plates are incubated for an additional 5- 6 hours at 37 °C, 5% CO₂, and 95% humidity. Plates are read on a Synergy2 or equivalent reader (Biotek, Winooski VT) using an excitation of 540 nm and an emission of 600 nm. Data is analyzed using Prism software (GraphPad, San Diego, CA) to calculate IC₅₀ values.

H2405 Cell Proliferation Assay (2)

H2405 cells (catalog #CRL-5994) are obtained from the American Type Culture Collect (ATTC, Manassas, VA). Briefly, cells were grown in RPMI 1640 supplemented with 5% characterized fetal bovine serum (Invitrogen, Carlsbad, CA) and 1% Penicillin/Streptomycin/L-Glutamine at 37 °C, 5% CO₂, and 95% humidity. Cells are expanded until reaching 70-95% confluency at which point they are sub-cultured or harvested for assay use. A serial dilution of test compound is dispensed into a 384-well black clear bottom plate in triplicate. Seven hundred fifty cells are added per well in 50 µL complete growth medium in the 384-well plate. Plates are incubated for 67-72 h at 37 °C, 5% CO₂, and 95% humidity. At the end of the incubation, 10 µL of a 440 µM solution of resazurin (Sigma, St. Louis, MO) in PBS is added to each well of the plate and plates are incubated for an additional 5-6 h at 37 °C, 5% CO₂, and 95% humidity. Plates are read on a Synergy2 or equivalent reader (Biotek, Winooski VT) using an excitation of 540 nm and an emission of 600 nm. Data is analyzed using Prism software (GraphPad, San Diego, CA) to calculate IC₅₀ values

WM3928 Cell Proliferation Assay (1)

[000317] WM3928 cells (#WM3928-01-0001) are obtained from Rockland Immunochemicals Inc (Gilbertsville, PA). Briefly, cells were grown in MCDB 153 medium (Sigma, #M7403, St. Louis, MO) supplemented with 20% Leibovitz's L-15 (ThermoFisher

#11415-064, Waltham, MA), 2% heat inactivated fetal bovine serum (ThermoFisher, #A3840001, Waltham, MA), 5 µg/mL Insulin (Bovine Pancreas) (Sigma, #I0516, St. Louis, MO), 1.68 mM Calcium Chloride (Sigma, #C-34006, St. Louis, MO) and 1% Penicillin/Streptomycin/L-Glutamine (ThermoFisher #10378016, Waltham, MA) at 37 °C, 5% CO₂, and 95% humidity. Cells are expanded until reaching 70-95% confluency at which point they are subcultured or harvested for assay use. A serial dilution of test compound is dispensed into a 96-well black clear bottom plate in triplicate. Three thousand cells are added per well in 200 µL complete growth medium in the 96-well plate. Plates are incubated for 67-72 hours at 37 °C, 5% CO₂, and 95% humidity. At the end of the incubation, 40 µL of a 440 µM solution of resazurin (Sigma, #199303, St. Louis, MO) in PBS is added to each well of the plate and plates are incubated for an additional 6-7 hours at 37 °C, 5% CO₂, and 95% humidity. Plates are read on a Synergy2 or equivalent reader (Biotek, Winooski VT) using an excitation of 540 nm and an emission of 600 nm. Data is analyzed using Prism software (GraphPad, San Diego, CA) to calculate IC₅₀ values.

WM3928 Cell Proliferation Assay (2)

[000318] WM3928 cells (#WM3928-01-0001) are obtained from Rockland Immunochemicals Inc (Gilbertsville, PA). Briefly, cells were grown in MCDB 153 medium (Sigma, #M7403, St. Louis, MO) supplemented with 20% Leibovitz's L-15 (ThermoFisher #11415-064, Waltham, MA), 2% heat inactivated fetal bovine serum (ThermoFisher, #A3840001, Waltham, MA), 5 µg/mL Insulin (Bovine Pancreas) (Sigma, #I0516, St. Louis, MO), 1.68 mM Calcium Chloride (Sigma, #C-34006, St. Louis, MO) and 1% Penicillin/Streptomycin/L-Glutamine (ThermoFisher #10378016, Waltham, MA) at 37 °C, 5% CO₂, and 95% humidity. Cells are expanded until reaching 70-95% confluency at which point they are sub-cultured or harvested for assay use. Using the Beckman Coulter Echo 650, a serial dilution of test compound is dispensed into a 384-well black clear bottom plate in triplicate. Seven hundred fifty cells are added per well in 50 µL complete growth medium in the 384-well plate. Plates are incubated for 67-72 hours at 37 °C, 5% CO₂, and 95% humidity. At the end of the incubation, 10 µL of a 440 µM solution of resazurin (Sigma, #199303, St. Louis, MO) in PBS is added to each well of the plate and plates are incubated for an additional 3-6 hours at 37 °C, 5% CO₂, and 95% humidity. Plates are read on a Synergy2 or equivalent reader (Biotek, Winooski VT) using an excitation of 540 nm and an

emission of 600 nm. Data is analyzed using Prism software (GraphPad, San Diego, CA) to calculate IC₅₀ values.

WM3629 Cell Proliferation Assay (1)

[000319] WM3629 cells (#WM3629-01-0001) are obtained from Rockland Immunochemicals Inc (Gilbertsville, PA). Briefly, cells were grown in MCDB 153 medium (Sigma, #M7403, St. Louis, MO) supplemented with 20% Leibovitz's L-15 (ThermoFisher #11415-064, Waltham, MA), 2% heat inactivated fetal bovine serum (ThermoFisher, #A3840001, Waltham, MA), 5 µg/mL Insulin (Bovine Pancreas) (Sigma, #I0516, St. Louis, MO), 1.68 mM Calcium Chloride (Sigma, #C-34006, St. Louis, MO) and 1% Penicillin/Streptomycin/L-Glutamine (ThermoFisher #10378016, Waltham, MA) at 37 °C, 5% CO₂, and 95% humidity. Cells are expanded until reaching 70-95% confluency at which point they are subcultured or harvested for assay use. A serial dilution of test compound is dispensed into a 96-well black clear bottom plate in triplicate. Four thousand five hundred cells are added per well in 200 µL complete growth medium in the 96-well plate. Plates are incubated for 67-72 hours at 37 °C, 5% CO₂, and 95% humidity. At the end of the incubation, 40 µL of a 440 µM solution of resazurin (Sigma, #199303, St. Louis, MO) in PBS is added to each well of the plate and plates are incubated for an additional 6-7 hours at 37 °C, 5% CO₂, and 95% humidity. Plates are read on a Synergy2 or equivalent reader (Biotek, Winooski VT) using an excitation of 540 nm and an emission of 600 nm. Data is analyzed using Prism software (GraphPad, San Diego, CA) to calculate IC₅₀ values.

WM3629 Cell Proliferation Assay (2)

[000320] WM3629 cells (#WM3629-01-0001) are obtained from Rockland Immunochemicals Inc (Gilbertsville, PA). Briefly, cells were grown in MCDB 153 medium (Sigma, #M7403, St. Louis, MO) supplemented with 20% Leibovitz's L-15 (ThermoFisher #11415-064, Waltham, MA), 2% heat inactivated fetal bovine serum (ThermoFisher, #A3840001, Waltham, MA), 5 µg/mL Insulin (Bovine Pancreas) (Sigma, #I0516, St. Louis, MO), 1.68 mM Calcium Chloride (Sigma, #C-34006, St. Louis, MO) and 1% Penicillin/Streptomycin/L-Glutamine (ThermoFisher #10378016, Waltham, MA) at 37 °C, 5% CO₂, and 95% humidity. Cells are expanded until reaching 70-95% confluency at which point they are sub-cultured or harvested for assay use. Using the Beckman Coulter Echo 650,

a serial dilution of test compound is dispensed into a 384-well black clear bottom plate in triplicate. One thousand one hundred twenty-five cells are added per well in 50 μ L complete growth medium in the 384-well plate. Plates are incubated for 67-72 hours at 37 °C, 5% CO₂, and 95% humidity. At the end of the incubation, 10 μ L of a 440 μ M solution of resazurin (Sigma, #199303, St. Louis, MO) in PBS is added to each well of the plate and plates are incubated for an additional 3-6 hours at 37 °C, 5% CO₂, and 95% humidity. Plates are read on a Synergy2 or equivalent reader (Biotek, Winooski VT) using an excitation of 540 nm and an emission of 600 nm. Data is analyzed using Prism software (GraphPad, San Diego, CA) to calculate IC₅₀ values.

MiaPaca-2 Cell Proliferation Assay (1)

[000321] Miapaca-2 cells (catalog #CRL-1420) are obtained from the American Type Culture Collect (ATTC, Manassas, VA). Briefly, cells were grown in DMEM supplemented with 10% characterized fetal bovine serum (Invitrogen, Carlsbad, CA), 2.5% New Zealand sourced horse serum and 1% Penicillin/Streptomycin/L-Glutamine at 37 °C, 5% CO₂, and 95% humidity. Cells are expanded until reaching 70-95% confluency at which point they are subcultured or harvested for assay use. A serial dilution of test compound is dispensed into a 96-well black clear bottom plate in triplicate. Three thousand cells are added per well in 200 μ L complete growth medium in the 96-well plate. Plates are incubated for 67-72 hours at 37 °C, 5% CO₂, and 95% humidity. At the end of the incubation, 40 μ L of a 440 μ M solution of resazurin (Sigma, St. Louis, MO) in PBS is added to each well of the plate and plates are incubated for an additional 5-6 hours at 37 °C, 5% CO₂, and 95% humidity. Plates are read on a Synergy2 or equivalent reader (Biotek, Winooski VT) using an excitation of 540 nm and an emission of 600 nm. Data is analyzed using Prism software (GraphPad, San Diego, CA) to calculate IC₅₀ values.

MiaPaca-2 Cell Proliferation Assay (2)

[000322] Miapaca-2 cells (catalog #CRL-1420) are obtained from the American Type Culture Collect (ATTC, Manassas, VA). Briefly, cells were grown in DMEM supplemented with 10% characterized fetal bovine serum (Invitrogen, Carlsbad, CA), 2.5% New Zealand sourced horse serum and 1% Penicillin/Streptomycin/L-Glutamine at 37 °C, 5% CO₂, and 95% humidity. Cells are expanded until reaching 70-95% confluency at which point they are sub-cultured or harvested for assay use. A serial dilution of test compound is dispensed into

a 384-well black clear bottom plate in triplicate. Seven hundred fifty cells are added per well in 50 μ L complete growth medium in the 384-well plate. Plates are incubated for 67-72 h at 37 °C, 5% CO₂, and 95% humidity. At the end of the incubation, 10 μ L of a 440 μ M solution of resazurin (Sigma, St. Louis, MO) in PBS is added to each well of the plate and plates are incubated for an additional 5-6 h at 37 °C, 5% CO₂, and 95% humidity. Plates are read on a Synergy2 or equivalent reader (Biotek, Winooski VT) using an excitation of 540 nm and an emission of 600 nm. Data is analyzed using Prism software (GraphPad, San Diego, CA) to calculate IC₅₀ values.

MiaPaca-2 Combination Cell proliferation Assay (1)

[000323] Miapaca-2 cells (catalog #CRL-1420) are obtained from the American Type Culture Collect (ATCC, Manassas, VA). Briefly, cells were grown in DMEM supplemented with 10% characterized fetal bovine serum (Invitrogen, Carlsbad, CA), 2.5% New Zealand sourced horse serum and 1% Penicillin/Streptomycin/L-Glutamine at 37 °C, 5% CO₂, and 95% humidity. Cells are expanded until reaching 70-95% confluency at which point they are subcultured or harvested for assay use. A serial dilution of test compound was dispensed into multiple 96-well black clear bottom plates in triplicate. A serial dilution of complete growth medium containing cobimetinib was prepared at twice the final concentration and 100 μ L was dispensed across the test compound titration in triplicate. Three thousand cells are added per well in 100 μ L complete growth medium in each 96-well plate. Plates are incubated for 67-72 hours at 37 °C, 5% CO₂, and 95% humidity. At the end of the incubation, 40 μ L of a 440 μ M solution of resazurin (Sigma, St. Louis, MO) in PBS is added to each well of the plate and plates are incubated for an additional 5-7 hours at 37 °C, 5% CO₂, and 95% humidity. Plates are read on a Synergy2 or equivalent reader (Biotek, Winooski VT) using an excitation of 540 nm and an emission of 600 nm. Drug synergy was assessed via BLISS analysis in the Combenefit software (Cancer Research UK Cambridge Institute, Cambridge, UK). Data is analyzed using Prism software (GraphPad, San Diego, CA) to calculate IC₅₀ values. Shifts in test compound IC₅₀ values are reported from top-constrained combination therapy curves.

MiaPaca-2 Combination Cell proliferation Assay (2)

[000324] Miapaca-2 cells (catalog #CRL-1420) are obtained from the American Type Culture Collect (ATCC, Manassas, VA). Briefly, cells were grown in DMEM supplemented

with 10% characterized fetal bovine serum (Invitrogen, Carlsbad, CA), 2.5% New Zealand sourced horse serum and 1% Penicillin/Streptomycin/L-Glutamine at 37 °C, 5% CO₂, and 95% humidity. Cells are expanded until reaching 70-95% confluency at which point they are subcultured or harvested for assay use. Using the Beckman Coulter Echo 650, a threefold, 8-point serial dilution of compound was spotted column wise into a 384 well black, clear bottom, tissue culture treated plate. Likewise, a threefold, 8-point serial dilution of cobimetinib was spotted row wise into the 384 well black, clear bottom plate containing compound. DMSO concentration was constant across all wells at 0.4%. Seven hundred fifty cells are added per well in 50 µL complete growth medium in each 384-well plate. Plates are incubated for 67-72 hours at 37 °C, 5% CO₂, and 95% humidity. At the end of the incubation, 10 µL of a 440 µM solution of resazurin (Sigma, St. Louis, MO) in PBS is added to each well of the plate and plates are incubated for an additional 4-6 hours at 37 °C, 5% CO₂, and 95% humidity. Plates are read on a Synergy2 or equivalent reader (Biotek, Winooski VT) using an excitation of 540 nm and an emission of 600 nm. Drug synergy was assessed via BLISS analysis in the Combeneft software (Cancer Research UK Cambridge Institute, Cambridge, UK). Data is analyzed using Prism software (Graphpad, San Diego, CA) to calculate IC₅₀ values. Shifts in test compound IC₅₀ values are reported from top-constrained combination therapy curves.

Table M. Inhibition of cell proliferation in A375 (1), H2405 (1), WM3928 (1), WM3629 (1), MiaPaca-2 (1), and combination with cobimetinib in MiaPaca-2 (1) by exemplary compounds (“Ex. No.”).

Ex. No.	A375 (1) IC ₅₀	H2405 (1) IC ₅₀	WM3928 (1) IC ₅₀	WM3629 (1) IC ₅₀	MiaPaca-2 (1) IC ₅₀	MiaPaca-2 Combo (1) IC ₅₀
1	+					
2	++++					
3	+++				++++	+
4	+++	++			++++	
5	++				++++	
6	++++					
7	++++	+	++		++++	+
8						
9	++					
10	++	+++	++			
11	++++					
12						

13	++++					
14						
15	++++					
16						
17						
18	++++				++++	
19	++++					
20	+++					
21	++++					
22	++++	++++	++++		++++	
23	+++	++	++		++++	
24	++	++			++++	+
25	++++					
26	++++					
27	+++					
28	++					
29	++++					
30	++++					
31	++++					
32	++++					
33	+	+	+		++	+
34	++++	++	++		++++	
35						
36	++++					
37	++++					
38						
39	++++					
40	++++					
41	++++					
42	++++	++++			++++	
43	+	++			++	
44					++++	
45					++++	
46						
47	+				+++	
48	++++				++++	
49	++++	++			++++	
50	++++				++++	
51	++++				++++	
52	++++				++++	
53	+				+++	
54	++				++++	
55	++++				++++	+
56	+++					

57	++				++++	
58						
59	++++				++++	
60	++++				++++	
61	++++				++++	
62						
63	+				++++	+
64	++++		++		++++	
65	++++		++		++++	
66	++++	++++	++		++++	
67	++++	++	++++		++++	
68	++++				++++	
69	++++	++++			++++	
70						
71	++++				++++	
72	++++				++++	
73	++	++	+		++++	
74						
75	++++	++++	+++		++++	
76	+	+	+		++++	++
77	+	++	+		++++	
78	++++	++++	+++		++++	
79	++++	+++	++		++++	
80	+	+	+		++++	
81	++++	++	+++		++++	
82						
83	++++	++	++		++++	
84	++++	++++	+++		++++	
85	++	++	++		+++	
86						
87	++	++	+		++++	++
88	++++	++++	++++		++++	
89	++++	++++	++++		++++	
90	++++	+++	+++		++++	
91	+++	++	++		++++	
92	++++	++++	++++		++++	
93	++++					
94	+++	++	++		++++	
95	++++					
96	++++	++++				
97	++++	+++	++		++++	
98	++++					
99	++++	++	++		++++	
100	++++	++++	+++		++++	

101	++++	++++	++++		++++	
102	++++	++++	++++		++++	
103	++++	++++	+++		++++	
104	++++	++	++		++++	
105	++++	+++	+++		++++	
106	++	++	+		++++	
107	++++	++	++	+	++++	
108	+++	++	++		++++	
109	++++	++++	++		++++	
110	++++	++++	++++		++++	
111	++++	++++	++++		++++	
112	++++	++++	++++		++++	
113	++	++	+		++++	+
114	++++	+++	+++		++++	
115	++	+++	+	+	++++	
116	++++					
117	++++	++			++++	
118	++++	+++			++++	
119	++++	++++	++++	++	++++	
120	++++	++++	++++		++++	
121	++++	++++			++++	
122	+++	+++			++++	
123	++++	++++			++++	
124	++++	++++				
125	++++	++++				
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127	++++	++++				
128	++++	++++				
129	++++	++++				
130	++++	++++				
131	+	++			++++	
132	++++	++++			++++	
133	+++	+++			++++	
134	++++	+++				
135	++++	++++				
136	++++	++++				
137	++++	++++				
138	++++	++++				
139	++++	+++			++++	
140	++++	++++			++++	
141	++++	++++			++++	
142	++++	+++			++++	
143	++++	++++			++++	
144	+++	++	+++		++++	

145	++++	+++			++++	
146	++++	++++			++++	
147	++++	++++			++++	
148	++++	++++			++++	
149	++++	++++				
150	++++	+++	++++			
151	++++	++				
152	++++	++++				
153	++++	++++				
154	++++	++++				
155	++++	++++				
156	++++	++	++	+		
157	++++	++++				
158	+	+	+		++++	
159	++++	++				
160	++++	++++				
161	++	+	+			
162	++++	++++				
163	++++	++++				
164	+	++				
165	++++	++	++++			
166	++++	+++				
167	+	+				
168	++	+				
169	++++	++				
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171	++++	++++				
172	++++	++++				
173	+++	++				
174	++++	+++				
175	++	+				
176	++++	++++				
177	++++	++++				
178	++++	++++				
179	++++	++++				
180	++	++++				
181	++++	++++				
182	++++	++++				
183	++++					
184	++++	++++				
185	++	++				
186	++++	++	+++			
187	++++	++++				
188	+++	+++				

189						
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193	++++	++++				
194	+	++	+			
195	++	++	+		++++	
196	++++	+++	+++			
197	++	++	++			
198						
199						
200	++	++	+	+	++++	++
201	+++	++	++	+	++++	++
202	++++	++++	++++			
203						
204						
205	++				++++	
206	++++		++++			
207	++++		+++			
208	+++	+++	+++			
209	++++	++++	++++			
210	++	++	++			
211	+++	++	++			
212						
213	++++	++++	++++			
214						
215	++++		+++	+		
216	++	++	+		++++	
217	+	++	+	+	+++	
218	++	++	++			
219	+++	++	+++			
220		+++			++++	
221	+	+	+	+	+++	
222	++	++	+			
223	++++	++++	++++			
224	++	++	++	+		
225		++		+		
226		+++				

For Table M, “+” refers to an IC₅₀ less than or equal to 100 nM; “++” refers to an IC₅₀ greater than 100 nM and less than or equal to 500 nM; “+++” refers to an IC₅₀ greater than 500 nM and less than or equal to 1000 nM; and “++++” refers to an IC₅₀ greater than 1000 nM and less than or equal to 10000 nM.

Table N. Inhibition of cell proliferation in A375 (2), H2405 (2), WM3928 (2), WM3629 (2), MiaPaca-2 (2), and combination with cobimetinib in MiaPaca-2 (2) by exemplary compounds (“Ex. No.”).

Ex. No.	A375 (2) IC ₅₀	H2405 (2) IC ₅₀	WM3928 (2) IC ₅₀	WM3629 (2) IC ₅₀	MiaPaca-2 (2) IC ₅₀	MiaPaca-2 Combo (2) IC ₅₀
195	++	+	+			
215		++				+++
216	++	+	+			
220	++++		+++			
224		+				
225	++		++			
226	+++		++			
227	++++	++++	++			
228	++++	++	++			++++
229	++	+++	++			

For Table N, “+” refers to an IC₅₀ less than or equal to 100 nM; “++” refers to an IC₅₀ greater than 100 nM and less than or equal to 500 nM; “+++” refers to an IC₅₀ greater than 500 nM and less than or equal to 1000 nM; and “++++” refers to an IC₅₀ greater than 1000 nM and less than or equal to 10000 nM.

EQUIVALENTS

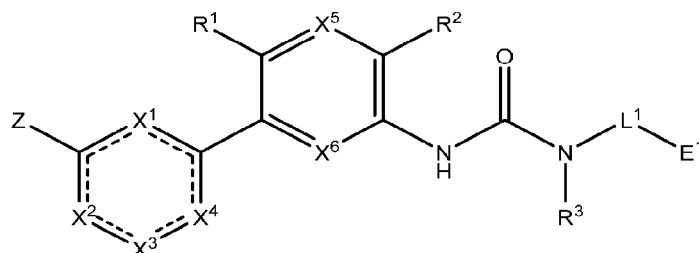
[000325] While specific embodiments have been discussed, the above specification is illustrative and not restrictive. Many variations of the embodiments will become apparent to those skilled in the art upon review of this specification. The full scope of what is disclosed should be determined by reference to the claims, along with their full scope of equivalents, and the specification, along with such variations.

[000326] Unless otherwise indicated, all numbers expressing quantities of ingredients, reaction conditions, and so forth used in the specification and claims are to be understood as being modified in all instances by the term “about.” Accordingly, unless indicated to the contrary, the numerical parameters set forth in this specification and attached claims are approximations that may vary depending upon the desired properties sought to be obtained.

CLAIMS

WHAT IS CLAIMED IS:

1. A compound represented by Formula I:



Formula I

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^1 and X^4 are each independently CR^5 or N;

X^5 and X^6 are each independently CH, CF, or N;

X^2 is N, CH, C=O, C-O-L²-E², C-L²-E², C-N(R⁴)-L²-E², or N-L²-E²;

X^3 is C-O-L³-E³, C-L³-E³, C-N(R⁴)-L³-E³, CH, C=O, N, or N-L³-E³,

provided that not more than two of X^1 , X^2 , X^3 , and X^4 are N;

provided that when X^2 is N, X^3 is C-O-L³-E³, C-L³-E³, C-N(R⁴)-L³-E³,

N, or CH;

provided that when X^3 is N, X^2 is N, CH, C-O-L²-E², C-L²-E², or C-

N(R⁴)-L²-E²;

provided that when X^2 is C=O, X^3 is N-L³-E³;

provided that when X^3 is C=O, X^2 is N-L²-E²;

L^1 is selected from a direct bond and a C₁-C₆alkyl optionally substituted with (E¹¹)_m, or when taken together with R³ and the N atom to which L^1 and R³ are attached form an optionally substituted heterocycle having from 4 to 8 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

L^2 is a direct bond or a C₁-C₆alkyl optionally substituted with (E²¹)_p;

L^3 is a direct bond or a C₁-C₆alkyl optionally substituted with (E³¹)_p;

E^1 is selected from the group consisting of H, hydroxy, alkoxy, cyano, haloalkoxy, halogen,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, amine, alkylamine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of aryl, alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, heterocyclyl, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, and heterocyclyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, alkoxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E¹¹, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E¹¹ taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

E² is selected from the group consisting of H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, sulfone, hydroxy, alkoxy, alkoxyalkyl, cyano, sulfonyl, and

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E²¹, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E²¹ taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

E³ is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, sulfonyl, haloalkoxy, H, alkyl, acyl, amine, aminoalkyl, amide, haloalkyl, cyano, sulfone,

optionally substituted heterocyclyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted heteroaryl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

optionally substituted cycloalkyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E³¹, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E³¹ taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is L⁷-E⁷ wherein:

L⁷ is a direct bond

E⁷ is selected from the group consisting of:

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, cycloalkyl, alkoxy, alkoxyalkyl, amine, acyl, carbamoyl, formyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group

consisting of alkyl, alkoxy, amide, urea, amine, amidine, acyl, carbamoyl, formyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

each occurrence of m is independently 0, 1, 2, 3, or 4;

each occurrence of p is independently 0, 1, or 2;

R¹ is selected from the group consisting of H, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, and halogen;

R² is selected from the group consisting of H and F;

R³ is selected from the group consisting of H, C₁-C₅alkyl, and C₃-C₅cycloalkyl;

R⁴, at each occurrence, is independently H or alkyl; and

R⁵, at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen;

with the proviso that

when E⁷ is morpholinyl, X² and X⁴ are both N, X³ is C-L³-E³, and L³ is a direct bond, then E³ is not heteroaryl;

when E⁷ is morpholinyl, X¹ and X⁴ are both N, X³ is C-L³-E³, and L³ is a direct bond, then E³ is not heteroaryl;

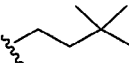
when E⁷ is morpholinyl, X¹, X⁴, X⁵, and X⁶ are CH, R¹ is -CH₃, X² is N, and X³ is C-L³-E³, then L³-E³ is not optionally substituted C₁-C₈ alkyl, optionally substituted C₃-C₆ cycloalkyl, optionally substituted C₄-C₈ cycloalkylalkyl, optionally substituted C₃-C₆ heterocyclyl, optionally substituted C₄-C₈ heterocyclylalkyl, optionally substituted 5- or 6-membered heteroaryl, or amide;

when X¹, X⁴, X⁵, and X⁶ are CH, R¹ is -CH₃, X² is N, X³ is C-L³-E³, L³ is a direct bond, and E³ is morpholinyl, then E⁷ is not optionally substituted C₃-C₆ heterocyclyl or optionally substituted 5- or 6-membered heteroaryl;

when E⁷ is morpholinyl, X¹ is CH, X² is N, X³ is C-O-L³-E³, X⁴ is CH, X⁶ is CH, CD, or CF, and R³ is H, then L¹-E¹ is not optionally substituted alkyl, optionally substituted C₃-C₆ cycloalkyl, optionally substituted C₃-C₆ cycloalkylalkyl, optionally substituted C₄-C₆ heterocyclyl, or optionally substituted heterocyclylalkyl; when E⁷ is morpholinyl, X¹ is CH, X² is C-O-L²-E², X³ is N, X⁴ is CH, X⁶ is CH, CD, or CF, and R³ is H, then L¹-E¹ is not optionally substituted alkyl, optionally substituted C₃-C₆ cycloalkyl, optionally substituted C₃-C₆ cycloalkylalkyl, optionally substituted C₄-C₆ heterocyclyl, or optionally substituted heterocyclylalkyl;

when E^7 is morpholinyl, X^1 is CH, X^2 is N, X^3 is C-O-L³-E³, X^4 is CH, and X^6 is CH, CD, or CF, then L¹ is not taken together with R³ and the N atom to which L¹ and R³ are attached form an optionally substituted heterocycle having from 4 to 8 atoms in the ring structure;

when E^7 is morpholinyl, X^1 is CH, X^2 is C-O-L²-E², X^3 is N, X^4 is CH, and X^6 is CH, CD, or CF, then L¹ is not taken together with R³ and the N atom to which L¹ and R³ are attached form an optionally substituted heterocycle having from 4 to 8 atoms in the ring structure;

when L¹-E¹ is , R¹ is methyl, R² is H, R³ is H, X¹ is N or CH, X⁴ is N or CH, X⁵ is N or CH, X⁶ is CH, E⁷ is a substituent selected from the group consisting of oxetanyl, tetrahydrofuranyl, and tetrahydropyranyl, and

X² is selected from the group consisting of:

(i) C-L²-E², wherein L²-E² is selected from H;

(ii) C-O-L²-E², wherein O-L²-E² is selected from the group consisting of methoxy, ethoxy, isopropoxy, 2-methoxyethoxy, 2-hydroxyethoxy, (tetrahydro-2H-pyran-4-yl)oxy, and (1-ethylpiperidin-4-yl)oxy;

(iii) C-N(R⁴)-L²-E², wherein N(R⁴)-L²-E² is selected from the group consisting of (2-methoxyethyl)amino, (2-hydroxyethyl)(methyl)amino, and (1-hydroxypropan-2-yl)amino; and

(iv) N,

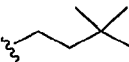
then X³ is not selected from the group consisting of:

(i) C-L³-E³, wherein L³-E³ is selected from the group consisting of H, methyl, 3-hydroxyoxetan-3-yl, 4-hydroxy-piperidin-1-yl, 4-amino-4-methylpiperidin-1-yl, and 2-oxooxazolidin-3-yl;

(ii) C-O-L³-E³, wherein O-L³-E³ is selected from the group consisting of methoxy, 2-hydroxyethoxy, and 2,3-dihydroxypropoxy;

(iii) C-N(R⁴)-L³-E³, wherein N(R⁴)-L³-E³ is selected from the group consisting of bis(2-hydroxyethyl)amino and (2-hydroxyethyl)amino; and

(iv) N;

when L¹-E¹ is , R¹ is methyl, R² is H, R³ is H, X¹ is N or CH, X⁴ is N or CH, X⁵ is N or CH, X⁶ is CH, X³ is C-L³-E³, L³ is a direct bond, E³ is selected from the group consisting of oxetanyl, tetrahydrofuranyl, and tetrahydropyranyl, and

X^2 is selected from the group consisting of:

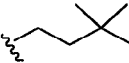
(i) $C-L^2-E^2$, wherein L^2-E^2 is selected from H;

(ii) $C-O-L^2-E^2$, wherein $O-L^2-E^2$ is selected from the group consisting of methoxy, ethoxy, isopropoxy, 2-methoxyethoxy, 2-hydroxyethoxy, (tetrahydro-2H-pyran-4-yl)oxy, and (1-ethylpiperidin-4-yl)oxy;

(iii) $C-N(R^4)-L^2-E^2$, wherein $N(R^4)-L^2-E^2$ is selected from the group consisting of (2-methoxyethyl)amino, (2-hydroxyethyl)(methyl)amino, and (1-hydroxypropan-2-yl)amino; and

(iv) N,

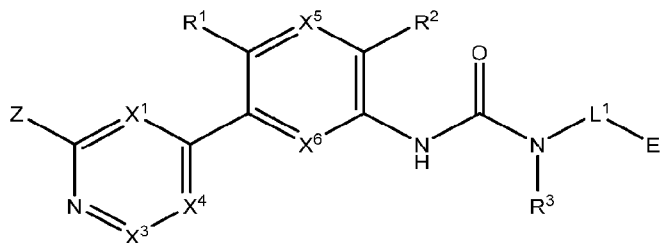
then E^7 is not selected from the group consisting of: 3-hydroxyoxetan-3-yl, 4-hydroxy-piperidin-1-yl, 4-amino-4-methylpiperidin-1-yl, and 2-oxooxazolidin-3-yl;

when L^1-E^1 is , R^1 is methyl, R^2 is H, R^3 is H, X^1 is N or CH, X^4 is

N or CH, X^5 is N or CH, X^6 is CH, E^7 is a substituent selected from the group consisting of oxetanyl, tetrahydrofuranyl, and tetrahydropyranyl, X^2 is C=O, and X^3 is $N-L^3-E^3$, then L^3-E^3 is not selected from the group consisting of: H, methyl, hydroxy-ethyl, hydroxy-propyl, and 2,3-dihydroxypropyl; and

when E^7 is 5- or 6- membered optionally substituted heteroaryl or 5- or 6-membered optionally substituted heterocyclyl, X^1 and X^4 are each independently N, CH, or CF, X^5 is CH, X^6 is CH, CD, or CF, X^2 is N, and X^3 is $C-O-L^3-E^3$ or $C-N(R^4)-L^3-E^3$, then L^1 is not taken together with R^3 and the N atom to which L^1 and R^3 are attached form an optionally substituted heterocycle having from 4 to 7 atoms in the ring structure.

2. A compound represented by Formula I-A:



Formula I-A

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^1 and X^4 are each independently CH, CR^5 , or N;

X^3 is $C-O-L^3-E^3$, $C-L^3-E^3$, $C-N(R^4)-L^3-E^3$, CH or N;

X⁵ and X⁶ are each independently CH, CF, or N;

provided that not more than one of X¹, X³, and X⁴ are N;

L¹ is selected from a direct bond and a C₁-C₆alkyl optionally substituted with (E¹¹)_m, or when taken together with R³ and the N atom to which L¹ and R³ are attached form an optionally substituted heterocycle having from 4 to 8 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

L³ is a direct bond or a C₁-C₆ alkyl optionally substituted with (E³¹)_p;

E¹ is selected from the group consisting of H, hydroxy, alkoxy, cyano, haloalkoxy, halogen,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, amine, alkylamine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of aryl, alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, heterocyclyl, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano and heterocyclyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, alkoxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E¹¹, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E¹¹ taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

E³ is selected from the group consisting of H, alkyl, acyl, amine, aminoalkyl, amide, haloalkyl, cyano, sulfone, haloalkoxy, hydroxy, alkoxy, alkoxyalkyl, sulfonyl, optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E³¹, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E³¹ taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is L⁷-E⁷ wherein:

L⁷ is a direct bond;

E⁷ is selected from the group consisting of:

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, cycloalkyl, alkoxy, alkoxyalkyl, amine, acyl, carbamoyl, formyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, urea, amine, amidine, acyl, carbamoyl, formyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

each occurrence of m is independently 0, 1, 2, 3, or 4;

each occurrence of p is independently 0, 1, or 2;

R¹ is selected from the group consisting of H, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, and halogen;

R² is selected from the group consisting of H and F;

R³ is selected from the group consisting of H, C₁-C₅ alkyl, and C₃-C₅ cycloalkyl;

R⁴, at each occurrence, is independently H or alkyl; and

R⁵, at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen;
with the proviso that

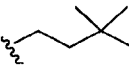
when E⁷ is morpholinyl, X⁴ is N, X³ is C-L³-E³, and L³ is a direct bond, then E³ is not heteroaryl;

when E⁷ is morpholinyl, X¹, X⁴, X⁵, and X⁶ are CH, R¹ is -CH₃, and X³ is C-L³-E³, then L³-E³ is not optionally substituted C₁-C₈ alkyl, optionally substituted C₃-C₆ cycloalkyl, optionally substituted C₄-C₈ cycloalkylalkyl, optionally substituted C₃-C₆ heterocyclyl, optionally substituted C₄-C₈ heterocyclylalkyl, optionally substituted 5- or 6-membered heteroaryl, or amide;

when X¹, X⁴, X⁵, and X⁶ are CH, R¹ is -CH₃, X³ is C-L³-E³, L³ is a direct bond, and E³ is morpholinyl, then E⁷ is not optionally substituted C₃-C₆ heterocyclyl or optionally substituted 5- or 6-membered heteroaryl;

when E⁷ is morpholinyl, X¹ is CH, X³ is C-O-L³-E³, X⁴ is CH, X⁶ is CH or CF, and R³ is H, then L¹-E¹ is not optionally substituted alkyl, optionally substituted C₃-C₆ cycloalkyl, optionally substituted C₃-C₆ cycloalkylalkyl, optionally substituted C₄-C₆ heterocyclyl, or optionally substituted heterocyclylalkyl;

when E⁷ is morpholinyl, X¹ is CH, X³ is C-O-L³-E³, X⁴ is CH, and X⁶ is CH, CD, or CF, then L¹ is not taken together with R³ and the N atom to which L¹ and R³ are attached form an optionally substituted heterocycle having from 4 to 8 atoms in the ring structure;

when L¹-E¹ is , R¹ is methyl, R² is H, R³ is H, X¹ is N or CH, X⁴ is N or CH, X⁵ is N or CH, X⁶ is CH, and E⁷ is a substituent selected from the group consisting of oxetanyl, tetrahydrofuranyl, and tetrahydropyranyl,

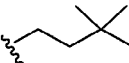
then X³ is not selected from the group consisting of:

(i) C-L³-E³, wherein L³-E³ is selected from the group consisting of H, methyl, 3-hydroxyoxetan-3-yl, 4-hydroxy-piperidin-1-yl, 4-amino-4-methylpiperidin-1-yl, and 2-oxooxazolidin-3-yl;

(ii) C-O-L³-E³, wherein O-L³-E³ is selected from the group consisting of methoxy, 2-hydroxyethoxy, and 2,3-dihydroxypropoxy;

(iii) C-N(R⁴)-L³-E³, wherein N(R⁴)-L³-E³ is selected from the group consisting of bis(2-hydroxyethyl)amino and (2-hydroxyethyl)amino; and

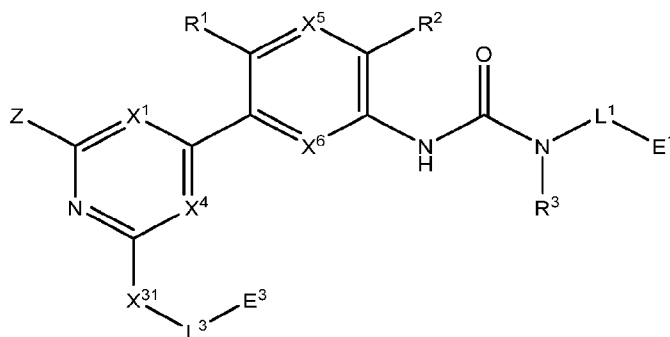
(iv) N;

when L¹-E¹ is , R¹ is methyl, R² is H, R³ is H, X¹ is N or CH, X⁴ is N or CH, X⁵ is N or CH, X⁶ is CH, X³ is C-L³-E³, L³ is a direct bond, and E³ is selected from the group consisting of oxetanyl, tetrahydrofuranyl, and tetrahydropyranyl,

then E⁷ is not selected from the group consisting of: 3-hydroxyoxetan-3-yl, 4-hydroxy-piperidin-1-yl, 4-amino-4-methylpiperidin-1-yl, and 2-oxooxazolidin-3-yl;

when E⁷ is 5- or 6- membered optionally substituted heteroaryl or 5- or 6-membered optionally substituted heterocyclyl, X¹ and X⁴ are each independently N, CH, or CF, X⁵ is CH, X⁶ is CH, CD, or CF, X² is N, and X³ is C-O-L³-E³ or C-N(R⁴)-L³-E³, then L¹ is not taken together with R³ and the N atom to which L¹ and R³ are attached form an optionally substituted heterocycle having from 4 to 7 atoms in the ring structure.

3. A compound represented by Formula I-B:



Formula I-B

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X¹ and X⁴ are each independently CH, CR⁵, or N;

provided that not more than one of X^1 and X^4 are N;

X^5 and X^6 are each independently CH, CF, or N;

X^{31} is O or N(R^4);

L^1 is selected from a direct bond and a C_1 - C_6 alkyl optionally substituted with $(E^{11})_m$, or when taken together with R^3 and the N atom to which L^1 and R^3 are attached form an optionally substituted heterocycle having from 4 to 8 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

L^3 is a direct bond or a C_1 - C_6 alkyl optionally substituted with $(E^{31})_p$;

E^1 is selected from the group consisting of H, hydroxy, alkoxy, cyano, haloalkoxy, halogen,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, amine, alkylamine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of aryl, alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, heterocyclyl, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano and heterocyclyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, alkoxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E^{11} , at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E¹¹ taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

E³ is selected from the group consisting of haloalkoxy, H, alkyl, acyl, amine, aminoalkyl, amide, haloalkyl, cyano, sulfone, hydroxy, alkoxy, alkoxyalkyl, cyano, sulfonyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E³¹, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E³¹ taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is L⁷-E⁷ wherein:

L⁷ is a direct bond;

E⁷ is selected from the group consisting of:

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, cycloalkyl, alkoxy, alkoxyalkyl, amine, acyl, carbamoyl, formyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group

consisting of alkyl, alkoxy, amide, urea, amine, amidine, acyl, carbamoyl, formyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

each occurrence of m is independently 0, 1, 2, 3, or 4;

each occurrence of p is independently 0, 1, or 2;

R¹ is selected from the group consisting of H, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, and halogen;

R² is selected from the group consisting of H and F;

R³ is selected from the group consisting of H, C₁-C₅ alkyl, and C₃-C₅ cycloalkyl;

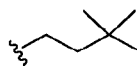
R⁴, at each occurrence, is independently H or alkyl; and

R⁵, at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen;

with the proviso that

when E⁷ is morpholinyl, X¹ is CH, X³¹ is O, X⁴ is CH, X⁶ is CH or CF, and R³ is H, then L¹-E¹ is not optionally substituted alkyl, optionally substituted C₃-C₆ cycloalkyl, optionally substituted C₃-C₆ cycloalkylalkyl, optionally substituted C₄-C₆ heterocyclyl, or optionally substituted heterocyclalkyl;

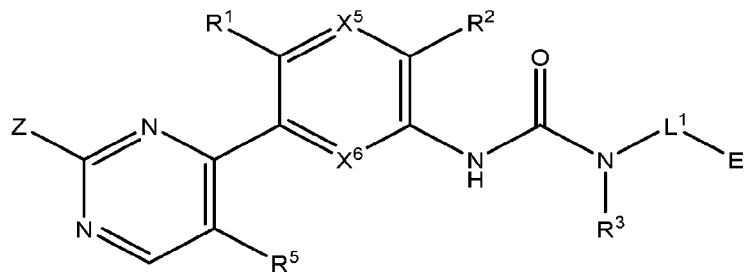
when E⁷ is morpholinyl, X¹ is CH, X³¹ is O, X⁴ is CH, and X⁶ is CH, CD, or CF, then L¹ is not taken together with R³ and the N atom to which L¹ and R³ are attached form an optionally substituted heterocycle having from 4 to 8 atoms in the ring structure;

when L¹-E¹ is , R¹ is methyl, R² is H, R³ is H, X¹ is N or CH, X⁴ is N or CH, X⁵ is N or CH, X⁶ is CH, and E⁷ is a substituent selected from the group consisting of oxetanyl, tetrahydrofuranyl, and tetrahydropyranyl,

then X³¹-L³-E³ is not selected from the group consisting of: methoxy, 2-hydroxyethoxy, 2,3-dihydroxypropoxy, bis(2-hydroxyethyl)amino, and (2-hydroxyethyl)amino; and

when E⁷ is 5- or 6- membered optionally substituted heteroaryl or 5- or 6-membered optionally substituted heterocyclyl, X¹ and X⁴ are each independently N, CH, or CF, X⁵ is CH, and X⁶ is CH, CD, or CF, then L¹ is not taken together with R³ and the N atom to which L¹ and R³ are attached form an optionally substituted heterocycle having from 4 to 7 atoms in the ring structure.

4. A compound represented by Formula I-CA:



Formula I-CA

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^5 and X^6 are each independently CH, CF, or N;

L^1 is selected from a direct bond and a C_1 - C_6 alkyl optionally substituted with $(E^{11})_m$, or when taken together with R^3 and the N atom to which L^1 and R^3 are attached form an optionally substituted heterocycle having from 4 to 8 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^1 is selected from the group consisting of hydroxy, alkoxy, cyano, haloalkoxy, halogen,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, amine, alkylamine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of aryl, alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, heterocyclyl, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano and heterocyclyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of

alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, alkoxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently H, alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E¹¹, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E¹¹ taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is L⁷-E⁷ wherein:

L⁷ is a direct bond;

E⁷ is optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, urea, amine, amidine, acyl, carbamoyl, formyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

each occurrence of m is independently 0, 1, 2, 3, or 4;

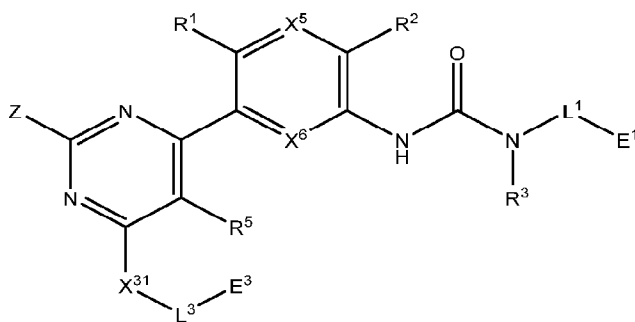
R¹ is selected from the group consisting of H, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, and halogen;

R² is selected from the group consisting of H and F;

R³ is selected from the group consisting of H, C₁-C₅ alkyl, and C₃-C₅ cycloalkyl; and

R⁵, at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen.

5. A compound represented by Formula I-DA:



Formula I-DA

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^{31} is O or N(R⁴);

X^5 and X^6 are each independently CH, CF, or N;

L^1 is selected from a direct bond and a C₁-C₆alkyl optionally substituted with (E¹¹)_m, or when X^5 is N, L^1 may be taken together with R³ and the N atom to which L^1 and R³ are attached form an optionally substituted heterocycle having from 4 to 8 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

L^3 is a direct bond or a C₁-C₆ alkyl optionally substituted with (E³¹)_p;

E^1 is selected from the group consisting of hydroxy, alkoxy, cyano, haloalkoxy, halogen,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, amine, alkylamine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of aryl, alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, heterocyclyl, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano and heterocyclyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, alkoxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E^{11} , at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{11} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

E^3 is selected from the group consisting of haloalkoxy, alkyl, acyl, amine, aminoalkyl, amide, haloalkyl, cyano, sulfone, hydroxy, alkoxy, alkoxyalkyl, cyano, sulfonyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E^{31} , at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{31} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is L^7-E^7 wherein:

L^7 is a direct bond;

E^7 is optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, urea, amine, amidine, acyl, carbamoyl, formyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

each occurrence of m is independently 0, 1, 2, 3, or 4;

each occurrence of p is independently 0, 1, or 2;

R^1 is selected from the group consisting of H, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, and halogen;

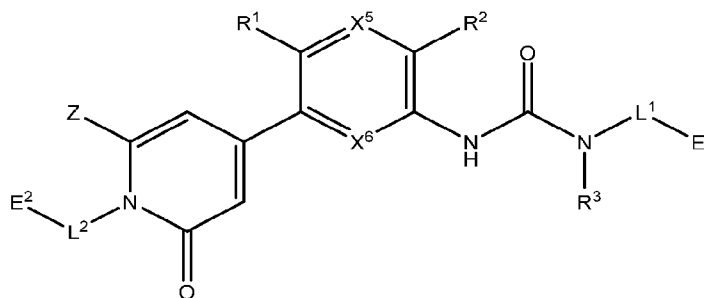
R^2 is selected from the group consisting of H and F;

R^3 is selected from the group consisting of H, C_1 - C_5 alkyl, and C_3 - C_5 cycloalkyl;

R^4 , at each occurrence, is independently H or alkyl; and

R^5 , at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen.

6. A compound of Formula I-EA:



Formula I-EA

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^5 and X^6 are each independently CH, CF, or N;

L^1 is selected from a direct bond and a C_1 - C_6 alkyl optionally substituted with $(E^{11})_m$, or when taken together with R^3 and the N atom to which L^1 and R^3 are attached form an optionally substituted heterocycle having from 4 to 8 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is

independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

L^2 is a direct bond;

E^1 is selected from the group consisting of hydroxy, alkoxy, cyano, haloalkoxy, halogen,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, amine, alkylamine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of aryl, alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, heterocyclyl, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano and heterocyclyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, alkoxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of H, alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E^{11} , at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{11} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

E^2 is alkyl;

Z is L^7-E^7 wherein:

L^7 is a direct bond;

E^7 is optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, urea, amine, amidine, acyl, carbamoyl, formyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

each occurrence of m is independently 0, 1, 2, 3, or 4;

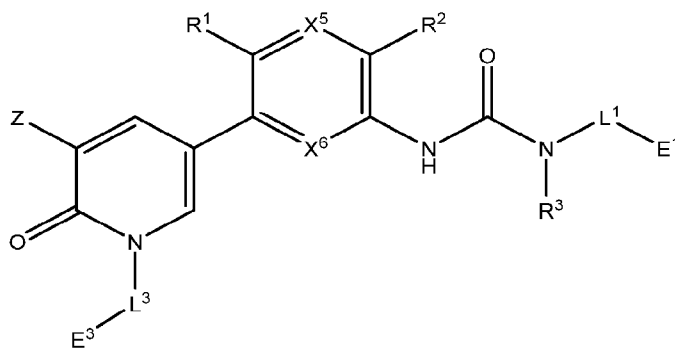
R^1 is selected from the group consisting of H, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, and halogen;

R^2 is selected from the group consisting of H and F;

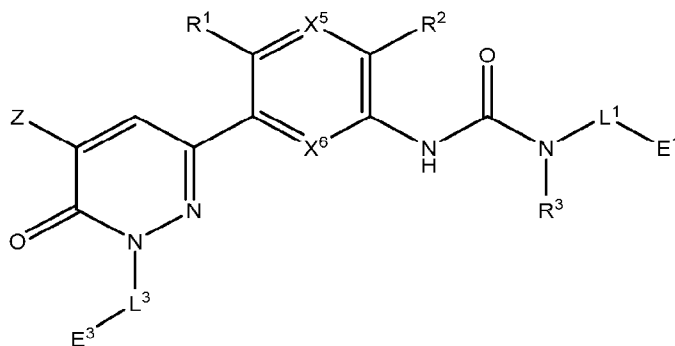
R^3 is selected from the group consisting of H, C_1 - C_5 alkyl, and C_3 - C_5 cycloalkyl; and

R^5 , at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen.

7. A compound represented by Formula I-FA or Formula I-FB:



Formula I-FA



Formula I-FB

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^5 and X^6 are each independently CH, CF, or N;

L^1 is selected from a direct bond and a C_1 - C_6 alkyl optionally substituted with $(E^{11})_m$, or when taken together with R^3 and the N atom to which L^1 and R^3 are attached form an optionally substituted heterocycle having from 4 to 8 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

L^3 is a direct bond;

E^1 is selected from the group consisting of hydroxy, alkoxy, cyano, haloalkoxy, halogen,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, amine, alkylamine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of aryl, alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, heterocyclyl, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano and heterocyclyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, alkoxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E^{11} , at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E¹¹ taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

E³ is alkyl;

Z is L⁷-E⁷ wherein:

L⁷ is a direct bond;

E⁷ is optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, cycloalkyl, alkoxy, alkoxyalkyl, amine, acyl, carbamoyl, formyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone;

each occurrence of m is independently 0, 1, 2, 3, or 4;

R¹ is selected from the group consisting of H, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, and halogen;

R² is selected from the group consisting of H and F;

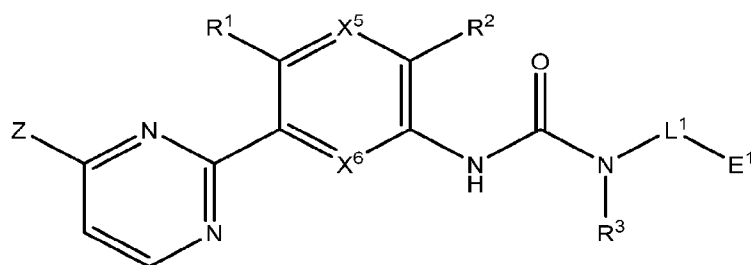
R³ is selected from the group consisting of H, C₁-C₅ alkyl, and C₃-C₅ cycloalkyl;; and

R⁵, at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen;

with the proviso that

E⁷ is not oxetanyl, tetrahydrofuranyl, or tetrahydropyranyl.

8. A compound represented by Formula I-GA:



Formula I-GA

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X⁵ and X⁶ are each independently CH, CF, or N;

L¹ is selected from a direct bond and a C₁-C₆alkyl optionally substituted with (E¹¹)_m, or when taken together with R³ and the N atom to which L¹ and R³ are

attached form an optionally substituted heterocycle having from 4 to 8 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^1 is selected from the group consisting of hydroxy, alkoxy, cyano, haloalkoxy, halogen,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, amine, alkylamine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of aryl, alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, heterocyclyl, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano and heterocyclyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, alkoxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E^{11} , at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{11} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is L^7-E^7 wherein:

L^7 is a direct bond;

E^7 is optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the

group consisting of alkyl, alkoxy, amide, urea, amine, amidine, acyl, carbamoyl, formyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

each occurrence of m is independently 0, 1, 2, 3, or 4;

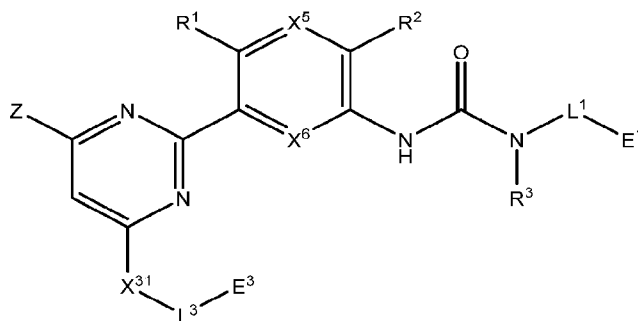
R^1 is selected from the group consisting of H, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, and halogen;

R^2 is selected from the group consisting of H and F;

R^3 is selected from the group consisting of H, C₁-C₅ alkyl, and C₃-C₅ cycloalkyl; and

R^5 , at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen.

9. A compound represented by Formula I-HA:



Formula I-HA

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^{31} is O or N(R^4);

X^5 and X^6 are each independently CH, CF, or N;

L^1 is selected from a direct bond and a C₁-C₆alkyl optionally substituted with (E^{11})_m, or when taken together with R^3 and the N atom to which L^1 and R^3 are attached form an optionally substituted heterocycle having from 4 to 8 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

L^3 is a direct bond or a C₁-C₆ alkyl optionally substituted with (E^{31})_p;

E¹ is selected from the group consisting of hydroxy, alkoxy, cyano, haloalkoxy, halogen,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, amine, alkylamine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of aryl, alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, heterocyclyl, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano and heterocyclyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, alkoxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E¹¹, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E¹¹ taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

E³ is selected from the group consisting of haloalkoxy, H, alkyl, acyl, amine, aminoalkyl, amide, haloalkyl, cyano, sulfone, hydroxy, alkoxy, alkoxyalkyl, cyano, sulfonyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of H, alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E^{31} , at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{31} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is L^7-E^7 wherein:

L^7 is a direct bond;

E^7 is optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, urea, amine, amidine, acyl, carbamoyl, formyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

each occurrence of m is independently 0, 1, 2, 3, or 4;

each occurrence of p is independently 0, 1, or 2;

R^1 is selected from the group consisting of H, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, and halogen;

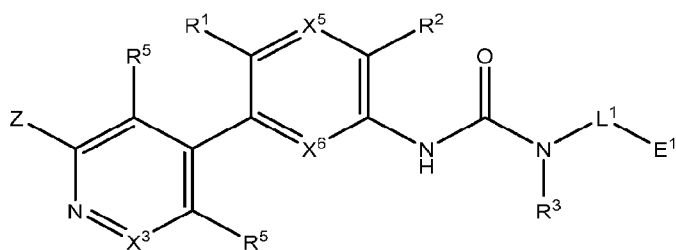
R^2 is selected from the group consisting of H and F;

R^3 is selected from the group consisting of H, C_1-C_5 alkyl, and C_3-C_5 cycloalkyl;

R^4 , at each occurrence, is independently H or alkyl; and

R^5 , at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen.

10. A compound represented by Formula I-JA:



Formula I-JA

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^3 is C- L^3 - E^3 or CH;

X^5 and X^6 are each independently CH, CF, or N;

L^1 is selected from a direct bond and a C_1 - C_6 alkyl optionally substituted with $(E^{11})_m$, or when taken together with R^3 and the N atom to which L^1 and R^3 are attached form an optionally substituted heterocycle having from 4 to 8 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

L^3 is a direct bond;

E^1 is selected from the group consisting of hydroxy, alkoxy, cyano, haloalkoxy, halogen;

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, amine, alkylamine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of aryl, alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, heterocyclyl, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano and heterocyclyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of

alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, alkoxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E^{11} , at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{11} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

E^3 is selected from the group consisting of alkyl and

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

Z is L^7-E^7 wherein:

L^7 is selected from the group consisting of a direct bond;

E^7 is optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, urea, amine, amidine, acyl, carbamoyl, formyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

each occurrence of m is independently 0, 1, 2, 3, or 4;

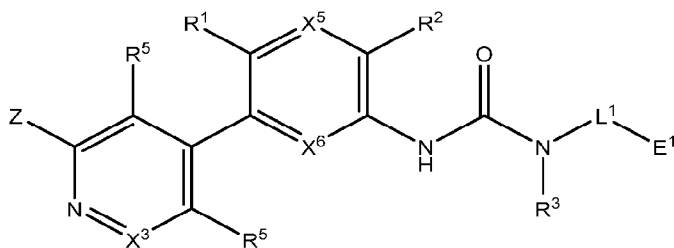
R^1 is selected from the group consisting of H, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, and halogen;

R^2 is selected from the group consisting of H and F;

R^3 is selected from the group consisting of H, C_1-C_5 alkyl, and C_3-C_5 cycloalkyl; and

R^5 , at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen.

11. A compound represented by Formula I-JB:



Formula I-JB

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^3 is $C-O-L^3-E^3$, $C-L^3-E^3$, $C-N(R^4)-L^3-E^3$, or CH ;

X^5 and X^6 are each independently CH , CF , or N ;

L^1 is selected from a direct bond and a C_1 - C_6 alkyl optionally substituted with $(E^{11})_m$, or when taken together with R^3 and the N atom to which L^1 and R^3 are attached form an optionally substituted heterocycle having from 4 to 8 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

L^3 is a direct bond or a C_1 - C_6 alkyl optionally substituted with $(E^{31})_p$;

E^1 is selected from the group consisting of

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano and heterocyclyl, and

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E^{11} , at each occurrence, is independently selected from the group consisting of H , alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{11} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

E³ is selected from the group consisting of haloalkoxy, H, alkyl, acyl, amine, aminoalkyl, amide, haloalkyl, cyano, sulfone, hydroxy, alkoxy, alkoxyalkyl, cyano, sulfonyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, or sulfone, and

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E³¹, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E³¹ taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is L⁷-E⁷ wherein:

L⁷ is selected from the group consisting of a direct bond;

E⁷ is optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, cycloalkyl, alkoxy, alkoxyalkyl, amine, acyl, carbamoyl, formyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

each occurrence of m is independently 0, 1, 2, 3, or 4;

each occurrence of p is independently 0, 1, or 2;

R¹ is selected from the group consisting of H, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, and halogen;

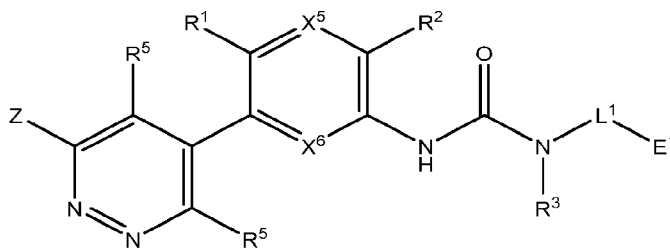
R² is selected from the group consisting of H and F;

R³ is selected from the group consisting of H, C₁-C₅ alkyl, and C₃-C₅ cycloalkyl;

R⁴, at each occurrence, is independently H or alkyl; and

R⁵, at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen.

12. A compound represented by Formula I-JC:



Formula I-JC

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^5 and X^6 are each independently CH, CF, or N;

L^1 is selected from a direct bond and a C_1 - C_6 alkyl optionally substituted with $(E^{11})_m$, or when taken together with R^3 and the N atom to which L^1 and R^3 are attached form an optionally substituted heterocycle having from 4 to 8 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^1 is selected from the group consisting of hydroxy, alkoxy, cyano, haloalkoxy, halogen;

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, amine, alkylamine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of aryl, alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, heterocyclyl, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano and heterocyclyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, alkoxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E^{11} , at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{11} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is L^7-E^7 wherein:

L^7 is selected from the group consisting of a direct bond;

E^7 is optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, urea, amine, amidine, acyl, carbamoyl, formyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

each occurrence of m is independently 0, 1, 2, 3, or 4;

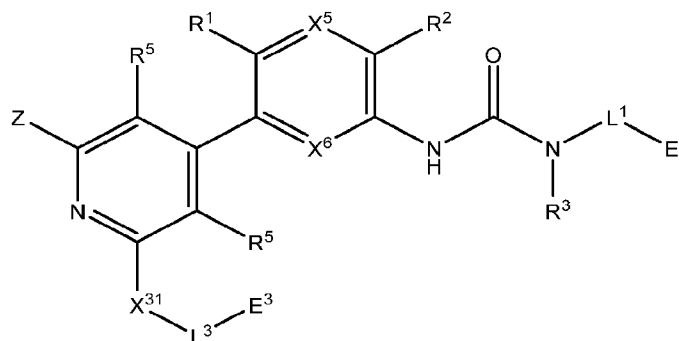
R^1 is selected from the group consisting of H, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, and halogen;

R^2 is selected from the group consisting of H and F;

R^3 is selected from the group consisting of H, C_1 - C_5 alkyl, and C_3 - C_5 cycloalkyl; and

R^5 , at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen.

13. A compound represented by Formula I-KA:



Formula I-KA

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^5 and X^6 are each independently CH, CF, or N;

X^{31} is O or N(R^4);

L^1 is selected from a direct bond and a C_1 - C_6 alkyl optionally substituted with $(E^{11})_m$, or when X^5 is N, L^1 may be taken together with R^3 and the N atom to which L^1 and R^3 are attached form an optionally substituted heterocycle having from 4 to 8 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

L^3 is a direct bond or a C_1 - C_6 alkyl optionally substituted with $(E^{31})_p$;

E^1 is selected from the group consisting of hydroxy, alkoxy, cyano, haloalkoxy, halogen,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, amine, alkylamine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of aryl, alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, heterocyclyl, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano and heterocyclyl, the site covalently linked to H or the optionally substituted substituent,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, alkoxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E^{11} , at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{11} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

E^3 is selected from the group consisting of haloalkoxy, H, alkyl, acyl, amine, aminoalkyl, amide, haloalkyl, cyano, sulfone, hydroxy, alkoxy, alkoxyalkyl, cyano, sulfonyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, or sulfone,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, or cyano, cyanoalkyl, heterocyclyl, and

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, hydroxy, or cyano;

E^{31} , at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{31} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is L^7-E^7 wherein:

L^7 is a direct bond;

E^7 is optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, urea, amine, amidine, acyl, carbamoyl, formyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

each occurrence of m is independently 0, 1, 2, 3, or 4; and

each occurrence of p is independently 0, 1, or 2;

R¹ is selected from the group consisting of H, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, and halogen;

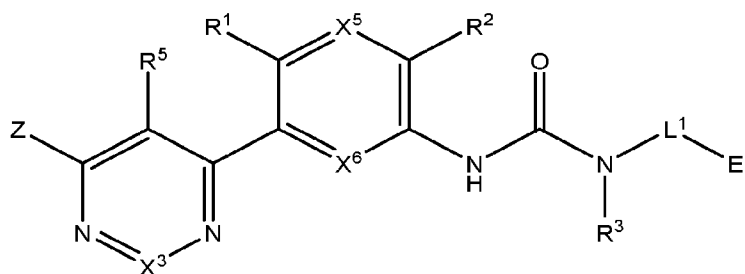
R² is selected from the group consisting of H and F;

R³ is selected from the group consisting of H, C₁-C₅ alkyl, and C₃-C₅ cycloalkyl;

R⁴, at each occurrence, is independently H or alkyl; and

R⁵, at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen.

14. A compound represented by Formula I-LA:



Formula I-LA

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X³ is C-L³-E³ or CH;

X⁵ and X⁶ are each independently CH, CF, or N;

L¹ is selected from a direct bond and a C₁-C₆alkyl optionally substituted with (E¹¹)_m, or when taken together with R³ and the N atom to which L¹ and R³ are attached form an optionally substituted heterocycle having from 4 to 8 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

L³ is a direct bond or a C₁-C₆ alkyl optionally substituted with (E³¹)_p;

E¹ is selected from the group consisting of hydroxy, alkoxy, cyano, haloalkoxy, halogen,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, amine, alkylamine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of aryl, alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, heterocyclyl, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano and heterocyclyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, alkoxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E¹¹, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E¹¹ taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

E³ is selected from the group consisting of alkyl and

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E³¹, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E³¹ taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is L⁷-E⁷ wherein:

L⁷ is a direct bond

E^7 is optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, urea, amine, amidine, acyl, carbamoyl, formyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

each occurrence of m is independently 0, 1, 2, 3, or 4;

each occurrence of p is independently 0, 1, or 2;

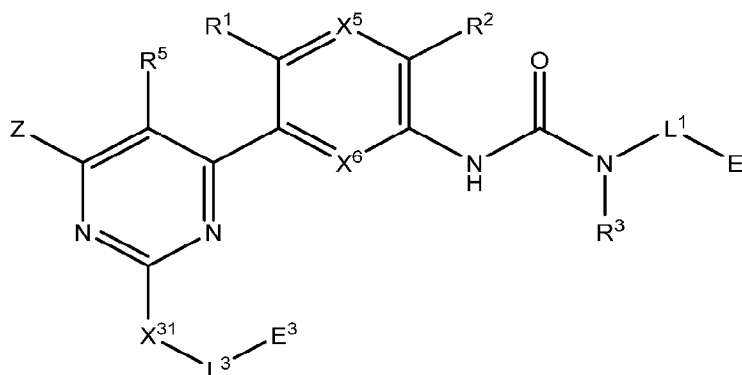
R^1 is selected from the group consisting of H, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, and halogen;

R^2 is selected from the group consisting of H and F;

R^3 is selected from the group consisting of H, C_1 - C_5 alkyl, and C_3 - C_5 cycloalkyl; and

R^5 , at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen.

15. A compound represented by Formula I-MA:



Formula I-MA

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^5 and X^6 are each independently CH, CF, or N;

X^{31} is O or $N(R^4)$;

L^1 is selected from a direct bond and a C_1 - C_6 alkyl optionally substituted with $(E^{11})_m$, or when X^5 is N, L^1 may be taken together with R^3 and the N atom to which L^1 and R^3 are attached form an optionally substituted heterocycle having from 4 to 8 atoms in the ring structure wherein the optionally substituted substituent, at each

occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

L^3 is a direct bond or a C_1 - C_6 alkyl optionally substituted with $(E^{31})_p$;

E^1 is selected from the group consisting of hydroxy, alkoxy, cyano, haloalkoxy, halogen,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, amine, alkylamine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of aryl, alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, heterocyclyl, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano and heterocyclyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, alkoxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E^{11} , at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{11} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

E^3 is selected from the group consisting of haloalkoxy, H, alkyl, acyl, amine, aminoalkyl, amide, haloalkyl, cyano, sulfone, hydroxy, alkoxy, alkoxyalkyl, cyano, sulfonyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E^{31} , at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{31} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is L^7-E^7 wherein:

L^7 is a direct bond;

E^7 is optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, urea, amine, amidine, acyl, carbamoyl, formyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

each occurrence of m is independently 0, 1, 2, 3, or 4;

each occurrence of p is independently 0, 1, or 2;

R^1 is selected from the group consisting of H, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, and halogen;

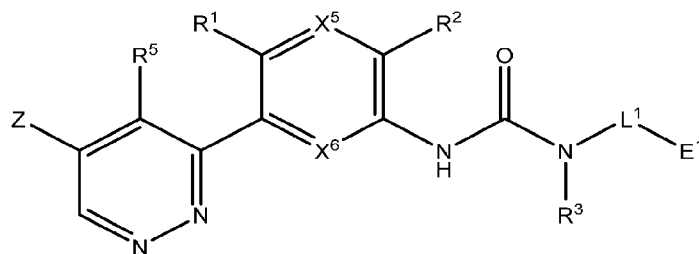
R^2 is selected from the group consisting of H and F;

R^3 is selected from the group consisting of H, C_1-C_5 alkyl, and C_3-C_5 cycloalkyl;

R^4 , at each occurrence, is independently H or alkyl; and

R^5 , at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen.

16. A compound represented by Formula I-NA:



Formula I-NA

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^5 and X^6 are each independently CH, CF, or N;

L^1 is selected from a direct bond and a C_1 - C_6 alkyl optionally substituted with $(E^{11})_m$, or when taken together with R^3 and the N atom to which L^1 and R^3 are attached form an optionally substituted heterocycle having from 4 to 8 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^1 is selected from the group consisting of hydroxy, alkoxy, cyano, haloalkoxy, halogen,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, amine, alkylamine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of aryl, alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, heterocyclyl, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano and heterocyclyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, alkoxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E^{11} , at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{11} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is L^7-E^7 wherein:

L^7 is a direct bond;

E^7 is optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, urea, amine, amidine, acyl, carbamoyl, formyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

each occurrence of m is independently 0, 1, 2, 3, or 4;

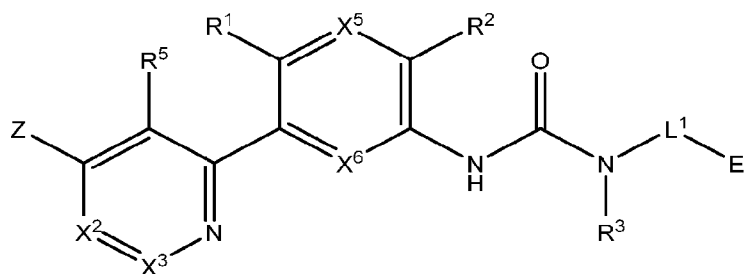
R^1 is selected from the group consisting of H, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, and halogen;

R^2 is selected from the group consisting of H and F;

R^3 is selected from the group consisting of H, C_1 - C_5 alkyl, and C_3 - C_5 cycloalkyl; and

R^5 , at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen.

17. A compound represented by Formula I-OA:



Formula I-OA

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^2 is C-O-L²-E², C-L²-E², C-N(R⁴)-L²-E², CH, or N;

X^3 is CH, C-O-L³-E³, C-L³-E³, C-N(R⁴)-L³-E³, or N;

provided that not more than one of X^2 and X^3 are N;

X^5 and X^6 are each independently CH, CF, or N;

L^1 is selected from a direct bond and a C₁-C₆alkyl optionally substituted with (E¹¹)_m, or when taken together with R³ and the N atom to which L^1 and R³ are attached form an optionally substituted heterocycle having from 4 to 8 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

L^2 is a direct bond or a C₁-C₆ alkyl optionally substituted with (E²¹)_p;

L^3 is a direct bond or a C₁-C₆ alkyl optionally substituted with (E³¹)_p;

E¹ is selected from the group consisting of hydroxy, alkoxy, cyano, haloalkoxy, halogen,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, amine, alkylamine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of aryl, alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, heterocyclyl, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano and heterocyclyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, alkoxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E¹¹, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E¹¹ taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

E² is selected from the group consisting of H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, sulfone, hydroxy, alkoxy, alkoxyalkyl, cyano, sulfonyl, and optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl,

E²¹, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E²¹ taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

E³ is selected from the group consisting of haloalkoxy, H, alkyl, acyl, amine, aminoalkyl, amide, haloalkyl, cyano, sulfone, hydroxy, alkoxy, alkoxyalkyl, cyano, sulfonyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, or cyano, cyanoalkyl, heterocyclyl, and

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E^{31} , at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{31} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is L^7-E^7 wherein:

L^7 is a direct bond;

E^7 is optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, urea, amine, amidine, acyl, carbamoyl, formyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

each occurrence of m is independently 0, 1, 2, 3, or 4;

each occurrence of p is independently 0, 1, or 2;

R^1 is selected from the group consisting of H, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, and halogen;

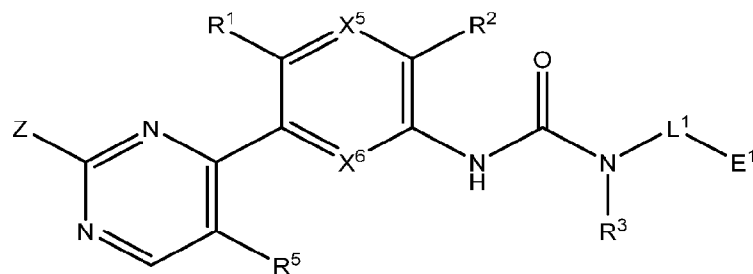
R^2 is selected from the group consisting of H and F;

R^3 is selected from the group consisting of H, C_1 - C_5 alkyl, and C_3 - C_5 cycloalkyl;

R^4 , at each occurrence, is independently H or alkyl; and

R^5 , at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen.

18. A compound represented by Formula I-PA:



Formula I-PA

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X⁵ and X⁶ are each independently CH, CF, or N;

L¹ is selected from a direct bond and a C₁-C₆alkyl optionally substituted with (E¹¹)_m, or when taken together with R³ and the N atom to which L¹ and R³ are attached form an optionally substituted heterocycle having from 4 to 8 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E¹ is selected from the group consisting of hydroxy, alkoxy, cyano, haloalkoxy, halogen,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, amine, alkylamine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of aryl, alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, heterocyclyl, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano and heterocyclyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, alkoxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E¹¹, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E¹¹ taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is L⁷-E⁷ wherein:

L^7 is a direct bond;

E^7 is optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, urea, amine, amidine, acyl, carbamoyl, formyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

each occurrence of m is independently 0, 1, 2, 3, or 4;

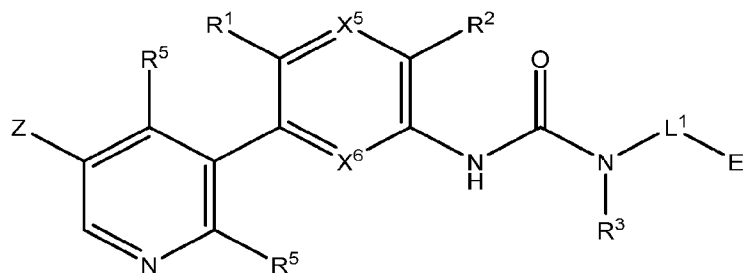
R^1 is selected from the group consisting of H, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, and halogen;

R^2 is selected from the group consisting of H and F;

R^3 is selected from the group consisting of H, C_1 - C_5 alkyl, and C_3 - C_5 cycloalkyl; and

R^5 , at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen.

19. A compound represented by Formula I-QA:



Formula I-QA

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^1 is each independently CR^5 or N;

X^5 and X^6 are each independently CH, CF, or N;

L^1 is selected from a direct bond and a C_1 - C_6 alkyl optionally substituted with $(E^{11})_m$, or when taken together with R^3 and the N atom to which L^1 and R^3 are attached form an optionally substituted heterocycle having from 4 to 8 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E¹ is selected from the group consisting of hydroxy, alkoxy, cyano, haloalkoxy, halogen,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, amine, alkylamine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of aryl, alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, heterocyclyl, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano and heterocyclyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, alkoxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E¹¹, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E¹¹ taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is L⁷-E⁷ wherein:

L⁷ a direct bond;

E⁷ is optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, urea, amine, amidine, acyl, carbamoyl, formyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

each occurrence of m is independently 0, 1, 2, 3, or 4;

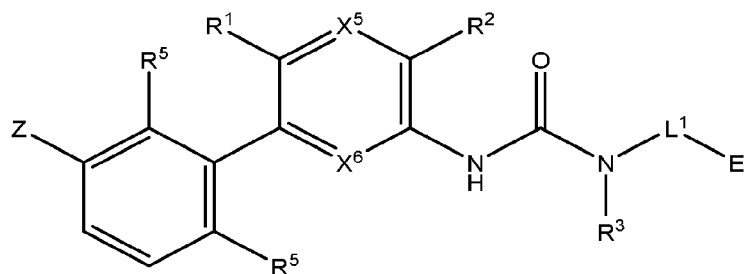
R^1 is selected from the group consisting of H, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, and halogen;

R^2 is selected from the group consisting of H and F;

R^3 is selected from the group consisting of H, C₁-C₅ alkyl, and C₃-C₅ cycloalkyl; and

R^5 , at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen.

20. A compound represented by Formula I-RA:



Formula I-RA

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^5 and X^6 are each independently CH, CF, or N;

L^1 is selected from a direct bond and a C₁-C₆alkyl optionally substituted with (E¹¹)_m, or when taken together with R^3 and the N atom to which L^1 and R^3 are attached form an optionally substituted heterocycle having from 4 to 8 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^1 is selected from the group consisting of hydroxy, alkoxy, cyano, haloalkoxy, halogen,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, amine, alkylamine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of aryl, alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, heterocyclyl, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano and heterocyclyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, alkoxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E^{11} , at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{11} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is L^7-E^7 wherein:

L^7 a direct bond;

E^7 is optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, urea, amine, amidine, acyl, carbamoyl, formyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

each occurrence of m is independently 0, 1, 2, 3, or 4;

R^1 is selected from the group consisting of H, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, and halogen;

R^2 is selected from the group consisting of H and F;

R^3 is selected from the group consisting of H, C_1-C_5 alkyl, and C_3-C_5 cycloalkyl; and

R^5 , at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen.

21. The compound of any one of claims 1-20, wherein:

E¹ is selected from the group consisting of hydroxy, C₁-C₆ alkoxy, cyano, C₁-C₆ haloalkoxy, C₁-C₆ haloalkyl, halogen,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, amine, alkylamine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

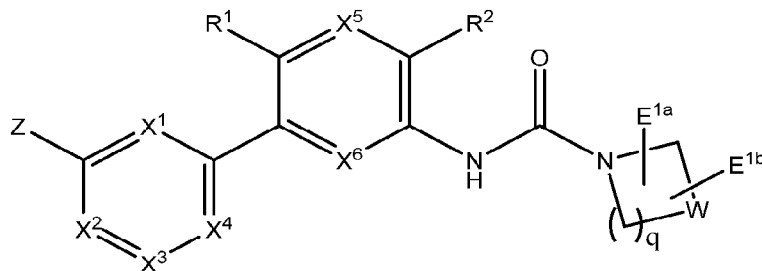
optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of aryl, C₁-C₆ alkyl, C₁-C₆ alkoxy, amine, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, halogen, hydroxy, heterocyclyl, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ alkoxy, amine, amide, acyl, C₁-C₆ alkoxyalkyl, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, halogen, hydroxy, cyano and heterocyclyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ alkoxy, amide, amine, C₁-C₆ acyl, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, halogen, hydroxy, C₁-C₆ hydroxyalkyl, C₁-C₆ alkoxyalkyl, oxo, cyano, C₁-C₆ cyanoalkyl, and sulfone; and

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ alkoxy, amide, amine, C₁-C₆ acyl, C₁-C₆ alkoxyalkyl, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, halogen, hydroxy, and cyano.

22. A compound represented by Formula I-SA:



Formula I-SA

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^1 and X^4 are each independently CR^5 , or N;

X^5 and X^6 are each independently CH, CF, or N;

X^2 is N, CH, C=O, C-O-L²-E², C-L²-E², C-N(R⁴)-L²-E², or N-L²-E²;

X^3 is C-O-L³-E³, C-L³-E³, C-N(R⁴)-L³-E³, CH, C=O, N, or N-L³-E³,

provided that not more than two of X^1 , X^2 , X^3 , and X^4 are N;

provided that when X^2 is N, X^3 is C-O-L³-E³, C-L³-E³, C-N(R⁴)-L³-E³,

N, or CH;

provided that when X^3 is N, X^2 is N, CH, C-O-L²-E², C-L²-E², or C-N(R⁴)-L²-E²;

provided that when X^2 is C=O, X^3 is N-L³-E³;

provided that when X^3 is C=O, X^2 is N-L²-E²;

L² is a direct bond or a C₁-C₆alkyl optionally substituted with (E²¹)_p;

L³ is a direct bond or a C₁-C₆alkyl optionally substituted with (E³¹)_p;

each of E^{1a} and E^{1b} is independently selected from the group consisting of H, alkoxy, cyano, haloalkoxy, halogen,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano, and

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone;

or wherein E^{1a} and E^{1b} taken together with the carbon atom to which they are attached form an optionally substituted cycloalkyl ring or an optionally substituted heterocyclyl ring having from 3 to 6 atoms in the ring structure, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

or, when E^{1a} and E^{1b} are attached to the same carbon atom, E^{1a} and E^{1b} are taken together with the carbon atom to which they are attached to form oxo;

E^2 is selected from the group consisting of H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, sulfone, hydroxy, alkoxy, alkoxyalkyl, cyano, sulfonyl, and optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21} , at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{21} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

E^3 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, sulfonyl, haloalkoxy, H, alkyl, acyl, amine, aminoalkyl, amide, haloalkyl, cyano, sulfone,

optionally substituted heterocyclyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted heteroaryl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

optionally substituted cycloalkyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E^{31} , at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{31} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

W is selected from the group consisting of CH_2 , O, or $N-R^{10}$,

Z is L^7-E^7 wherein:

L^7 is a direct bond;

E⁷ is optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, urea, amine, amidine, acyl, carbamoyl, formyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

R¹ is selected from the group consisting of H, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, and halogen;

R^2 is selected from the group consisting of H and F;

R³ is selected from the group consisting of H, C₁-C₅ alkyl, and C₃-C₅ cycloalkyl;

R⁴, at each occurrence, is independently H or alkyl; and

R⁵, at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen;

R¹⁰, at each occurrence, is independently selected from the group consisting of H, C₁-C₆ alkyl, C₃-C₅ cycloalkyl, and C₁-C₆ acyl;

each occurrence of m is independently 0, 1, 2, 3, or 4;

each occurrence of p is independently 0, 1, or 2;

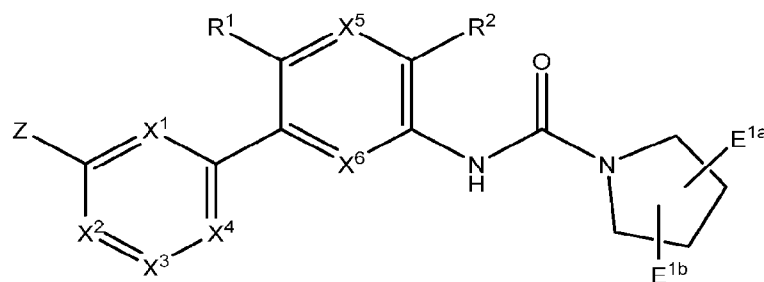
each occurrence of q is independently 1, 2, or 3;

with the proviso that

when X¹, X⁴, X⁵, and X⁶ are CH, R¹ is -CH₃, X² is N, X³ is C-L³-E³, and L³ is a direct bond, E³ is not morpholinyl; and

when X¹ and X⁴ are each independently N, CH, or CF, X⁵ is CH, and X⁶ is CH, CD, or CF, E⁷ is not 5- or 6- membered optionally substituted heteroaryl.

23. A compound represented by Formula I-TA:



Formula I-TA

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^1 and X^4 are each independently CR^5 , or N;

X^5 and X^6 are each independently CH, CF, or N;

X^2 is N, CH, C=O, C-O-L²-E², C-L²-E², C-N(R⁴)-L²-E², or N-L²-E²;

X^3 is C-O-L³-E³, C-L³-E³, C-N(R⁴)-L³-E³, CH, C=O, N, or N-L³-E³,

provided that not more than two of X^1 , X^2 , X^3 , and X^4 are N;

provided that when X^2 is N, X^3 is C-O-L³-E³, C-L³-E³, C-N(R⁴)-L³-E³,

N, or CH;

provided that when X^3 is N, X^2 is N, CH, C-O-L²-E², C-L²-E², or C-N(R⁴)-L²-E²;

provided that when X^2 is C=O, X^3 is N-L³-E³;

provided that when X^3 is C=O, X^2 is N-L²-E²;

L² is a direct bond or a C₁-C₆alkyl optionally substituted with (E²¹)_p;

L³ is a direct bond or a C₁-C₆alkyl optionally substituted with (E³¹)_p;

each of E^{1a} and E^{1b} is independently selected from the group consisting of H, alkoxy, cyano, haloalkoxy, halogen,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano, and

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone;

or wherein E^{1a} and E^{1b} taken together with the carbon atom to which they are attached form an optionally substituted cycloalkyl ring or an optionally substituted heterocyclyl ring having from 3 to 6 atoms in the ring structure, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

or, when E^{1a} and E^{1b} are attached to the same carbon atom, E^{1a} and E^{1b} are taken together with the carbon atom to which they are attached to form oxo;

E² is selected from the group consisting of H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, sulfone, hydroxy, alkoxy, alkoxyalkyl, cyano, sulfonyl, and optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E²¹, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E²¹ taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

E³ is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, sulfonyl, haloalkoxy, H, alkyl, acyl, amine, aminoalkyl, amide, haloalkyl, cyano, sulfone,

optionally substituted heterocyclyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, or sulfone,

optionally substituted heteroaryl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

optionally substituted cycloalkyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E³¹, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E³¹ taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is L⁷-E⁷ wherein:

L⁷ is a direct bond;

E⁷ is optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, urea, amine, amidine, acyl, carbamoyl, formyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

each occurrence of m is independently 0, 1, 2, 3, or 4;

each occurrence of p is independently 0, 1, or 2;

R¹ is selected from the group consisting of H, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, and halogen;

R² is selected from the group consisting of H and F;

R³ is selected from the group consisting of H, C₁-C₅ alkyl, and C₃-C₅ cycloalkyl;

R⁴, at each occurrence, is independently H or alkyl; and

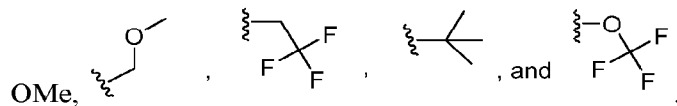
R⁵, at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen;
with the proviso that

when X¹, X⁴, X⁵, and X⁶ are CH, R¹ is -CH₃, X² is N, X³ is C-L³-E³, and L³ is a direct bond, E³ is not morpholinyl; and

when X¹ and X⁴ are each independently N, CH, or CF, X⁵ is CH, and X⁶ is CH, CD, or CF, then E⁷ is not 5- or 6- membered optionally substituted heteroaryl.

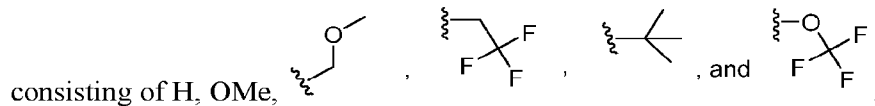
24. The compound of claim 22 or 23, wherein E^{1a} is selected from the group consisting of H and OMe.

25. The compound of claim 24, wherein E^{1a} is selected from the group consisting of H,



26. The compound of any one of claims 22-25, wherein E^{1b} is selected from the group consisting of H and OMe.

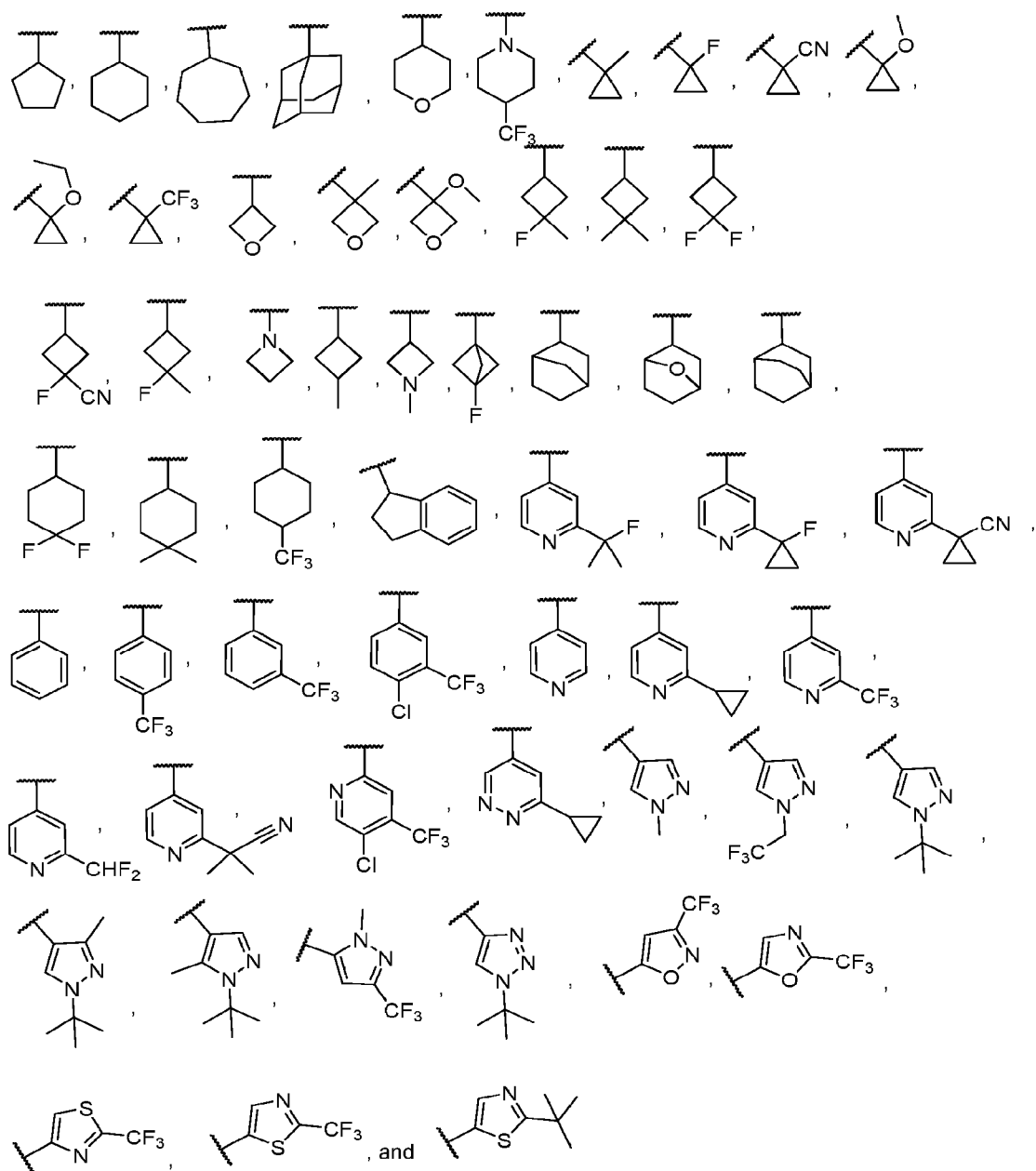
27. The compound of any one of claims 22-25, wherein E^{1b} is selected from the group



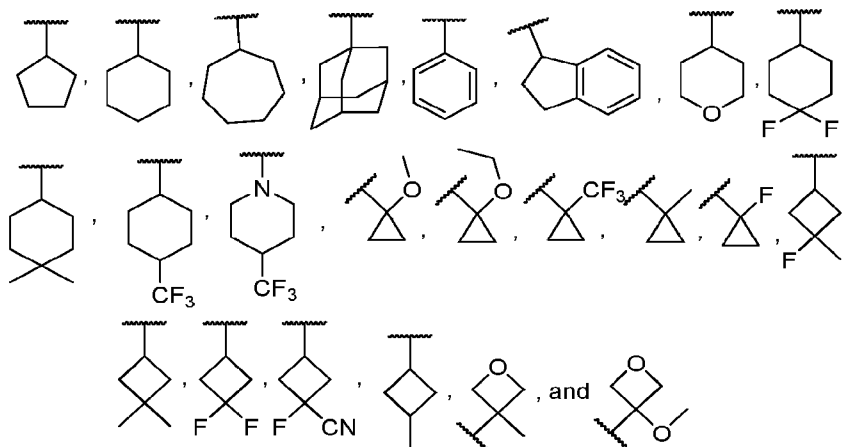
28. The compound of any one of claims 22 and 24-27, wherein W is CH₂ or O.

29. The compound of claim 28, wherein W is CH₂.

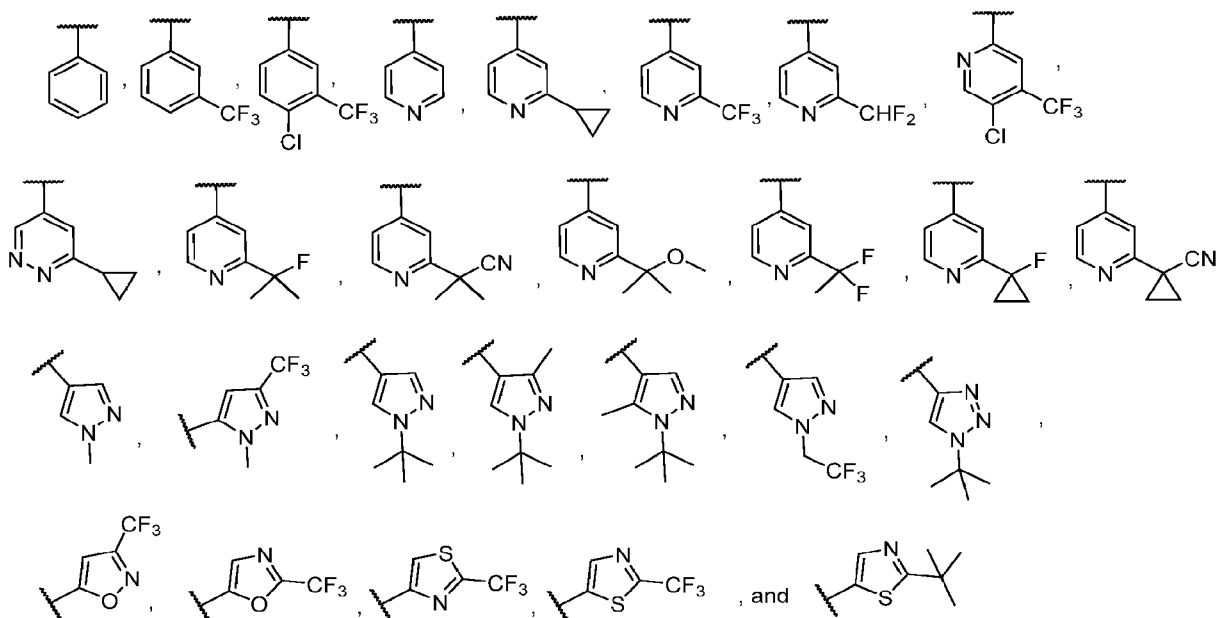
30. The compound of any one of claims 1-21, wherein E¹ is selected from the group consisting of H, Me, Et, CF₃, CH₂CF₃, OMe, OEt, OCF₃, CH₂OCH₃, F, CN,



31. The compound of any one of claims 1-21 and 30, wherein E¹ is selected from the group consisting of



32. The compound of any one of claims 1-21 and 30, wherein E¹ is selected from the group consisting of

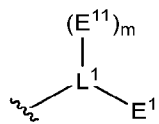


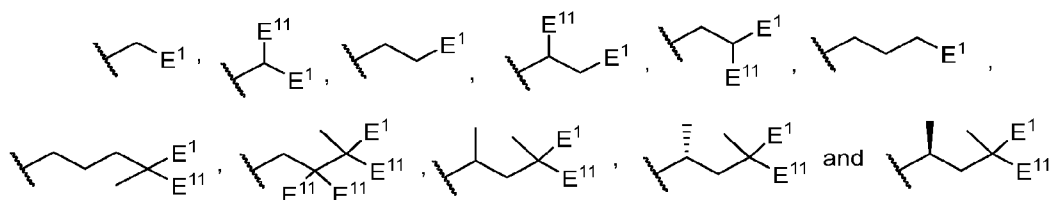
33. The compound of any one of claims 1-21 and 30-32, wherein E¹¹, at each occurrence, is independently selected from the group consisting of H, C₁-C₆ alkyl, C₃-C₅ cycloalkyl, C₁-C₆ alkoxy, oxetanyl, cyano, C₁-C₆ haloalkoxy, C₁-C₆ haloalkyl, hydroxy, C₁-C₆ hydroxyalkyl, and halogen,

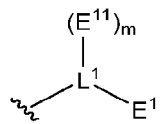
or wherein two occurrences of E¹¹ taken together with the carbon atom to which they are attached form a C₃-C₆ cycloalkyl ring.

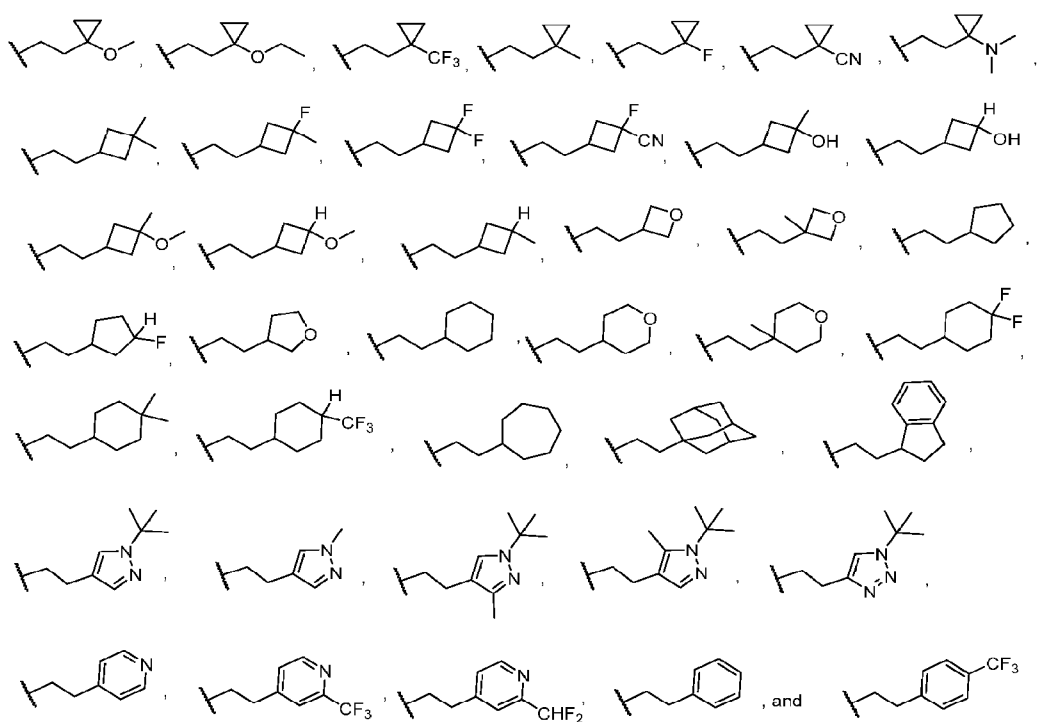
34. The compound of any one of claims 1-21 and 30-33, wherein E^{11} , at each occurrence, is independently selected from the group consisting of H, Me, CF_3 , OH, OMe, OEt, oxetanyl, OCF_3 , F, and CN,

or wherein two occurrences of E^{11} taken together with the carbon atom to which they are attached form cyclopropyl ring.

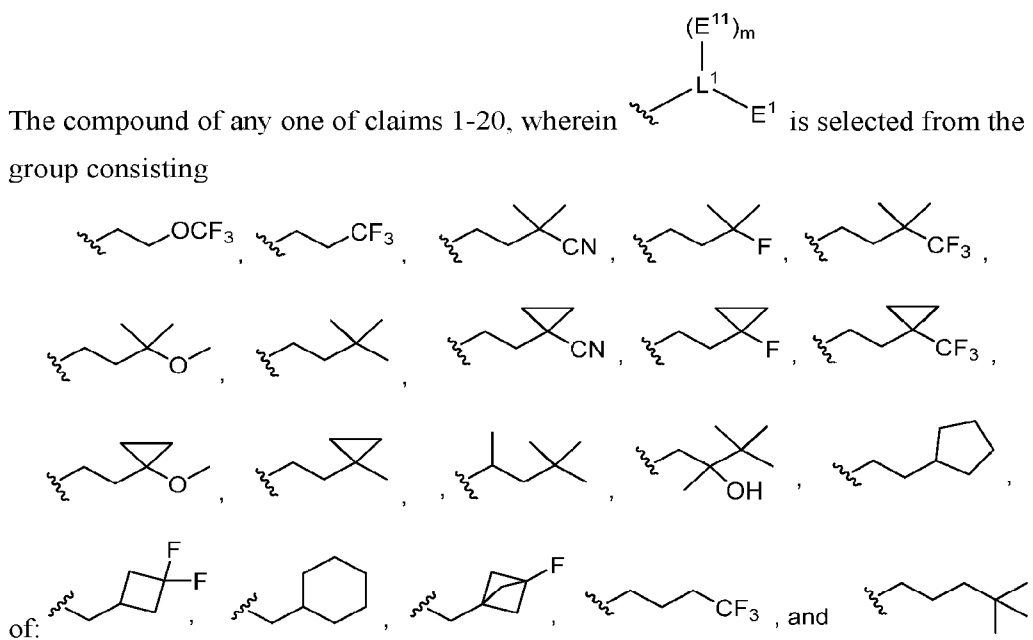
35. The compound of any one of claims 1-21 or 30-34, wherein  is selected from the group consisting of



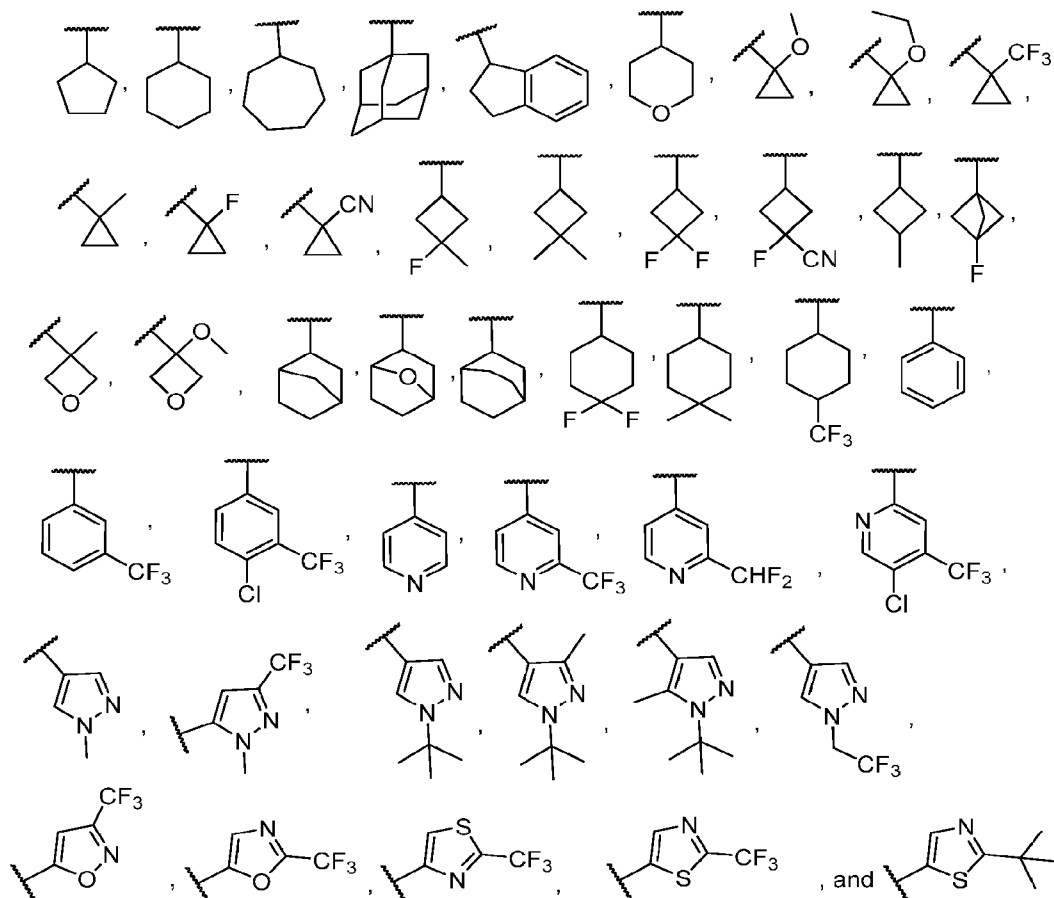
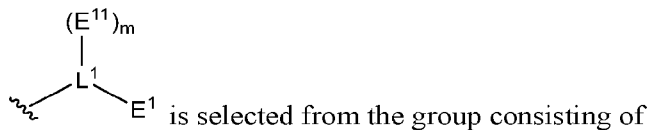
36. The compound of any one of claims 1-20, wherein  is selected from the group consisting of



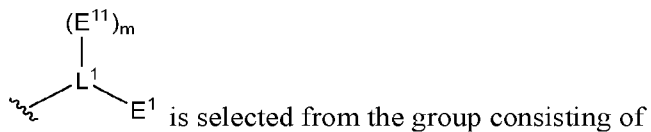
37. The compound of any one of claims 1-20, wherein  is selected from the group consisting

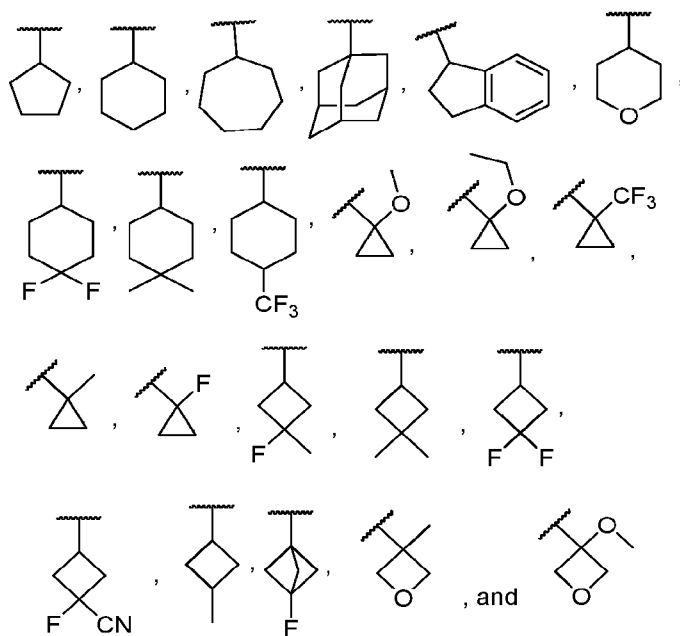


38. The compound of any one of claims 1-20, wherein when L^1 is a direct bond,

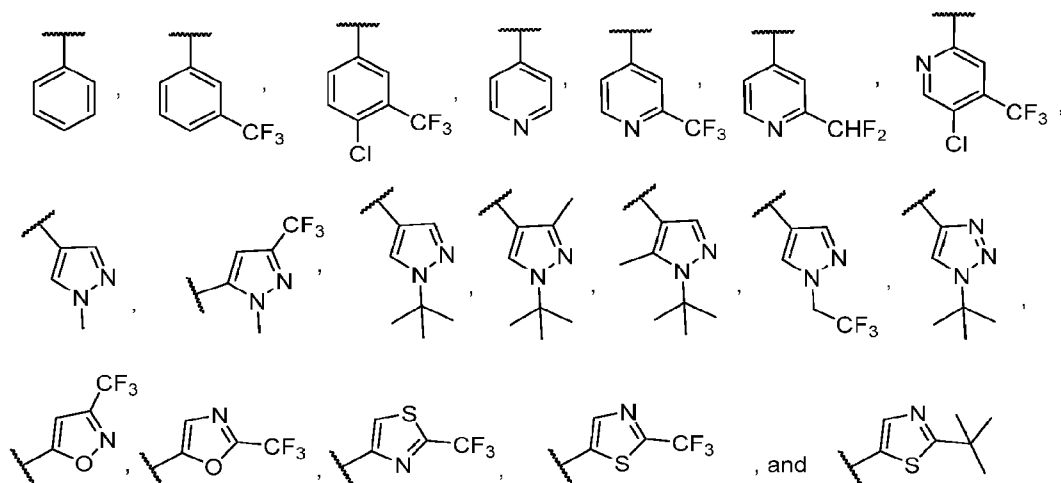
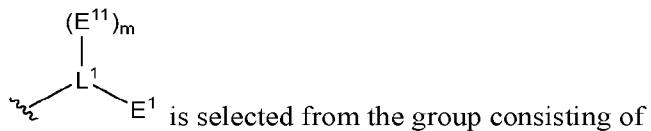


39. The compound of any one of claims 1-20, wherein when L^1 is a direct bond,



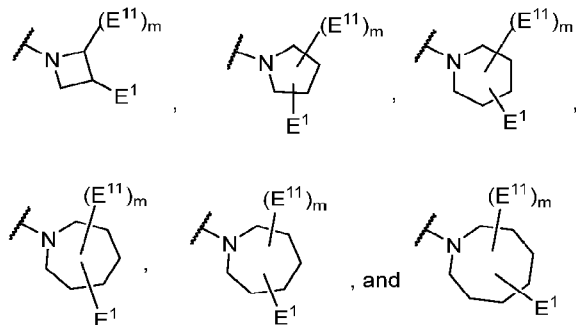


40. The compound of any one of claims 1-20, wherein when L^1 is a direct bond,

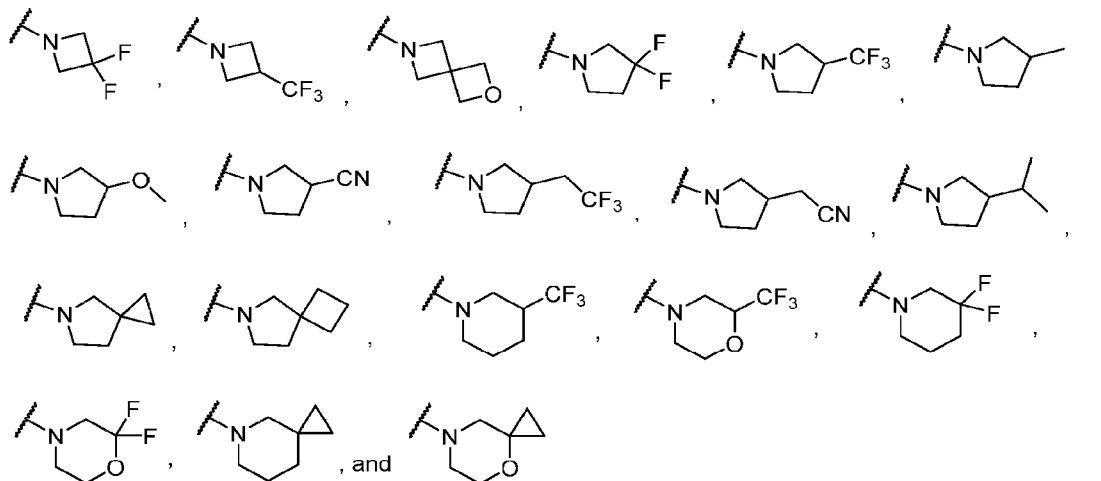


41. The compound of any one of claims 1-20, wherein L^1 and R^3 taken together with the N atom to which they are attached form a heterocycle having from 4 to 8 atoms in the

ring structure wherein the ring structure is selected from the group consisting of



42. The compound of any one of claims 1-20, wherein L¹ and R³ taken together with the N atom to which they are attached form a heterocycle having from 4 to 8 atoms in the ring structure wherein the ring structure is selected from the group consisting of

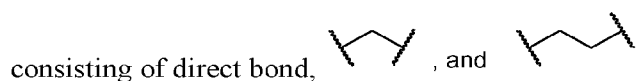


43. The compound of any one of claims 1-42, wherein E² is selected from the group consisting of hydroxy, C₁-C₆ alkoxy, C₁-C₆ alkoxyalkyl, cyano, sulfonyl, H, C₁-C₆ alkyl, amine, C₁-C₆ haloalkoxy, C₁-C₆ haloalkyl, sulfone, and optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ alkoxy, amide, amine, C₁-C₆ acyl, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, halogen, hydroxy, C₁-C₆ hydroxyalkyl, oxo, cyano, and C₁-C₆ cyanoalkyl.

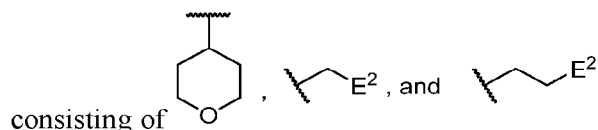
44. The compound of claim 43, wherein E² is selected from the group consisting of H,



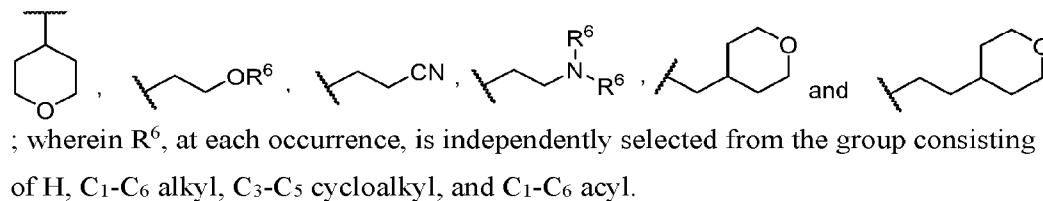
45. The compound of any one of claims 1-44, wherein L² is selected from the group



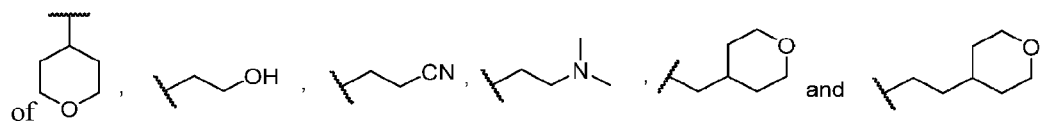
46. The compound of any one of claims 1-45, wherein L²-E² is selected from the group



47. The compound of any one of claims 1-46, wherein L²-E² is selected from the group consisting of



48. The compound of any one of claims 1-47, wherein L²-E² is selected from the group consisting



49. The compound of any one of claims 1-48, wherein:

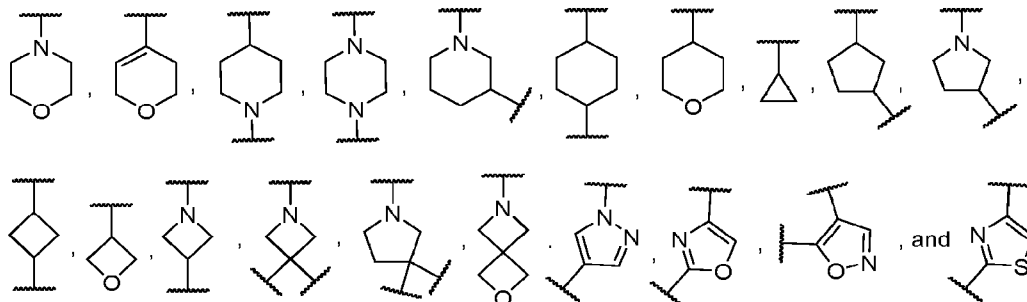
E³ is selected from the group consisting of hydroxy, C₁-C₆ alkoxy, C₁-C₆ alkoxyalkyl, cyano, sulfonyl, C₁-C₆ haloalkoxy, H, C₁-C₆ alkyl, C₁-C₆ acyl, amine, C₁-C₆ aminoalkyl, amide, C₁-C₆ haloalkyl,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkoxyalkyl, amide, amine, C₁-C₆ aminoalkyl, C₁-C₆ acyl, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, halogen, hydroxy, C₁-C₆ hydroxyalkyl, oxo, cyano, C₁-C₆ cyanoalkyl, and sulfone,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ alkoxy, amide, amine, C₁-C₆ acyl, C₁-C₆ alkoxyalkyl, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, halogen, hydroxy, C₁-C₆ hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

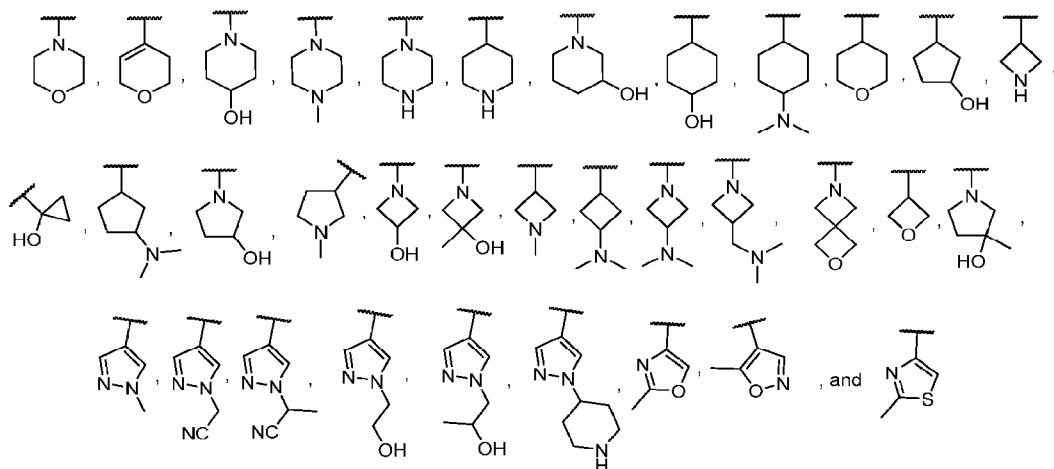
optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, halogen, hydroxy, and cyano.

50. The compound of any one of claims 1-48, wherein E³ is selected from the group consisting of H, Me, N(R⁶)₂, C(=O)Me, SO₂Me, OR⁶, CN,



; wherein R⁶, at each occurrence, is independently selected from the group consisting of H, C₁-C₆alkyl, C₃-C₅cycloalkyl, and C₁-C₆acyl.

51. The compound of any one of claims 1-48, wherein E³ is selected from the group consisting of H, Me, NMe₂, C(=O)Me, SO₂Me, OH, CN,



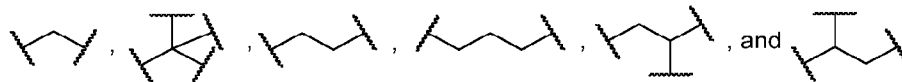
52. The compound of any one of claims 1-48, wherein E^{31} , at each occurrence is independently selected from the group consisting of H, C_1 - C_6 alkyl, C_3 - C_5 cycloalkyl, C_1 - C_6 alkoxy, oxetanyl, C_1 - C_6 alkoxylalkyl, cyano, C_1 - C_6 cyanoalkyl, C_1 - C_6 haloalkoxy, C_1 - C_6 haloalkyl, hydroxy, C_1 - C_6 hydroxyalkyl, and halogen,

or wherein two occurrences of E^{31} taken together with the carbon atom to which they are attached form a C_3 - C_6 cycloalkyl ring.

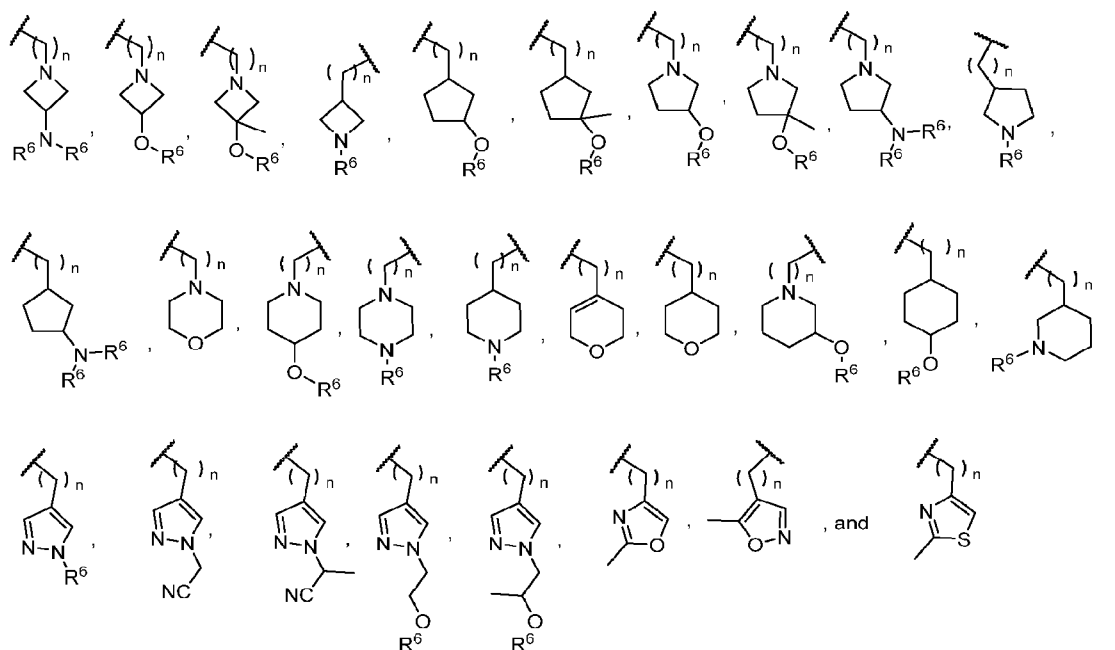
53. The compound of any one of claims 1-48, wherein E^{31} is, at each occurrence, independently selected from the group consisting of H, Me, CF_3 , OH, OMe, OEt, oxetanyl, OCF_3 , CH_2OH , F, and CN,

or wherein two occurrences of E^{31} taken together with the carbon atom to which they are attached form cyclopropyl ring.

54. The compound of any one of claims 1-53, wherein L^3 is selected from the group consisting of a direct bond,

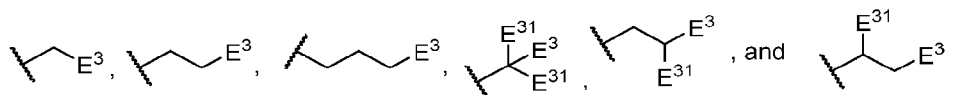


55. The compound of any one of claims 1-54, wherein $L^3(E^3)(E^{31})_p$ is selected from the group consisting of:

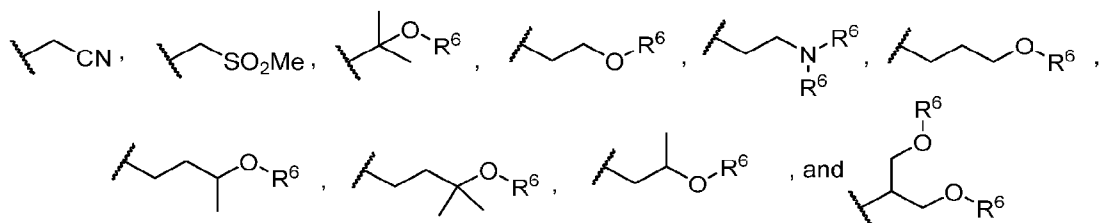


; wherein R⁶, at each occurrence, is independently selected from the group consisting of H, C₁-C₆alkyl, C₃-C₅cycloalkyl, and C₁-C₆acyl.

56. The compound of any one of claims 1-54, wherein L³(E³)(E³¹)_p is selected from the group consisting of



57. The compound of any one of claims 1-54, wherein L³(E³)(E³¹)_p is selected from the group consisting of



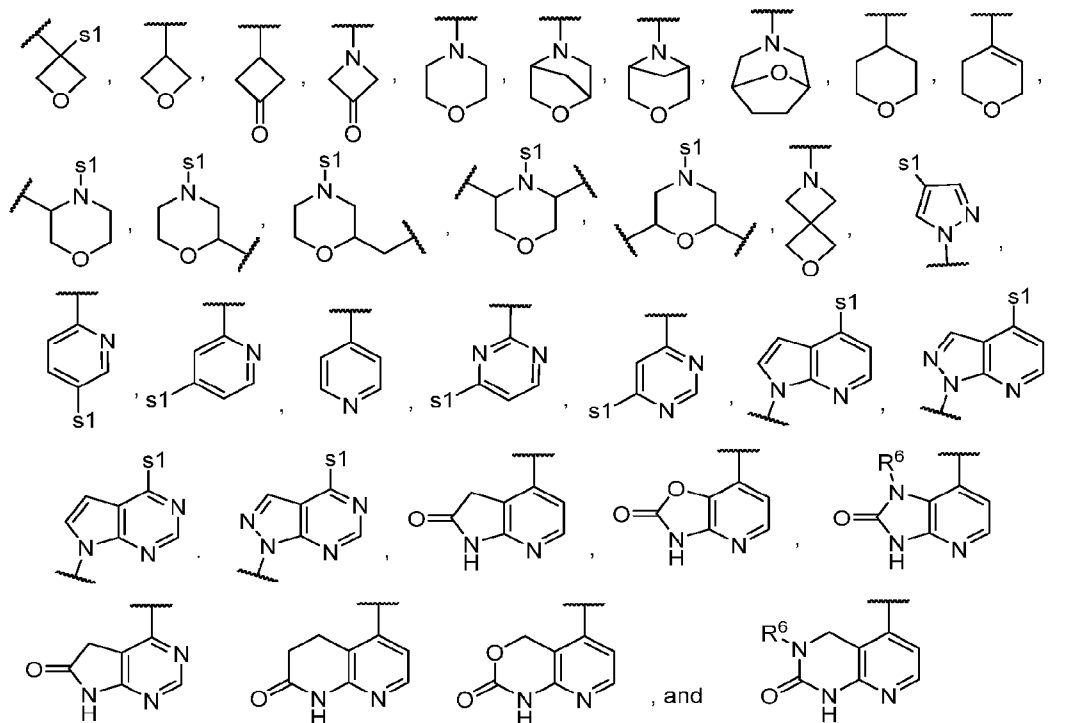
; wherein R⁶, at each occurrence, is independently selected from the group consisting of H, C₁-C₆alkyl, C₃-C₅cycloalkyl, and C₁-C₆acyl.

58. The compound of any one of claims 1-57, wherein E⁷ is selected from the group consisting of H, amide, urea, amine, cyano, hydroxy, alkoxy,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, cycloalkyl, alkoxy, alkoxyalkyl, amine, acyl, carbamoyl, formyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

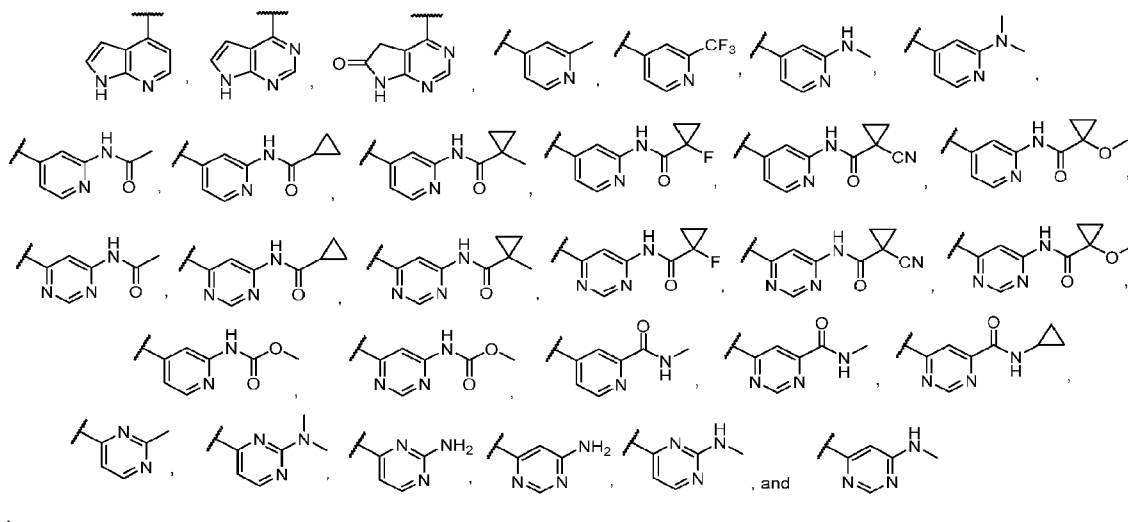
optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, urea, amine, acyl, carbamoyl, formyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano.

59. The compound of any one of claims 1-57, wherein E⁷ is selected from the group consisting of



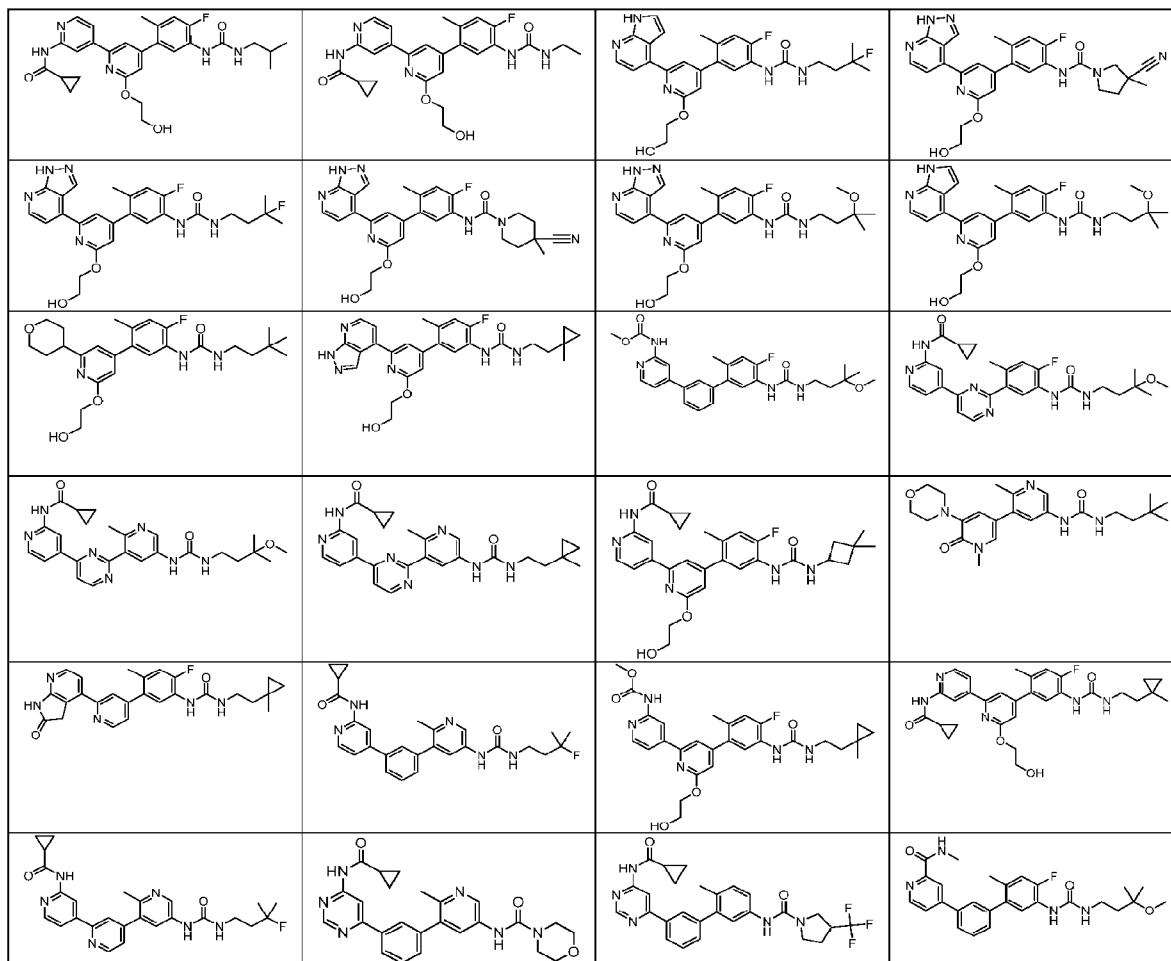
; wherein R⁶, at each occurrence, is independently selected from the group consisting of H, C₁-C₆alkyl, C₃-C₅cycloalkyl, and C₁-C₆acyl; and wherein s1 indicates the site of attachment to the ring and wherein  indicates site of optional substituent when s1 is present or  indicates site of attachment to ring when s1 is not present.

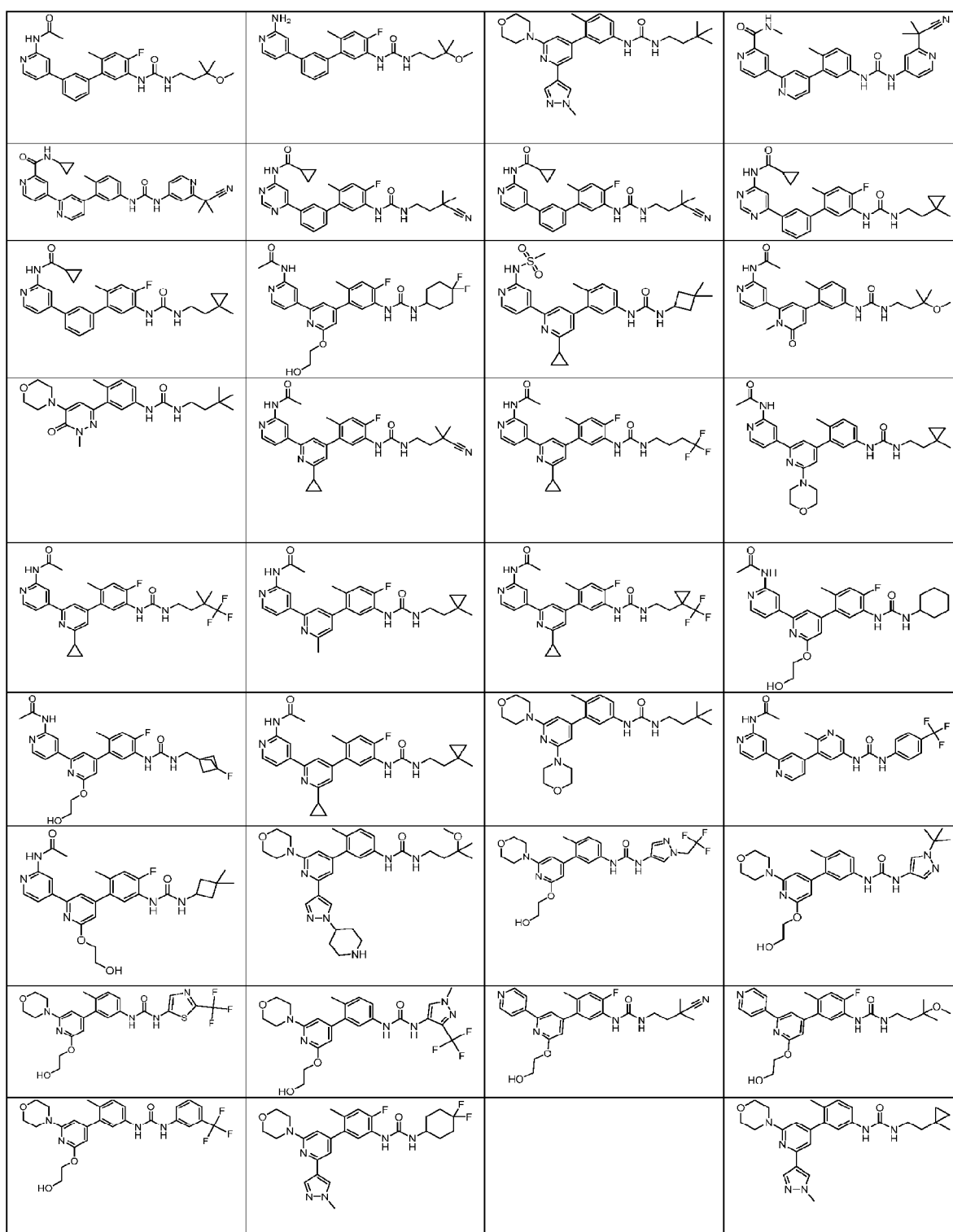
63. The compound of any one of claims 1-57, wherein E⁷ is selected from the group consisting of

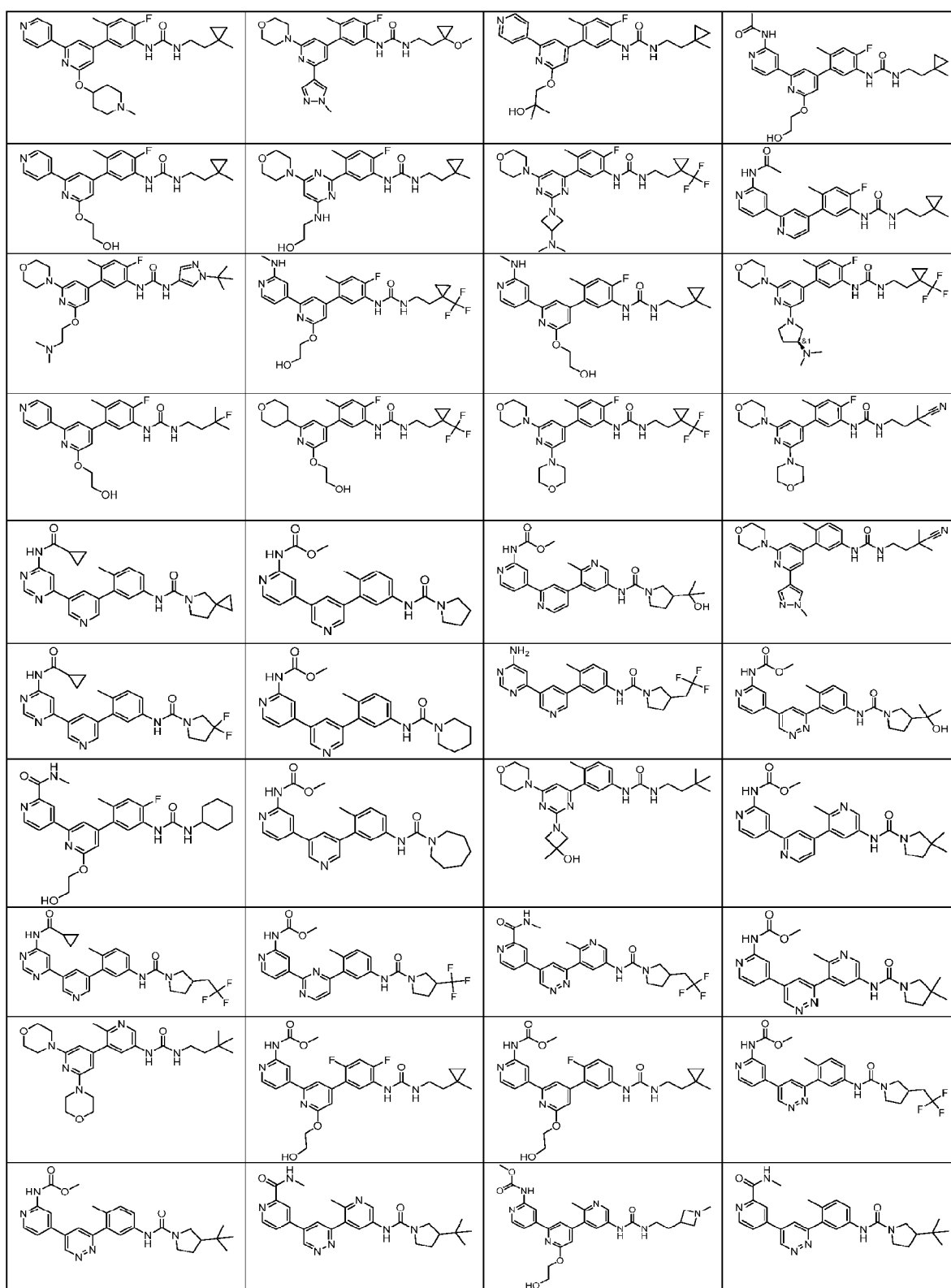


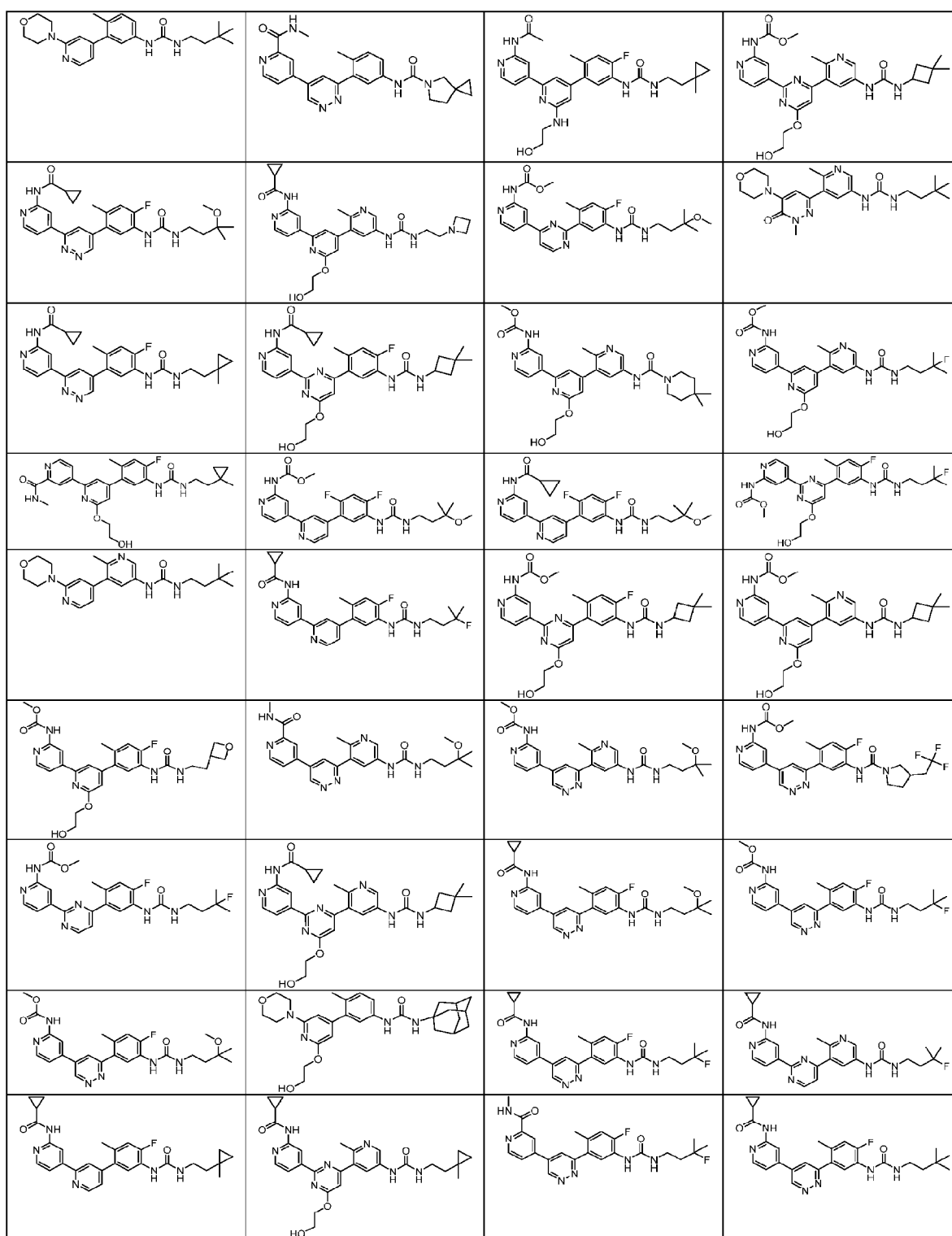
64. The compound of any one of claims 1-63, wherein X⁵ is N and X⁶ is CH or CF.
65. The compound of any one of claims 1-63, wherein X⁵ is CH or CF and X⁶ is N.
66. The compound of any one of claims 1-63, wherein X⁵ and X⁶ are CH or CF.
67. The compound of any one of claims 1-63, wherein X⁵ and X⁶ are CH.
68. The compound of any one of claims 1-67, wherein R¹ is selected from the group consisting of H, C₁-C₆ alkyl, CN and halogen.
69. The compound any one of claims 1-68, wherein R¹ is selected from the group consisting of H, Me, Et, F, Br, and Cl.
70. The compound of any one of claims 1-69, wherein R¹ is selected from the group consisting of Me and F.
71. The compound of any one of claims 1-70, wherein R² is selected from the group consisting of H and F.
72. The compound of any one of claims 1-71, wherein R² is H.
73. The compound of any one of claims 1-71, wherein R² is F.

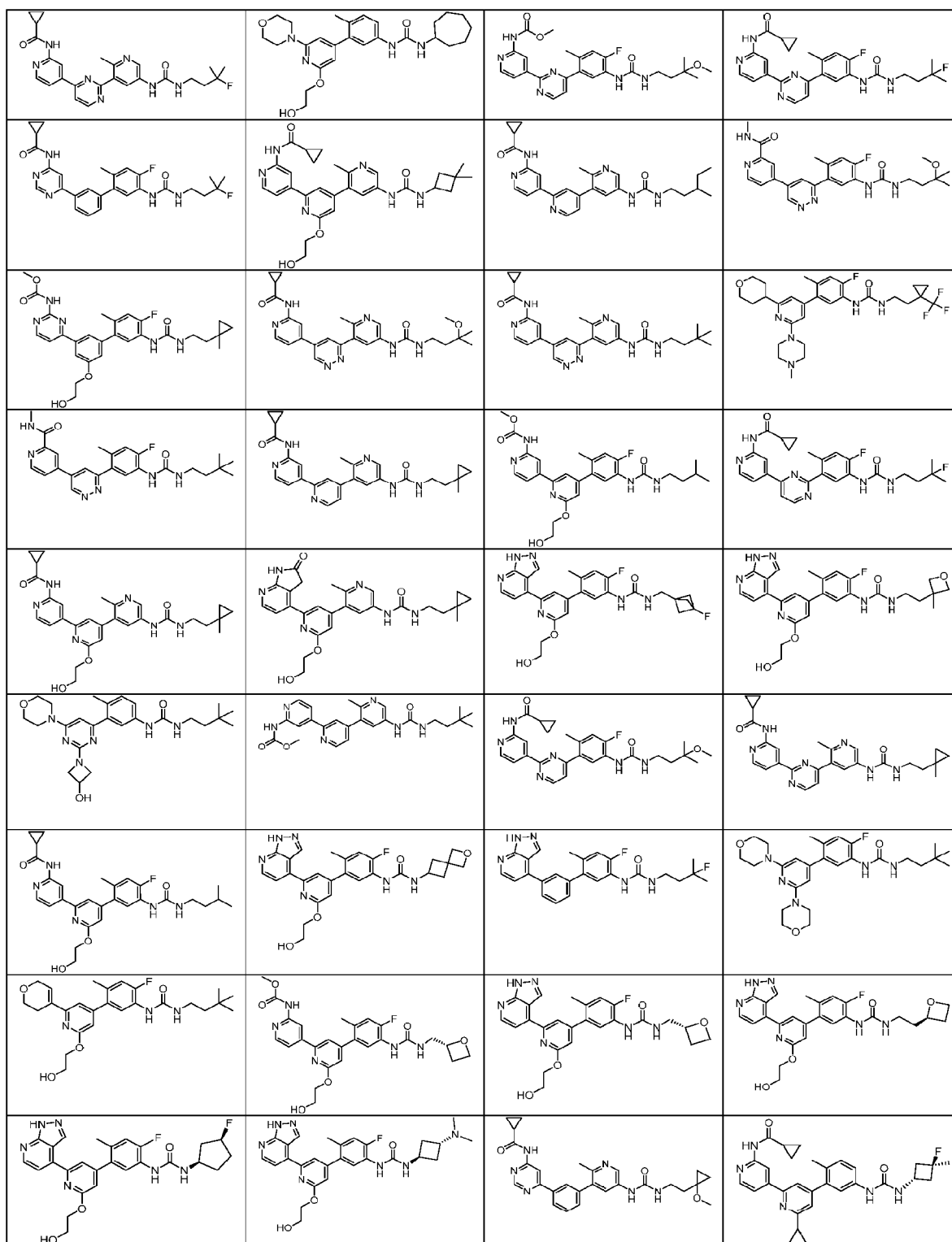
74. The compound of any one of claims 1-73, wherein R^3 is H or Me.
75. The compound of any one of claims 1-74, wherein R^3 is H.
76. The compound of any one of claims 1-75, wherein R^4 is H or C_1 - C_6 alkyl.
77. The compound of any one of claims 1-76, wherein R^4 is H or Me.
78. The compound of any one of claims 1-77, wherein R^5 is H, C_1 - C_6 alkyl, or halogen.
79. The compound of any one of claims 1-78, wherein R^5 is selected from the group consisting of H, Me, Et, F, and Cl.
80. The compound of any one of claims 1-79, wherein R^5 is H.
81. A compound selected from the group consisting of:

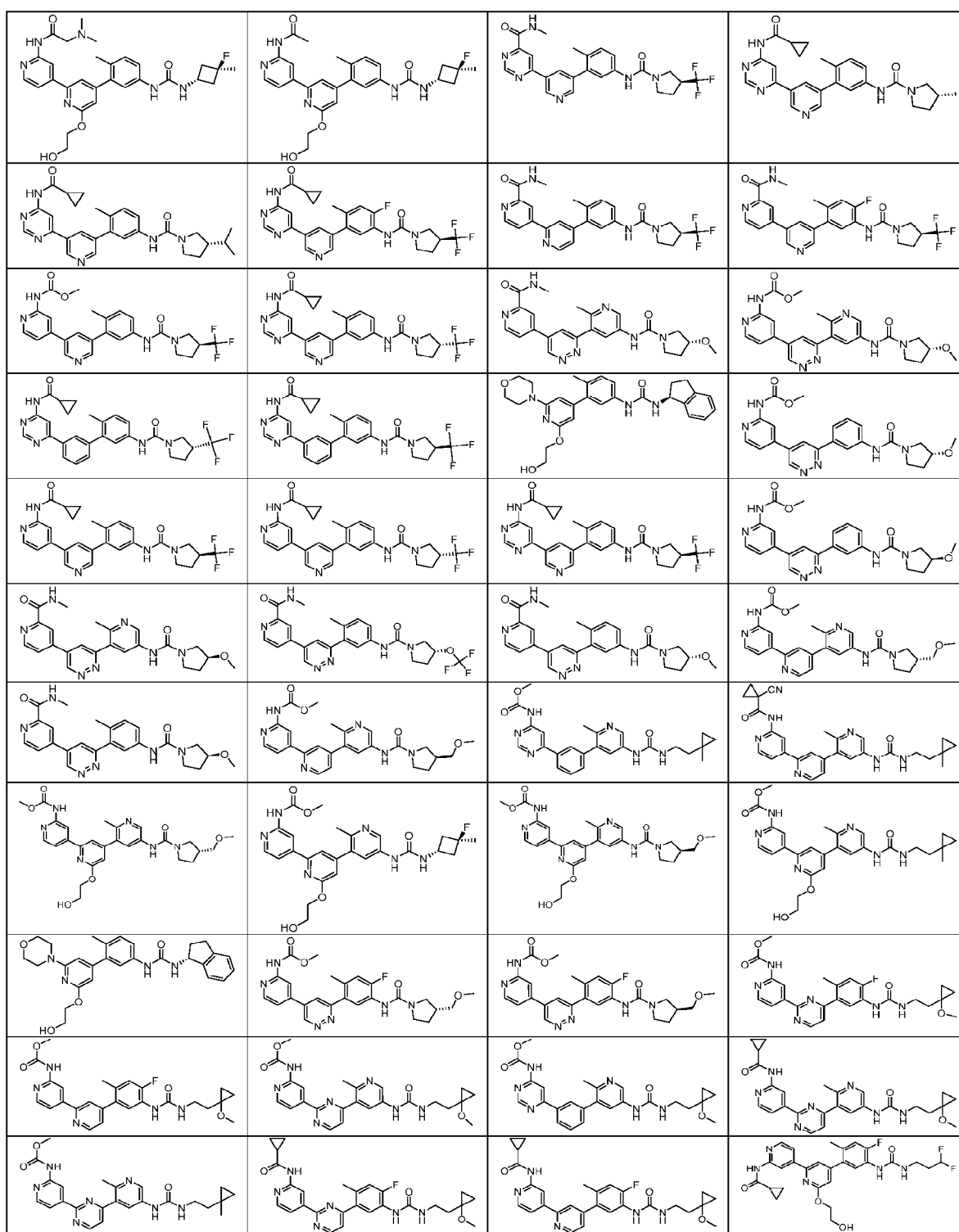


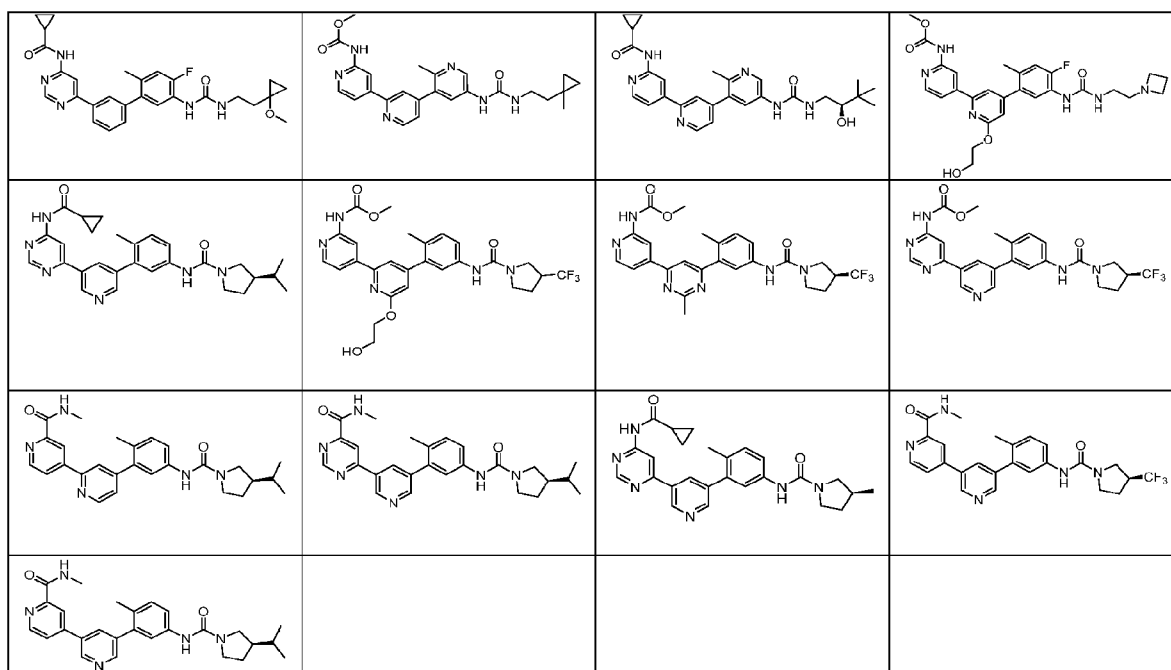








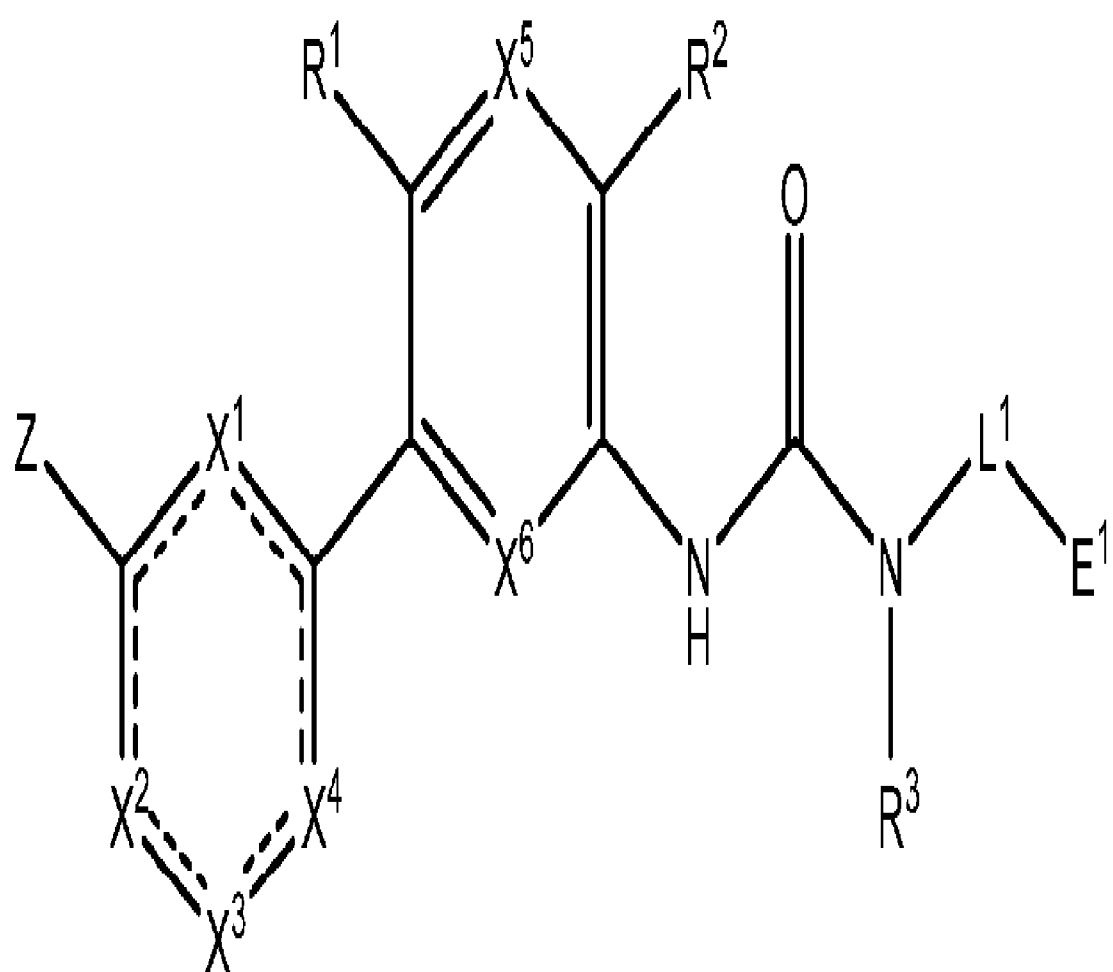




or pharmaceutically acceptable salts, enantiomers, stereoisomers, or tautomers thereof.

82. A pharmaceutical composition comprising the compound according to any one of claims 1-81, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.
83. A method of treating a cancer in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of the compound of any one of claims 1-81, or of the pharmaceutical composition of claim 82.
84. The method of claim 83, wherein the cancer is selected from the group consisting of melanoma, multiple myeloma, thyroid cancer, ovarian cancer, colorectal cancer, colon cancer, pancreatic cancer, lung cancer, bladder cancer, gastrointestinal stromal tumors, solid tumors, brain cancers, gliomas, glioblastomas, astrocytomas, blood-borne cancers, hairy cell leukemia, acute myelogenous leukemia (AML), or other cancers caused by activation of the $RAS \rightarrow RAF \rightarrow MEK \rightarrow ERK$ signaling pathway.
85. The method of claim 84, wherein the cancer has a BRAF oncogenic mutation.
86. The method of claim 84 or 85, wherein the cancer has a RAS oncogenic mutation.

87. The method of claim 86, wherein the RAS oncogenic mutation is RAS Q61R or Q61K mutation.
88. The method of claim 84, wherein the cancer has a NF1 oncogenic mutation.
89. A method of treating a disorder selected from the group consisting of melanoma, multiple myeloma, thyroid cancer, ovarian cancer, colorectal cancer, colon cancer, pancreatic cancer, lung cancer, bladder cancer, gastrointestinal stromal tumors, solid tumors, brain cancers, gliomas, glioblastomas, astrocytomas, blood-borne cancers, hairy cell leukemia, acute myelogenous leukemia (AML), other cancers caused by activation of the RAS→RAF→MEK→ERK signaling pathway in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of the compound of any one of claims 1-81 or of the pharmaceutical composition of claim 82.



(I)