

GCN2 AND PERK KINASE INHIBITORS AND METHODS OF USE THEREOF**CROSS-REFERENCE**

[0001] This application claims priority to U.S. Provisional Application No. 63/115,496 filed November 18, 2020 and U.S. Provisional Application No. 63/185,846 filed May 7, 2021, each of which is incorporated herein by reference in its entirety.

SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on October 28, 2021, is named DCP-098WO_SL.txt and is 23,670 bytes in size.

BACKGROUND

[0003] Cancer cells need a continuous supply of nutrients to maintain their abnormal growth and rapid division. As part of these nutrients, amino acids are essential to support the high metabolic demands of tumor cells.

[0004] GCN2 is a serine/threonine protein kinase, one of the eukaryotic initiation factor 2 (eIF2 α) kinases that are master regulators in the integrated stress response (ISR). The ISR is essential for maintaining cellular homeostasis under a wide range of stressors and is activated when cells adapt to stress conditions such as hypoxia and amino acid deprivation. The ISR is regulated by phosphorylation and activation of eIF2 α kinases, including GCN2, that act as early responders to disturbances in cellular homeostasis. In addition to GCN2, there are three other eIF2 α kinases family including PKR-like ER kinase (PERK), double-stranded RNA-dependent protein kinase (PKR), and heme-regulated eIF2 α kinase (HRI). All four eIF2 α kinases share extensive homology in their kinase catalytic domains but possess distinct regulatory domains. Each of the IF2 α kinases responds to distinct environmental and physiological stresses, which reflect their unique regulatory mechanisms. PERK kinase is activated under stress conditions including ATP depletion and the unfolded protein response, and like GCN2, PERK kinase activation leads to up-regulation of the key ISR transcription factor ATF4.

[0005] Under conditions of essential amino-acid limitation or other stressors (UV irradiation, redox stress or proteasome inhibition), GCN2 phosphorylates eIF2 α , which inhibits the formation of a new ternary complex and hence inhibition of mRNA translation initiation. While decreasing global mRNA translation, in tumor cells eIF2 α phosphorylation also increases the translation of the ISR transcription factor ATF4, which increases the expression of many stress response genes including

genes dedicated to providing amino acids to the tumor cell: i.e., amino acid synthesis enzymes and transporters that mediate influx of amino acids into the tumor cell. ATF4 is over-expressed in human solid and liquid tumors suggesting an important function in tumor progression.

[0006] Asparagine is an important amino acid involved in several biosynthetic pathways that significantly influence carcinogenesis and tumor biology. All cells need asparagine for their protein synthesis and growth. Normal cells will obtain most of their asparagine requirements through internal synthesis. Compared to normal cells, cancer cells require elevated amounts of asparagine to grow and proliferate, cannot produce that required amount themselves, and must rely on circulating asparagine in order to survive. Asparagine Synthetase (ASNS) catalyzes the synthesis of asparagine from aspartate and glutamine. L-asparaginase (ASNase) removes circulating asparagine, thereby depriving cancer cells of a key nutrient and causing them to die. The use of L-asparaginase, the first example of anti-cancer treatment targeting a tumor-specific metabolic feature, is a well-established treatment in pediatric acute lymphoblastic leukemia (ALL), but toxicity has limited its use beyond this patient population. The particularly low-level expression of ASNS in numerous ALL cell lines, as compared to that of normal cells, makes asparagine depletion an effective method of treatment due to the cells' unusual dependency on circulating serum asparagine as a necessary nutrition for growth. A poor response to asparaginase is associated with increased relapse risk. Other hematological and solid cancers express low levels of ASNS and, therefore, should also be asparagine auxotroph and asparaginase sensitive. Conversely, in some cancer types ASNS is overexpressed, promoting cell proliferation, chemoresistance, and a metastatic behavior. In case of asparaginase resistant cancers, the effect of blood asparagine depletion through L-asparaginase instead leads to significant ASNS overexpression to compensate, effectively nullifying the effect of the chemotherapy drug. Numerous studies have shown that ASNS is at the center of the cell response to amino acid deprivation and other forms of cellular stress. Through transcriptional regulation, the ASNS gene is a target of two signaling pathways aimed at ensuring cell survival. The first, named Amino Acid Response (AAR), is activated by the GCN2 kinase under conditions of imbalanced amino acid availability. The second pathway, named the Unfolded Protein Response (UPR), is activated by the PERK kinase under conditions of increased endoplasmic reticulum stress. The AAR and UPR pathways converge on the phosphorylation of eIF2 α , which provokes the attenuation of global protein synthesis and, at the same time, the preferential translation of a selected population of mRNAs, including the transcription factor ATF4. ATF4 is the major factor for ASNS induction, working as a trans-activator through the binding to an enhancer element within ASNS promoter.

[0007] GCN2 sensitizes cancer cells with low basal level expression of ASNS to the antileukemic agent L-asparaginase in vitro and in vivo. Treatment with GCN2 inhibitors rendered acute

lymphoblastic leukemia cells sensitive to L-asparaginase by preventing the induction of ASNS. GCN2 inhibitors exhibit synergistic antiproliferative effects with L-asparaginase in ASNS-low/deficient cancers. Therefore, combined treatment with GCN2 inhibitors and L-asparaginase shows promise for achieving improved outcomes in acute lymphoblastic leukemia and other types of cancer. Acute lymphoblastic leukemia, acute myeloid leukemia, and pancreatic cancer cells are particularly sensitive to combined treatment with L-asparaginase and GCN2 inhibitors. Previously reported studies demonstrated robust antitumor activities of combined treatment with ASNase and GCN2 inhibitors in acute lymphoblastic leukemia, acute myeloid leukemia, and pancreatic cancer cells compared with the results of single-agent L-asparaginase or GCN2 inhibitor treatment. Thus, GCN2 inhibitors may represent sensitizing agents to L-asparaginase used for treating these tumors. In summary, GCN2 inhibition enhances the sensitivity to L-asparaginase treatment by preventing ASNS induction in cancer cells with low ASNS expression at basal levels.

[0008] Inhibition of GCN2 may also be an effective strategy for targeting the tumor microenvironment, including the immune system, including tryptophan-dependent immunosurveillance of tumor cells.

[0009] The tumor microenvironment [TME; a series of extracellular components and stromal cells (endothelial cells, cancer-associated fibroblasts, tumor-associated macrophages, tumor-infiltrating T cells) that surround the tumor cells] is characterized by deficiencies in oxygen and key nutrients, such as glucose and amino acids, resulting in an overall immune suppressive environment.

[0010] Many tumors evolved to escape immune surveillance by taking advantage of their metabolic flexibility and redirecting nutrients for their own advantage. Stromal cells and myeloid-derived suppressor cells (MDSC) within the tumor create a nutrient-poor environment that inhibits immune function and supports tumor growth.

[0011] Elevated catabolism of tryptophan, one of the essential amino acids, driven by overexpression of critical enzymes in tryptophan metabolism [Indoleamine-2,3-dioxygenase (IDO) and tryptophan-2,3-dioxygenase (TDO)] is driven by cells of the tumor microenvironment, leading to an immunosuppressive microenvironment in many types of cancer. Local tryptophan depletion is considered to be a crucial T-cell immunosuppressive mechanism. In T cells, the GCN2 kinase has been identified as a molecular sensor of tryptophan deprivation. GCN2 activation by tryptophan depletion induces apoptosis and mitigates T cell proliferation. GCN2 is a key effector signaling component for IDO/TDO and is considered as a metabolic checkpoint of highly tryptophan-dependent T-cells.

[0012] The GCN2 pathway is not only important for tumoral immune escape but also plays an active role in modulating other aspects of the tumor microenvironment. GCN2 knockdown has been

demonstrated to prevent amino acid deprivation (AAD)-induced expression of Vascular Endothelial Growth Factor (VEGF) which tumors use to enhance nutrient supply via increased vascularization. Thus, activation of the GCN2/ATF4 pathway promotes tumor growth and angiogenesis through AAD-mediated VEGF expression. Abrogation of ATF4 or GCN2 expression significantly inhibited tumor growth in vivo.

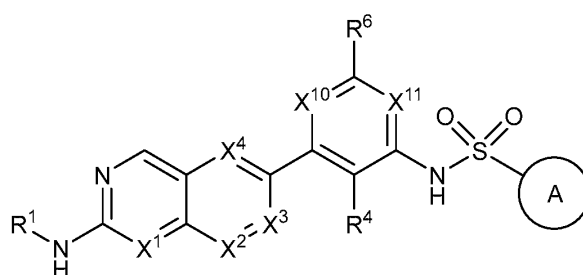
[0013] Therefore, selective inhibition of GCN2 can both increase the activity of the immune system and decrease vascularization in the tumor microenvironment. The GCN2-eIF2 α -ATF4 pathway is critical for maintaining metabolic homeostasis in tumor cells under conditions of stress, and for maintaining an immunosuppressed immune cell microenvironment. The PERK-ATF4 pathway is also critical for maintaining homeostasis in tumors cells under conditions of stress. It has been reported that there is cross talk regulation of both the GCN2 and PERK signaling pathways, such that inhibition of GCN2 can activate PERK as a compensatory mechanism, and vice versa, that inhibition of PERK an activate GCN2 as a compensatory mechanism.

[0014] There is a need for inhibitors of GCN2 and/or PERK that block the pro-tumoral aspects of GCN2 and/or PERK, both in the tumor cell (tumor cell autonomous) and in the tumor immune cell microenvironment.

SUMMARY

[0015] Described herein are compounds which display inhibitory activity of the GCN2 (general control nonderepressible 2) kinase and/or PERK (PKR-like ER kinase) kinase and methods of use thereof for the treatment of disorders, including GCN2 or PERK associated diseases.

[0016] In one embodiment, described herein is a compound represented by Formula I:

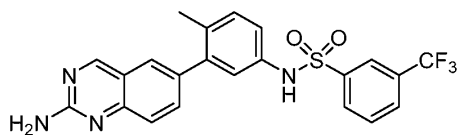


Formula I

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

X¹ is selected from the group consisting of CH and N; X² and X³ are each independently selected from the group consisting of N, CH, C-O-L²-E², C-L²-E², and C-N(R²)-L²-E², provided that X² is selected from the group consisting of CH and N, and X³ is selected from the group consisting of CH, C-O-L²-E², C-L²-E², and C-N(R²)-L²-E²; provided that X² is selected from the group consisting of

CH, C-O-L²-E², C-L²-E², and C-N(R²)-L²-E² and X³ is selected from the group consisting of CH and N; X⁴ is selected from the group consisting of CR³ and N; X¹⁰ is selected from the group consisting of CR⁵ and N; X¹¹ is selected from the group consisting of CR⁷ and N; R¹ is selected from the group consisting of H, alkyl, (C=O)R¹³, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; R² is selected from the group consisting of H and alkyl; R³ is selected from the group consisting of H, alkyl, and halogen; R⁴ and R⁵ are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN; R⁶ and R⁷ are each independently selected from the group consisting of halogen, H, and alkyl; R¹³ is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; A is selected from the group consisting of a substituted 5-membered heteroaryl, a substituted 6-membered heteroaryl, a pyridone, and a substituted aryl ring; L² is selected from the group consisting of a direct bond and alkyl, wherein alkyl is optionally substituted with (E²¹)_p; E² is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl, wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent 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, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and each p is independently 0, 1 or 2; provided that the compound is not:



[0017] In another embodiment, described herein is a pharmaceutical composition comprising a compound described herein (e.g., a compound of Formula I described herein) and a pharmaceutically acceptable carrier or excipient.

5 **[0018]** In another embodiment, described herein is a method of treating a disease caused by a dysregulation of an integrated stress response in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof, or of a pharmaceutical composition described herein.

[0019] In another embodiment, described herein is a method of treating a disease caused by a
 10 dysregulation of an integrated stress response and/or an unfolded protein response in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof, or of a pharmaceutical composition described herein.

[0020] In another embodiment, described herein is a method of modulating the activity of GCN2
 15 kinase in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof, or of a pharmaceutical composition described herein.

[0021] In another embodiment, described herein is a method of activating GCN2 kinase in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a
 20 compound described herein, or a pharmaceutically acceptable salt thereof, or of a pharmaceutical composition described herein.

[0022] In another embodiment, described herein is a method of modulating the activity of PERK kinase in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof, or of a
 25 pharmaceutical composition described herein.

[0023] In another embodiment, described herein is a method of activating PERK kinase in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof, or of a pharmaceutical composition described herein.

30 **[0024]** In another embodiment, described herein is a method of inhibiting GCN2 kinase and inhibiting PERK kinase in a patient in need thereof, comprising administering to the patient a

therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof, or of a pharmaceutical composition described herein.

[0025] In another embodiment, described herein is a method of modulating the activity of GCN2 kinase in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof, or of a pharmaceutical composition described herein.

[0026] In another embodiment, described herein is a method of inhibiting the activity of PERK kinase in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof, or of a pharmaceutical composition described herein.

[0027] In another embodiment, described herein is a method of treating a disease selected from a GCN2 associated disease and a PERK associated disease, in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof, or of a pharmaceutical composition described herein.

[0028] In another embodiment, described herein is a method of treating a disease selected from a GCN2 associated disease and a PERK associated disease, in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof, and a therapeutically effective amount of one or more therapeutic agents.

[0029] 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 Formula I described herein) or a pharmaceutically acceptable salt thereof, or pharmaceutical composition described herein.

[0030] In another embodiment, described herein is a method of treating a disorder selected from the group consisting of melanoma, fibrosarcoma, thyroid cancer, ovarian cancer, colon cancer, pancreatic cancer, lung cancer, bladder cancer, gastrointestinal stromal tumors, solid tumors, blood-borne cancers, acute myelogenous leukemia (AML), acute lymphoblastic leukemia (ALL) and other cancers caused by activation of the GCN2 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 Formula I described herein) or a pharmaceutically acceptable salt thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

[0031] Figure 1 depicts a graph of the stimulation of cellular ATF4 in H929 multiple myeloma cells induced by Compound 16.

5 [0032] Figure 2 depicts a plot of PERK oligomer stimulation by Compound 16 in an HEK293T NanoBRET based assay.

[0033] Figure 3 depicts stimulation PERK downstream signaling proteins ATF4 and CHOP with actin as a loading control. The figure shows that Compound 16 increases expression of the PERK signaling pathway in H929 multiple myeloma cells as detected Western blot analysis.

10 [0034] Figure 4 depicts fold increases (compared to DMSO control) in expression of PERK pathway target genes ATF4, CHOP, GADD34, GPT2, and VEGFA by Compound 16 in H929 multiple myeloma cells using qRT-PCR analysis.

[0035] Figure 5 illustrates effects of Compound 16 as a single agent on apoptotic pathway readouts in H929 multiple myeloma cells using Western blot analysis, including cleaved PARP, cleaved Caspase 7, and cleaved Caspase 3.

15 [0036] Figures 6A, 6B, 6C, and 6D show effects of Compound 16, as a single agent and in combination with standard of care treatment, on cell proliferation of RPMI8226 multiple myeloma cells (Figure 6A), H929 multiple myeloma cells (Figure 6B), GA-10 Burkitts lymphoma cells (Figure 6C), and DOHH-2 follicular lymphoma cells (Figure 6D).

20 [0037] Figures 7A and 7B show effects of Compound 16 in combination with asparaginase on ATF4 levels, measuring GCN2 activity, in an in vivo PK/PD model using Western blot analysis. Corresponding plasma levels of Compound 16 were determined at the PD time points of 2, 6, and 10 hours post dose. Figure 7A shows data plots of results obtained from the PK/PD model studies and Figure 7B depicts results in tabular form.

25 [0038] Figure 8 depicts a plot showing the effect of Compound 16 in combination with asparaginase on tumor growth in an MV-4-11 xenograft model.

DETAILED DESCRIPTION

[0039] The features and other details of the disclosure are more particularly described below. 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.

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Definitions

[0040] The definitions set forth in this application are intended to clarify terms used throughout this application.

[0041] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the 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.

[0042] 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 if such combinations result in stable compounds.

[0043] As used herein, the singular forms "a", "an" and "the" encompass plural references unless the context clearly indicates otherwise.

[0044] As used herein, the term "herein" means the entire application.

[0045] 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.

[0046] 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.

[0047] 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.

[0048] 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: hydroxy, 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.

[0049] 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.

[0050] Substituents can include any substituents described herein, for example, such substituents, if not otherwise specified, can include, for example, a halogen, a hydroxy, a carbonyl (such as a carboxyl, an alkoxy carbonyl, a formyl, or an acyl), an alkoxy, an amino, an amido, an imine, a cyano, 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, amido, sulfonyl and as well as ethers, carbonyls (including 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.

[0051] 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.

[0052] The term "Cx-Cy" 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 "Cx-Cy" 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.

[0053] 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.

[0054] 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-

[0055] 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.

[0056] 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).

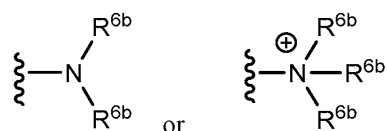
[0057] As used herein, the term "aryl" includes substituted or unsubstituted single-ring aromatic groups in which each atom of the ring is carbon. Preferably the ring is a 5- to 7-membered ring, more

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, indanyl, dihydrobenzofuranyl, dihydroisobenzofuranyl, indolinyl, isoindolinyl, and the like. Unless otherwise specified, aryl groups described herein may be optionally substituted.

10 **[0058]** 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.

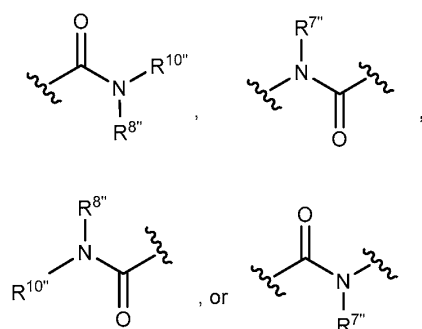
15 **[0059]** As used herein, the term "acyl" refers to a group $-C(=O)-R_w$ wherein R_w is optionally substituted alkyl. Examples of "acyl" include, but are not limited to, instances where R_w is C1-C10alkyl (C1-C10acyl) or C1-C6-alkyl (C1-C6acyl). In some embodiments, each occurrence of the optionally substituted substituent is independently selected from the group consisting of H, OH, alkoxy, cyano, F, and amino. Additional examples of "acyl" include $-C(=O)-CH_3$, $-C(=O)-CH_2-$
 20 CH_3 , $-C(=O)-CH_2-CH_2-CH_3$, or $-C(=O)-CH(CH_3)_2$.

[0060] 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:



wherein R^{6b} independently represent a hydrogen, alkyl or a cycloalkyl group, or R^{6b} 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.

[0061] As used herein, the terms "amide" and "amido" refers to a group represented by



wherein $R^{7''}$, $R^{8''}$, and $R^{10''}$ each independently represents a hydrogen or hydrocarbyl group, or $R^{8''}$ and $R^{10''}$ are taken together with the N atom to which they are attached complete a heterocyclyl having from 4 to 8 atoms in the ring structure.

[0062] As used herein, the term "acylamino" refers to an amino group, as defined above, substituted with an acyl group.

[0063] As used herein, the term "aminocarbonyl" refers to a carbonyl group substituted with an amino group.

10 [0064] As used herein, the term "alkylamino" refers to an amino group, as defined above, substituted with at least one alkyl group.

[0065] As used herein, the term "aminoalkyl" refers to an alkyl group substituted with an amino group.

15 [0066] As used herein, the term "amidoalkyl" refers to an alkyl group substituted with an amido group.

[0067] As used herein, the term "cyanoalkyl" refers to an alkyl group substituted with a cyano group.

20 [0068] As used herein, the term "cycloalkoxyalkyl" refers to an alkyl group (as defined above) substituted with a cycloalkoxy group and may be represented by the general formula cycloalkyl-O-alkyl. Examples of cycloalkoxyalkyl groups include but are not limited to cyclopropyl-O-methylene-, cyclopropyl-O-ethylene.

[0069] As used herein, the term "heteroarylalkyl" refers to an alkyl group substituted with heteroaryl group.

25 [0070] As used herein, the term "heterocyclylalkyl" refers to an alkyl group substituted with a heterocyclyl group.

[0071] As used herein, the term "hydroxyalkyl" refers to an alkyl group substituted with a hydroxy group.

[0072] 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. Cycloalkyls can be further substituted with alkyls, alkenyls, alkoxys, aminoalkyls, carbonyl-substituted alkyls, -CF₃, -CN, and the like.

[0073] As used herein, the term "cycloalkylalkyl" refers to an alkyl group substituted with a cycloalkyl group.

[0074] As used herein, the term "cyano" refers to -CN group.

[0075] As used herein, the term "hydroxy" or "hydroxyl" refers to -OH group.

[0076] As used herein, the term "halo" or "halogen" alone or in combination with other term(s) means chloro, fluoro, bromo, and iodo.

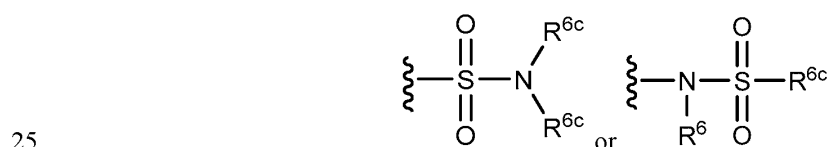
[0077] As used herein, the term "heteroatom" refers an atom of any element other than carbon or hydrogen. Exemplary heteroatoms are nitrogen (N), oxygen (O), sulfur (S), and silicon (Si).

[0078] 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 "heterocycloalkyl" 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 "heterocycloalkyl" refers to 5- to 6-membered ring selected from the group consisting of azetidiny, oxetanyl, imidazolidiny, pyrrolidiny, oxazolidiny, thiazolidiny, pyrazolidiny, tetrahydrofuranyl, piperidiny, piperaziny, tetrahydropyranyl, morpholiny, thiomorpholiny, 1,4-dioxanyl and N-

oxides thereof. More preferably, "heterocycloalkyl" includes azetidiny, pyrrolidinyl, morpholinyl and piperidinyl. Heterocycloalkyl are optionally substituted by one or more aforesaid groups.

[0079] 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, heteroaryls, and/or heterocyclyls. 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 heteroaryls 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, cinnolinyl, isoxazolyl, thiazolyl, isothiazolyl, 1H-tetrazolyl, oxadiazolyl, thiadiazolyl, triazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzofuranyl, benzothienyl, benzotriazinyl, phthalazinyl, thianthrene, dibenzofuranyl, dibenzothienyl, benzimidazolyl, indolyl, isoindolyl, indazolyl, quinolyl, isoquinolyl, quinazolinyl, quinoxalyl, purinyl, pteridinyl, 9H-carbazolyl, alpha-carboline, indolizyl, benzoisothiazolyl, benzoxazolyl, pyrrolopyridyl, furopyridinyl, purinyl, benzothiadiazolyl, benzoxadiazolyl, benzotriazolyl, benzotriadiazolyl, carbazolyl, dibenzothienyl, acridinyl and the like.

[0080] As used herein, the term "sulfonamide" is represented by:



wherein R^{6c} , at each occurrence, independently represents a hydrogen, alkyl or cycloalkyl group, or R^{6c} 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.

[0081] As used herein, the terms "sulfonyl" refers to the group $\text{-S(O)}_2\text{-R}^{6d}$ wherein R^{6d} represents alkyl or cycloalkyl.

30

[0082] A “combination therapy” is a treatment that includes the administration of two or more therapeutic agents, e.g., a compound of Formula I and the enzyme asparaginase (ASNase) or a derivative thereof, to a patient in need thereof.

[0083] “Disease,” “disorder,” and “condition” are used interchangeably herein.

5 [0084] “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
10 animals (e.g., cows, sheep, pigs, horses, and the like) and laboratory animals (e.g., rats, mice, guinea pigs, and the like).

[0085] The compounds described herein are useful for the treatment of diseases driven by GCN2 (sometimes to be abbreviated as “GCN2 associated disease” in the present specification), for example, cancer [e.g., colorectal cancer (e.g., colorectal cancer, rectal cancer, anal cancer, familial
15 colorectal cancer, hereditary nonpolyposis colorectal cancer, gastrointestinal stromal tumor), lung cancer (e.g., non-small cell lung cancer, small cell lung cancer, malignant mesothelioma), mesothelioma, pancreatic cancer (e.g., pancreatic duct cancer, pancreatic endocrine tumor), pharyngeal cancer, laryngeal cancer, esophagus cancer, gastric cancer (e.g., papillary adenocarcinoma, mucinous adenocarcinoma, adenosquamous carcinoma), duodenal cancer, small
20 intestinal cancer, breast cancer (e.g., invasive ductal carcinoma, ductal carcinoma in situ, inflammatory breast cancer), ovarian cancer (e.g., ovarian epithelial carcinoma, extragonadal germ cell tumor, ovarian germ cell tumor, ovarian low malignant potential tumor), testis tumor, prostate cancer (e.g., hormone-dependent prostate cancer, non-hormone dependent prostate cancer, castration-resistant prostate cancer), liver cancer (e.g., hepatoma, primary liver cancer, extrahepatic
25 bile duct cancer), thyroid cancer (e.g., medullary thyroid carcinoma), renal cancer (e.g., renal cell carcinoma (e.g., clear cell renal cell carcinoma), transitional cell carcinoma of renal pelvis and ureter), uterine cancer (e.g., cervical cancer, uterine body cancer, uterus sarcoma), gestational choriocarcinoma, brain tumor (e.g., medulloblastoma, glioma, pineal astrocytoma, pilocytic astrocytoma, diffuse astrocytoma, anaplastic astrocytoma, hypophyseal adenoma), retina blastoma,
30 skin cancer (e.g., basal cell carcinoma, malignant melanoma (melanoma)), sarcoma (e.g., rhabdomyosarcoma, leiomyosarcoma, soft tissue sarcoma, spindle cell sarcoma, osteosarcoma), malignant bone tumor, urinary bladder cancer, hematologic cancer (e.g., multiple myeloma, leukemia (e.g., acute myeloid leukemia, acute lymphocytic leukemia (including blast crisis of chronic leukemia))), malignant lymphoma, Hodgkin's disease, chronic myeloproliferative disease),

cancer of unknown primary nucleus], cancer growth inhibitor, cancer metastasis inhibitor, apoptosis promoter, and for the prophylaxis or treatment of precancerous lesion (e.g., bone marrow myelodysplastic syndrome).

[0086] The compounds described herein, e.g., a compound of Formula I as defined herein, may be used in combination with one or more additional therapeutic agents to treat a disorder described herein, such as a cancer described herein. In some embodiments, the compounds described herein may be used in combination with hormonal therapeutic agents, chemotherapeutic agents, immunotherapeutic agents, medicaments inhibiting actions of cell growth factor and receptor thereof, such as PERK inhibitors and autophagy inhibitors, the enzyme asparaginase (ASNase), and the like.

[0087] “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.

[0088] 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.

[0089] 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.

[0090] 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, glucuronate, 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.

[0091] 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 symbol “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.

[0092] 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.

[0093] “Treating” includes any effect, e.g., lessening, reducing, modulating, or eliminating, that results in the improvement of the condition, disease, disorder and the like.

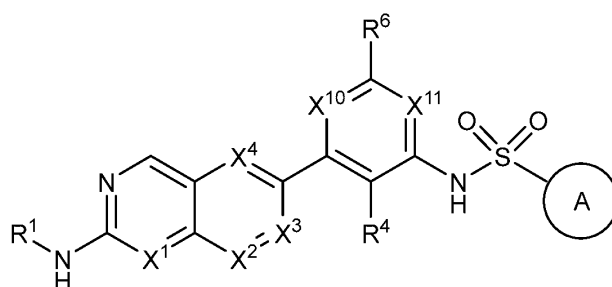
[0094] The disclosure also embraces isotopically labeled compounds which are identical to those recited herein, except that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into the disclosed compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine and chlorine, such as ²H, ³H, ¹³C, ¹⁴C, ¹⁵N, ¹⁸O, ¹⁷O, ³¹P, ³²P, ³⁵S, ¹⁸F, and ³⁶Cl, respectively. For example, a compound of the disclosure may have one or more H atom replaced with deuterium.

[0095] 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.

Compounds

- [0096]** In one embodiment, described herein is a compound represented by Formula I:



Formula I

- or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein: X¹ is selected from the group consisting of CH and N; X² and X³ are each independently selected from the group consisting of N, CH, C-O-L²-E², C-L²-E², and C-N(R²)-L²-E², provided that X² is selected from the group consisting of CH and N, and X³ is selected from the group consisting of CH, C-O-L²-E², C-L²-E², and C-N(R²)-L²-E²; provided that X² is selected from the group consisting of CH, C-O-L²-E², C-L²-E², and C-N(R²)-L²-E² and X³ is selected from the group consisting of CH and N; X⁴ is selected from the group consisting of CR³ and N; X¹⁰ is selected from the group consisting of CR⁵ and N; X¹¹ is selected from the group consisting of CR⁷ and N; R¹ is selected from the group consisting of H, alkyl, (C=O)R¹³, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl,

heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and wherein

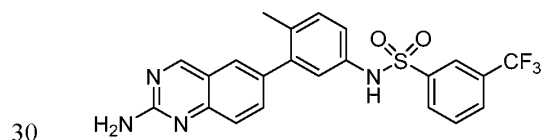
5 heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; R² is selected from the group consisting of H and alkyl; R³ is selected from the group consisting of H, alkyl, and halogen; R⁴ and R⁵ are each independently selected from the group consisting of halogen,

10 H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN; R⁶ and R⁷ are each independently selected from the group consisting of halogen, H, and alkyl; R¹³ is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl,

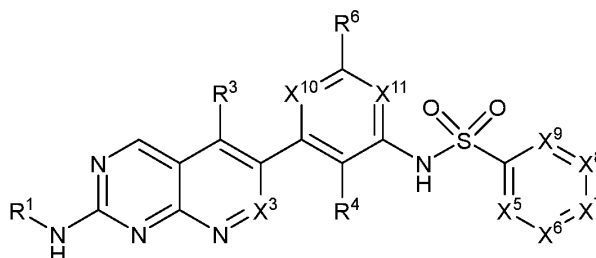
15 alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; A is selected from the group consisting of a substituted 5-

20 membered heteroaryl, a substituted 6-membered heteroaryl, a pyridone, and a substituted aryl ring; L² is selected from the group consisting of a direct bond and alkyl, wherein alkyl is optionally substituted with (E²¹)_p; E² is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl, wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent

25 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, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and each p is independently 0, 1 or 2; provided that the compound is not:



[0097] In some embodiments, the compound is represented by Formula I-A:

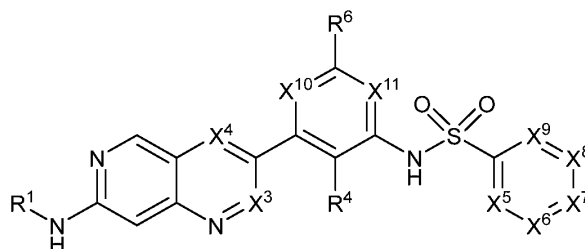


Formula I-A

- 5 or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein: X³ is selected from the group consisting of CH, C-O-L²-E², C-L²-E², and C-N(R²)-L²-E²; X⁵ is selected from the group consisting of CR⁸ and N; X⁶ is selected from the group consisting of CR⁹ and N; X⁷ is selected from the group consisting of CR¹⁰ and N; X⁸ is selected from the group consisting of CR¹¹ and N; X⁹ is selected from the group consisting of CR⁸ and N, provided that not more than three of
- 10 X⁵, X⁶, X⁷, X⁸, and X⁹ is N; X¹⁰ is selected from the group consisting of CR⁵ and N; X¹¹ is selected from the group consisting of CR⁷ and N; R¹ is selected from the group consisting of H, alkyl, (C=O)R¹³, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of
- 15 haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; R² is selected from the group
- 20 consisting of H and alkyl; R³ is selected from the group consisting of H, alkyl, and halogen; R⁴ and R⁵ are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN; R⁶ and R⁷ are each independently selected from the group consisting of halogen, H, and alkyl; R⁸ is selected from the group consisting of alkoxy, alkylamino, cycloalkoxy, cycloalkylamino, halogen, H, alkyl, haloalkoxy, haloalkyl, amide, alkoxycarbonyl, hydroxyalkyl, hydroxy, and CN; R⁹, R¹⁰ and R¹¹ are each independently selected from the group
- 25 consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, cycloalkoxy, cycloalkylamino, haloalkyl, heterocyclyl, alkoxycarbonyl, and

heterocyclalkyl; R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocycl, heterocyclalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocycl, and wherein heterocycl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; L^2 is selected from the group consisting of a direct bond and C_1 - C_6 alkyl, wherein C_1 - C_6 alkyl is optionally substituted with $(E^{21})_p$; E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocycl, wherein heterocycl is optionally substituted with one or more occurrences of a substituent 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, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and each p is independently 0, 1 or 2.

[0098] In some embodiments, the compound is represented by Formula I-B:

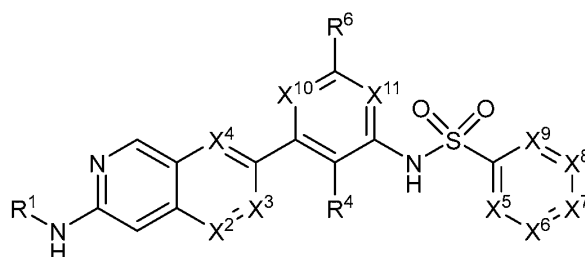


Formula I-B

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein: X^3 is selected from the group consisting of CH, $C-O-L^2-E^2$, $C-L^2-E^2$, and $C-N(R^2)-L^2-E^2$; X^4 is selected from the group consisting of CR^3 and N; X^5 is selected from the group consisting of CR^8 and N; X^6 is selected from the group consisting of CR^9 and N; X^7 is selected from the group consisting of CR^{10} and N; X^8 is selected from the group consisting of CR^{11} and N; X^9 is selected from the group consisting of CR^8 and N, provided that not more than three of X^5 , X^6 , X^7 , X^8 , and X^9 is N; X^{10} is selected from the group consisting of CR^5 and N; X^{11} is selected from the group consisting of CR^7 and N; R^1 is selected from the group consisting of H, alkyl, $(C=O)R^{13}$, cycloalkyl, alkoxyalkyl,

cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; R² is selected from the group consisting of H and alkyl; R³ is selected from the group consisting of H, alkyl, and halogen; R⁴ and R⁵ are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN; R⁶ and R⁷ are each independently selected from the group consisting of halogen, H, and alkyl; R⁸ is selected from the group consisting of alkoxy, alkylamino, cycloalkoxy, cycloalkylamino, halogen, H, alkyl, haloalkoxy, haloalkyl, amide, alkoxy carbonyl, hydroxyalkyl, hydroxy, and CN; R⁹, R¹⁰ and R¹¹ are each independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxy cycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, cycloalkoxy, cycloalkylamino, haloalkyl, heterocyclyl, alkoxy carbonyl, and heterocyclylalkyl; R¹³ is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; L² is selected from the group consisting of a direct bond and C₁-C₆alkyl, wherein C₁-C₆alkyl is optionally substituted with (E²¹)_p; E² is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl, wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent 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, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and each p is independently 0, 1 or 2.

[0099] In some embodiments, the compound is represented by Formula I-C:



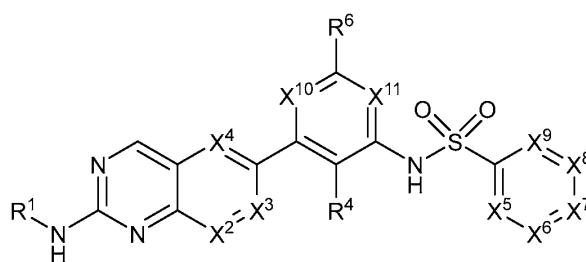
Formula I-C

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

- 5 X² and X³ are each independently selected from the group consisting of N, CH, C-O-L²-E², C-L²-E², and C-N(R²)-L²-E², provided that X² is selected from the group consisting of CH and N, and X³ is selected from the group consisting of CH, C-O-L²-E², C-L²-E², and C-N(R²)-L²-E²; provided that X² is selected from the group consisting of CH, C-O-L²-E², C-L²-E², and C-N(R²)-L²-E² and X³ is selected from the group consisting of CH and N; X⁴ is selected from the group consisting of CR³ and N; X⁵ is selected from the group consisting of CR⁸ and N; X⁶ is selected from the group consisting of CR⁹ and N; X⁷ is selected from the group consisting of CR¹⁰ and N; X⁸ is selected from the group consisting of CR¹¹ and N; X⁹ is selected from the group consisting of CR⁸ and N, provided that not more than three of X⁵, X⁶, X⁷, X⁸, and X⁹ is N; X¹⁰ is selected from the group consisting of CR⁵ and N; X¹¹ is selected from the group consisting of CR⁷ and N; R¹ is selected from the group consisting of H, alkyl, (C=O)R¹³, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; R² is selected from the group consisting of H and alkyl; R³ is selected from the group consisting of H, alkyl, and halogen; R⁴ and R⁵ are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN; R⁶ and R⁷ are each independently selected from the group consisting of halogen, H, and alkyl; R⁸ is selected from the group consisting of alkoxy, alkylamino, cycloalkoxy, cycloalkylamino, halogen, H, alkyl, haloalkoxy, haloalkyl, amide, alkoxyalkyl, hydroxyalkyl, hydroxy, and CN; R⁹, R¹⁰ and R¹¹ are each independently selected from the group

consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxy-cycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, cycloalkoxy, cycloalkylamino, haloalkyl, heterocycl-yl, alkoxy-carbonyl, and heterocycl-ylalkyl; R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocycl-yl, heterocycl-ylalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocycl-yl, and wherein heterocycl-yl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; L^2 is selected from the group consisting of a direct bond and C_1 - C_6 alkyl, wherein C_1 - C_6 alkyl is optionally substituted with $(E^{21})_p$; E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocycl-yl, wherein heterocycl-yl is optionally substituted with one or more occurrences of a substituent 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, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and each p is independently 0, 1 or 2.

[0100] In some embodiments, the compound is represented by Formula I-D:



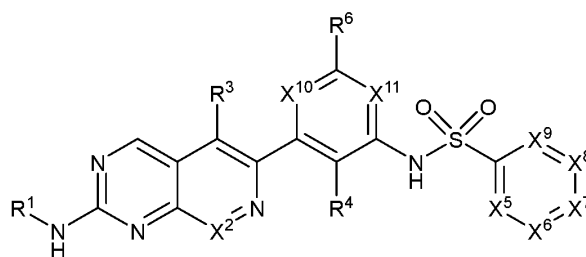
Formula I-D

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:
 X^2 and X^3 are each independently selected from the group consisting of N, CH, $C-O-L^2-E^2$, $C-L^2-E^2$, and $C-N(R^2)-L^2-E^2$, provided that X^2 is selected from the group consisting of CH and N, and X^3 is selected from the group consisting of CH, $C-O-L^2-E^2$, $C-L^2-E^2$, and $C-N(R^2)-L^2-E^2$; provided that X^2 is selected from the group consisting of CH, $C-O-L^2-E^2$, $C-L^2-E^2$, and $C-N(R^2)-L^2-E^2$ and X^3 is

selected from the group consisting of CH and N; X⁴ is selected from the group consisting of CR³ and N; X⁵ is selected from the group consisting of CR⁸ and N; X⁶ is selected from the group consisting of CR⁹ and N; X⁷ is selected from the group consisting of CR¹⁰ and N; X⁸ is selected from the group consisting of CR¹¹ and N; X⁹ is selected from the group consisting of CR⁸ and N, provided that not more than three of X⁵, X⁶, X⁷, X⁸, and X⁹ is N; X¹⁰ is selected from the group consisting of CR⁵ and N; X¹¹ is selected from the group consisting of CR⁷ and N; R¹ is selected from the group consisting of H, alkyl, (C=O)R¹³, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; R² is selected from the group consisting of H and alkyl; R³ is selected from the group consisting of H, alkyl, and halogen; R⁴ and R⁵ are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN; R⁶ and R⁷ are each independently selected from the group consisting of halogen, H, and alkyl; R⁸ is selected from the group consisting of alkoxy, alkylamino, cycloalkoxy, cycloalkylamino, halogen, H, alkyl, haloalkoxy, haloalkyl, amide, alkoxycarbonyl, hydroxyalkyl, hydroxy, and CN; R⁹, R¹⁰ and R¹¹ are each independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxy-cycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, cycloalkoxy, cycloalkylamino, haloalkyl, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl; R¹³ is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; L² is selected from the group consisting of a direct bond and C₁-C₆alkyl, wherein C₁-C₆alkyl is optionally substituted with (E²¹)_p; E² is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy,

haloalkyl, and heterocyclyl, wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent 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, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and each p is independently 0, 1 or 2.

[0101] In some embodiments, the compound is represented by Formula I-E:

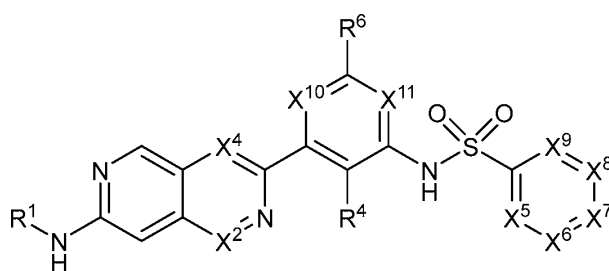


Formula I-E

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein: X² is selected from the group consisting of CH, C-O-L²-E², C-L²-E², and C-N(R²)-L²-E²; X⁵ is selected from the group consisting of CR⁸ and N; X⁶ is selected from the group consisting of CR⁹ and N; X⁷ is selected from the group consisting of CR¹⁰ and N; X⁸ is selected from the group consisting of CR¹¹ and N; X⁹ is selected from the group consisting of CR⁸ and N, provided that not more than three of X⁵, X⁶, X⁷, X⁸, and X⁹ is N; X¹⁰ is selected from the group consisting of CR⁵ and N; X¹¹ is selected from the group consisting of CR⁷ and N; R¹ is selected from the group consisting of H, alkyl, (C=O)R¹³, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; R² is selected from the group consisting of H and alkyl; R³ is selected from the group consisting of H, alkyl, and halogen; R⁴ and R⁵ are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN; R⁶ and R⁷ are each independently selected from the group consisting of halogen, H, and alkyl; R⁸ is selected from the group consisting of alkoxy, alkylamino,

cycloalkoxy, cycloalkylamino, halogen, H, alkyl, haloalkoxy, haloalkyl, amide, alkoxycarbonyl, hydroxyalkyl, hydroxy, and CN; R⁹, R¹⁰ and R¹¹ are each independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxy cycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, cycloalkoxy, cycloalkylamino, haloalkyl, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl; R¹³ is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; L² is selected from the group consisting of a direct bond and C₁-C₆alkyl, wherein C₁-C₆alkyl is optionally substituted with (E²¹)_p; E² is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl, wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent 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, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and each p is independently 0, 1 or 2.

[0102] In some embodiments, the compound is represented by Formula I-F:



Formula I-F

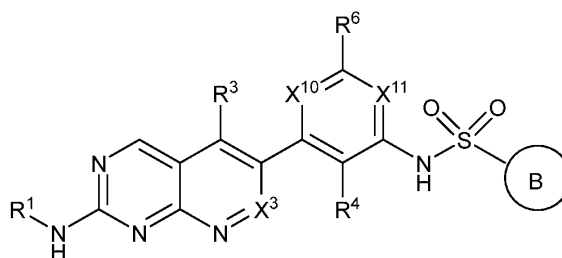
or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein: X² is selected from the group consisting of CH, C-O-L²-E², C-L²-E², and C-N(R²)-L²-E²; X⁴ is selected from the group consisting of CR³ and N; X⁵ is selected from the group consisting of CR⁸

and N; X⁶ is selected from the group consisting of CR⁹ and N; X⁷ is selected from the group consisting of CR¹⁰ and N; X⁸ is selected from the group consisting of CR¹¹ and N; X⁹ is selected from the group consisting of CR⁸ and N, provided that not more than three of X⁵, X⁶, X⁷, X⁸, and X⁹ is N; X¹⁰ is selected from the group consisting of CR⁵ and N; X¹¹ is selected from the group consisting of CR⁷ and N; R¹ is selected from the group consisting of H, alkyl, (C=O)R¹³, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; R² is selected from the group consisting of H and alkyl; R³ is selected from the group consisting of H, alkyl, and halogen; R⁴ and R⁵ are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN; R⁶ and R⁷ are each independently selected from the group consisting of halogen, H, and alkyl; R⁸ is selected from the group consisting of alkoxy, alkylamino, cycloalkoxy, cycloalkylamino, halogen, H, alkyl, haloalkoxy, haloalkyl, amide, alkoxy carbonyl, hydroxyalkyl, hydroxy, and CN; R⁹, R¹⁰ and R¹¹ are each independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxy cycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, cycloalkoxy, cycloalkylamino, haloalkyl, heterocyclyl, alkoxy carbonyl, and heterocyclalkyl; R¹³ is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; L² is selected from the group consisting of a direct bond and C₁-C₆alkyl, wherein C₁-C₆alkyl is optionally substituted with (E²¹)_p; E² is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl, wherein heterocyclyl is optionally substituted with one or more occurrences of a

substituent 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, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and each p is

5 independently 0, 1 or 2.

[0103] 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:

- 10 X³ is selected from the group consisting of CH, C-O-L²-E², C-L²-E², and C-N(R²)-L²-E²; X¹⁰ is selected from the group consisting of CR⁵ and N; X¹¹ is selected from the group consisting of CR⁷ and N; R¹ is selected from the group consisting of H, alkyl, (C=O)R¹³, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a
- 15 substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; R² is selected from the group consisting of H and alkyl; R³ is selected from the group consisting of H, alkyl, and halogen; R⁴ and R⁵ are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN; R⁶ and R⁷ are each independently selected from the group consisting of halogen, H, and alkyl; R¹² is individually and independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl,
- 20 alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, haloalkyl, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, and heterocyclylalkyl; R¹³ is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl,
- 25

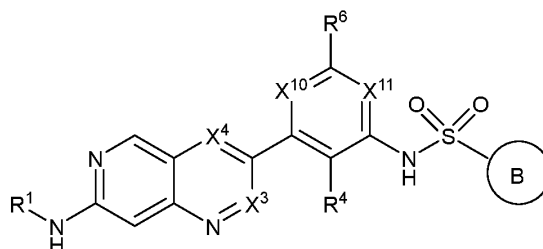
heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and wherein heterocyclyl is optionally substituted with one or more

5 occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; B is selected from the group consisting of a five-membered heteroaryl, a six-membered heteroaryl, and a pyridone, wherein the five- or six-membered heteroaryl ring, or the pyridone is optionally substituted by R^{12} at each substitutable position; L^2 is selected

10 from the group consisting of a direct bond and C_1 - C_6 alkyl, wherein C_1 - C_6 alkyl is optionally substituted with $(E^{21})_p$; E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl, wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl,

15 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, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and each p is independently 0, 1 or 2.

[0104] In some embodiments, the compound is represented by Formula I-H:



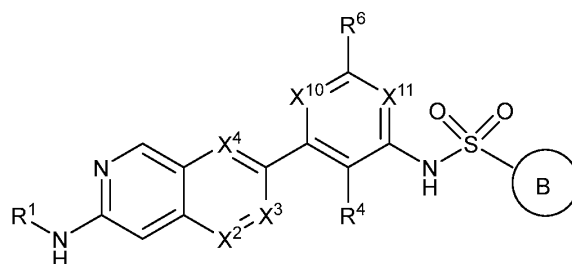
Formula I-H

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein: X^3 is selected from the group consisting of CH, C-O- L^2 - E^2 , C- L^2 - E^2 , and C-N(R^2)- L^2 - E^2 ; X^4 is selected from the group consisting of CR³ and N; X^{10} is selected from the group consisting of CR⁵ and N; X^{11} is selected from the group consisting of CR⁷ and N; R^1 is selected from the group

25 consisting of H, alkyl, (C=O) R^{13} , cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide,

acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; R² is
5 selected from the group consisting of H and alkyl; R³ is selected from the group consisting of H, alkyl, and halogen; R⁴ and R⁵ are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN; R⁶ and R⁷ are each independently selected from the group consisting of halogen, H, and alkyl; R¹² is individually and independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxyalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, haloalkyl, alkoxy,
10 alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, and heterocyclylalkyl; R¹³ is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a
15 substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano,
20 cyanoalkyl, and sulfonyl; B is selected from the group consisting of a five-membered heteroaryl, a six-membered heteroaryl, and a pyridone, wherein the five- or six-membered heteroaryl ring, or the pyridone, is optionally substituted by R¹² at each substitutable position; L² is selected from the group consisting of a direct bond and C₁-C₆alkyl, wherein C₁-C₆alkyl is optionally substituted with (E²¹)_p; E² is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl,
25 H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl, wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent 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, cyanoalkyl, haloalkoxy, haloalkyl,
30 hydroxy, hydroxyalkyl, and halogen; and each p is independently 0, 1 or 2.

[0105] In some embodiments, the compound is represented by Formula I-J:

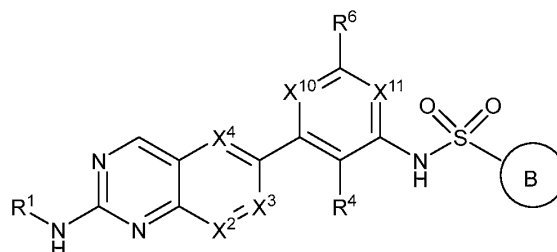


Formula I-J

- or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:
- 5 X² and X³ are each independently selected from the group consisting of N, CH, C-O-L²-E², C-L²-E², and C-N(R²)-L²-E², provided that X² is selected from the group consisting of CH and N, and X³ is selected from the group consisting of CH, C-O-L²-E², C-L²-E², and C-N(R²)-L²-E²; provided that X² is selected from the group consisting of CH, C-O-L²-E², C-L²-E², and C-N(R²)-L²-E² and X³ is selected from the group consisting of CH and N; X⁴ is selected from the group consisting of CR³ and N; X¹⁰ is selected from the group consisting of CR⁵ and N; X¹¹ is selected from the group consisting of CR⁷ and N; R¹ is selected from the group consisting of H, alkyl, (C=O)R¹³, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; R² is selected from the group consisting of H and alkyl; R³ is selected from the group consisting of H, alkyl, and halogen; R⁴ and R⁵ are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN; R⁶ and R⁷ are each independently selected from the group consisting of halogen, H, and alkyl; R¹² is individually and independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, haloalkyl, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, heterocyclyl, and heterocyclylalkyl; R¹³ is selected from the group consisting of H, alkyl, cycloalkyl, cycloalkoxy, cycloalkylamino, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is

optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; B is selected from the group consisting of a five-membered heteroaryl, a six-membered heteroaryl, and a pyridone, wherein the five- or six-membered heteroaryl ring, or the pyridone, is optionally substituted by R^{12} at each substitutable position; L^2 is selected from the group consisting of a direct bond and C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with $(E^{21})_p$; E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl, wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent 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, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and each p is independently 0, 1 or 2.

[0106] In some embodiments, the compound is represented by Formula I-K:

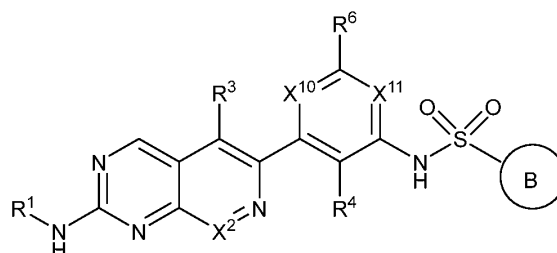


Formula I-K

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein: X^2 and X^3 are each independently selected from the group consisting of N, CH, $C-O-L^2-E^2$, $C-L^2-E^2$, and $C-N(R^2)-L^2-E^2$, provided that X^2 is selected from the group consisting of CH and N, and X^3 is selected from the group consisting of CH, $C-O-L^2-E^2$, $C-L^2-E^2$, and $C-N(R^2)-L^2-E^2$; provided that X^2 is selected from the group consisting of CH, $C-O-L^2-E^2$, $C-L^2-E^2$, and $C-N(R^2)-L^2-E^2$ and X^3 is selected from the group consisting of CH and N; X^4 is selected from the group consisting of CR^3 and N; X^{10} is selected from the group consisting of CR^5 and N; X^{11} is selected from the group consisting of CR^7 and N; R^1 is selected from the group consisting of H, alkyl, $(C=O)R^{13}$, cycloalkyl,

alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; R² is selected from the group consisting of H and alkyl; R³ is selected from the group consisting of H, alkyl, and halogen; R⁴ and R⁵ are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN; R⁶ and R⁷ are each independently selected from the group consisting of halogen, H, and alkyl; R¹² is individually and independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxyalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, haloalkyl, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, and heterocyclalkyl; R¹³ is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; B is selected from the group consisting of a five-membered heteroaryl, a six-membered heteroaryl, and a pyridone, wherein the five- or six-membered heteroaryl ring, or the pyridone, is optionally substituted by R¹² at each substitutable position; L² is selected from the group consisting of a direct bond and C₁-C₆alkyl, wherein C₁-C₆alkyl is optionally substituted with (E²¹)_p; E² is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl, wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent 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, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and each p is independently 0, 1 or 2.

[0107] In some embodiments, the compound is represented by Formula I-L:

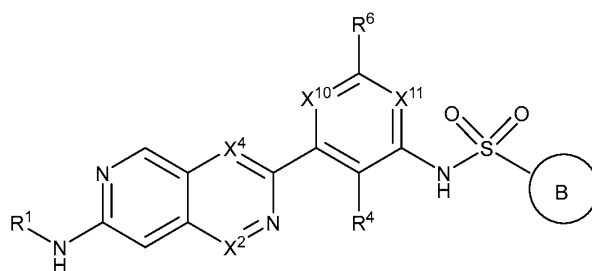


Formula I-L

- or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:
- 5 X^2 is selected from the group consisting of CH, C-O-L²-E², C-L²-E², and C-N(R²)-L²-E²; X^{10} is selected from the group consisting of CR⁵ and N; X^{11} is selected from the group consisting of CR⁷ and N; R¹ is selected from the group consisting of H, alkyl, (C=O)R¹³, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a
- 10 substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; R² is selected from the group consisting of H and alkyl; R³ is selected from the group consisting of H, alkyl, and halogen; R⁴ and R⁵ are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN; R⁶ and R⁷ are each independently selected from the group consisting of halogen, H, and alkyl; R¹² is individually and independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl,
- 20 alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, haloalkyl, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, heterocyclyl, and heterocyclylalkyl; R¹³ is selected from the group consisting of H, alkyl, cycloalkyl, cycloalkoxy, cycloalkylamino, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one
- 25 or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl,

oxo, cyano, cyanoalkyl, and sulfonyl; B is selected from the group consisting of a five-membered heteroaryl, a six-membered heteroaryl, and a pyridone, wherein the five- or six-membered heteroaryl ring, or the pyridone, is optionally substituted by R^{12} at each substitutable position; L^2 is selected from the group consisting of a direct bond and C_1 - C_6 alkyl, wherein C_1 - C_6 alkyl is optionally substituted with $(E^{21})_p$; E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl, wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent 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, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and each p is independently 0, 1 or 2.

[0108] In some embodiments, the compound is represented by Formula I-M:

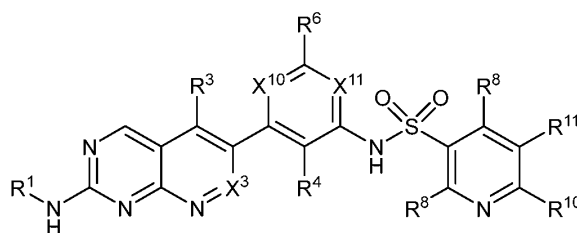


Formula I-M

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein: X^2 is selected from the group consisting of CH, C-O- L^2 - E^2 , C- L^2 - E^2 , and C-N(R^2)- L^2 - E^2 ; X^4 is selected from the group consisting of CR^3 and N; X^{10} is selected from the group consisting of CR^5 and N; X^{11} is selected from the group consisting of CR^7 and N; R^1 is selected from the group consisting of H, alkyl, $(C=O)R^{13}$, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; R^2 is selected from the group consisting of H and alkyl; R^3 is selected from the group consisting of H, alkyl, and halogen; R^4 and R^5 are each independently selected from the group consisting of halogen,

H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN; R⁶ and R⁷ are each independently selected from the group consisting of halogen, H, and alkyl; R¹² is individually and independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxyalkoxy, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, haloalkyl, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, and heterocyclylalkyl; R¹³ is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; B is selected from the group consisting of a five-membered heteroaryl, a six-membered heteroaryl, and a pyridone, wherein the five- or six-membered heteroaryl ring, or the pyridone, is optionally substituted by R¹² at each substitutable position; L² is selected from the group consisting of a direct bond and C₁-C₆alkyl, wherein C₁-C₆alkyl is optionally substituted with (E²¹)_p; E² is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl, wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent 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, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and each p is independently 0, 1 or 2.

[0109] In some embodiments, the compound is represented by Formula I-N:



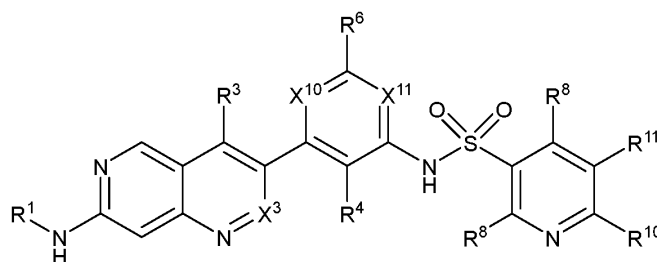
Formula I-N

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

X³ is selected from the group consisting of CH, C-O-L²-E², C-L²-E², and C-N(R²)-L²-E²; X¹⁰ is selected from the group consisting of CR⁵ and N; X¹¹ is selected from the group consisting of CR⁷ and N; R¹ is selected from the group consisting of H, alkyl, (C=O)R¹³, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; R² is selected from the group consisting of H and alkyl; R³ is selected from the group consisting of H, alkyl, and halogen; R⁴ and R⁵ are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN; R⁶ is selected from the group consisting of halogen, H, and alkyl; R⁷ is selected from the group consisting of H and F; R⁸ is selected from the group consisting of alkoxy, alkylamino, cycloalkoxy, cycloalkylamino, halogen, H, alkyl, haloalkoxy, haloalkyl, amide, alkoxy carbonyl, hydroxyalkyl, hydroxycycloalkyl, hydroxy, and CN; R¹⁰ and R¹¹ are each independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxy cycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxy carbonyl, and heterocyclalkyl; R¹³ is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; L² is selected from the group consisting of a direct bond and C₁-C₆alkyl, wherein C₁-C₆alkyl is optionally substituted with (E²¹)_p; E² is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl, wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and

cianoalkyl; E²¹, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and each p is independently 0, 1 or 2.

[0110] In some embodiments, the compound is represented by Formula I-O:



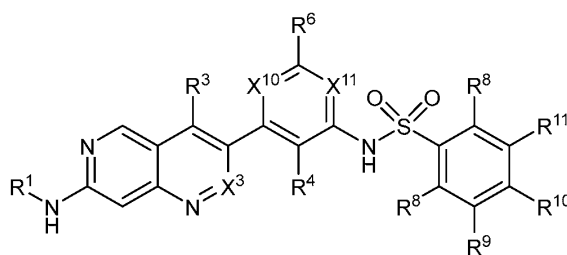
Formula I-O

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

X³ is selected from the group consisting of CH, C-O-L²-E², C-L²-E², and C-N(R²)-L²-E²; X¹⁰ is selected from the group consisting of CR⁵ and N; X¹¹ is selected from the group consisting of CR⁷ and N; R¹ is selected from the group consisting of H, alkyl, (C=O)R¹³, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; R² is selected from the group consisting of H and alkyl; R³ is selected from the group consisting of H, alkyl, and halogen; R⁴ and R⁵ are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN; R⁶ is selected from the group consisting of halogen, H, and alkyl; R⁷ is selected from the group consisting of H and F; R⁸ is selected from the group consisting of alkoxy, alkylamino, cycloalkoxy, cycloalkylamino, halogen, H, alkyl, haloalkoxy, haloalkyl, amide, alkoxycarbonyl, hydroxyalkyl, hydroxycycloalkyl, hydroxy, and CN; R¹⁰ and R¹¹ are each independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl; R¹³ is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl,

cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; L^2 is selected from the group consisting of a direct bond and C_1 - C_6 alkyl, wherein C_1 - C_6 alkyl is optionally substituted with $(E^{21})_p$; E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl, wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent 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, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and each p is independently 0, 1 or 2.

[0111] In some embodiments, the compound is represented by Formula I-P:

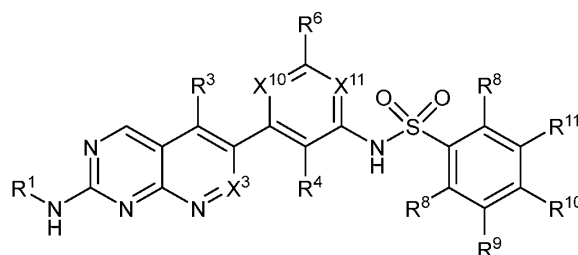


Formula I-P

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein: X^3 is selected from the group consisting of CH, C-O- L^2 - E^2 , C- L^2 - E^2 , and C-N(R^2)- L^2 - E^2 ; X^{10} is selected from the group consisting of CR^5 and N; X^{11} is selected from the group consisting of CR^7 and N; R^1 is selected from the group consisting of H, alkyl, $(C=O)R^{13}$, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide,

amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; R² is selected from the group consisting of H and alkyl; R³ is selected from the group consisting of H, alkyl, and halogen; R⁴ and R⁵ are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN; R⁶ is selected from the group consisting of halogen, H, and alkyl; R⁷ is selected from the group consisting of H and F; R⁸ is selected from the group consisting of alkoxy, alkylamino, cycloalkoxy, cycloalkylamino, halogen, H, alkyl, haloalkoxy, haloalkyl, amide, alkoxycarbonyl, hydroxyalkyl, hydroxycycloalkyl, hydroxy, and CN; R⁹, R¹⁰, and R¹¹ are each independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, cycloalkoxy, cycloalkylamino, haloalkyl, heterocyclyl, alkoxycarbonyl, and heterocyclalkyl; R¹³ is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; L² is selected from the group consisting of a direct bond and C₁-C₆alkyl, wherein C₁-C₆alkyl is optionally substituted with (E²¹)_p; E² is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl, wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent 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, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and each p is independently 0, 1 or 2.

[0112] In some embodiments, the compound is represented by Formula I-Q:



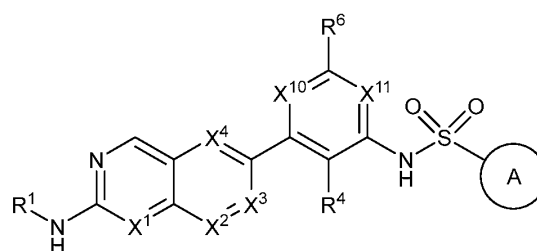
Formula I-Q

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

- 5 X³ is selected from the group consisting of CH, C-O-L²-E², C-L²-E², and C-N(R²)-L²-E²; X¹⁰ is selected from the group consisting of CR⁵ and N; X¹¹ is selected from the group consisting of CR⁷ and N; R¹ is selected from the group consisting of H, alkyl, (C=O)R¹³, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a
- 10 substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; R² is selected from the group consisting of H and alkyl; R³ is selected from the group consisting of H, alkyl, and halogen; R⁴ and R⁵ are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN; R⁶ is selected from the group consisting of halogen, H, and alkyl; R⁷ is selected from the group consisting of H and F; R⁸ is selected from the group consisting of alkoxy, alkylamino, cycloalkoxy, cycloalkylamino,
- 20 halogen, H, alkyl, haloalkoxy, haloalkyl, amide, alkoxycarbonyl, hydroxyalkyl, hydroxycycloalkyl, hydroxy, and CN; R⁹, R¹⁰, and R¹¹ are each independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, cycloalkoxy, cycloalkylamino, haloalkyl, heterocyclyl, alkoxycarbonyl, and
- 25 heterocyclylalkyl; R¹³ is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and

heterocyclyl, and wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; L^2 is selected from the group consisting of a direct bond and C_1 - C_6 alkyl, wherein C_1 - C_6 alkyl is optionally substituted with $(E^{21})_p$; E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl, wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent 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, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and each p is independently 0, 1 or 2.

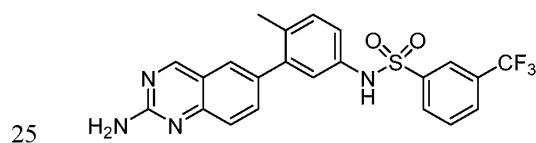
[0113] In some embodiments, the compound is represented by Formula I:



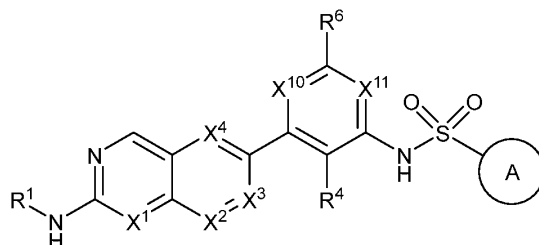
Formula I

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein: X^1 is selected from the group consisting of CH and N; X^2 and X^3 are each independently selected from the group consisting of N, CH, $C-O-L^2-E^2$, $C-L^2-E^2$, and $C-N(R^2)-L^2-E^2$, provided that X^2 is selected from the group consisting of CH and N, and X^3 is selected from the group consisting of CH, $C-O-L^2-E^2$, $C-L^2-E^2$, and $C-N(R^2)-L^2-E^2$; provided that X^2 is selected from the group consisting of CH, $C-O-L^2-E^2$, $C-L^2-E^2$, and $C-N(R^2)-L^2-E^2$ and X^3 is selected from the group consisting of CH and N; X^4 is selected from the group consisting of CR^3 and N; X^4 is selected from the group consisting of CR^3 and N; X^{10} is selected from the group consisting of CR^5 and N; X^{11} is selected from the group consisting of CR^7 and N; R^1 is selected from the group consisting of H, alkyl, $(C=O)R^{13}$, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent

independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; R^2 is selected from the group consisting of H and alkyl; R^3 is selected from the group consisting of H, alkyl, and halogen; R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN; R^6 and R^7 are each independently selected from the group consisting of halogen, H, and alkyl; R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; A is selected from the group consisting of a substituted 5-membered heteroaryl, a substituted 6-membered heteroaryl, a pyridone, and a substituted aryl ring; L^2 is selected from the group consisting of a direct bond and C_1 - C_6 alkyl, wherein C_1 - C_6 alkyl is optionally substituted with $(E^{21})_p$; E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl, wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent 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, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and each p is independently 0, 1 or 2; provided that the compound is not:



[0114] In some embodiments, the compound is represented by Formula I:



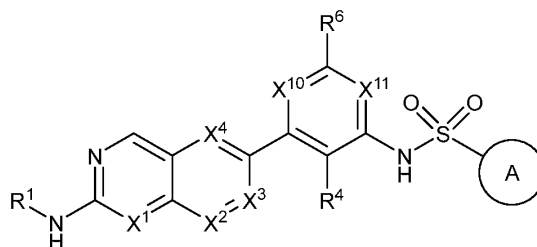
Formula I

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

X^1 is selected from the group consisting of CH and N; X^2 is selected from the group consisting of N, CH, C-O-L²-E², and C-L²-E²; X^3 is C-N(R²)-L²-E²; X^4 is selected from the group consisting of CR³ and N; X^{10} is selected from the group consisting of CR⁵ and N; X^{11} is selected from the group consisting of CR⁷ and N; R¹ is selected from the group consisting of H, alkyl, (C=O)R¹³, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; R² is selected from the group consisting of H and alkyl; R³ is selected from the group consisting of H, alkyl, and halogen; R⁴ and R⁵ are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN; R⁶ and R⁷ are each independently selected from the group consisting of halogen, H, and alkyl; R¹³ is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; A is selected from the group consisting of a substituted 5-membered heteroaryl, a substituted 6-membered heteroaryl, a pyridone, and a substituted aryl ring; L² is selected from the group consisting of a direct bond and C₁-C₆alkyl, wherein C₁-C₆alkyl is optionally substituted with (E²¹)_p; E² is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl, wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent 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, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and each p is independently 0, 1 or 2.

[0115] In one embodiment, described herein is a compound represented by Formula I:



Formula I

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

X¹ is CH; X² and X³ are each independently selected from the group consisting of N, CH, C-O-L²-E², C-L²-E², and C-N(R²)-L²-E², provided that X² is selected from the group consisting of CH and N, and X³ is selected from the group consisting of CH, C-O-L²-E², C-L²-E², and C-N(R²)-L²-E²;

provided that X² is selected from the group consisting of CH, C-O-L²-E², C-L²-E², and C-N(R²)-L²-E² and X³ is selected from the group consisting of CH and N; X⁴ is selected from the group

consisting of CR³ and N; X¹⁰ is selected from the group consisting of CR⁵ and N; X¹¹ is selected

from the group consisting of CR⁷ and N; R¹ is selected from the group consisting of H, alkyl,

(C=O)R¹³, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl,

aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted

with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy,

hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and wherein heterocyclyl is optionally

substituted with one or more occurrences of a substituent independently selected from the group

consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy,

halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; R² is selected from the group

consisting of H and alkyl; R³ is selected from the group consisting of H, alkyl, and halogen; R⁴ and

R⁵ are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino,

amino, alkyl, haloalkyl and CN; R⁶ and R⁷ are each independently selected from the group consisting

of halogen, H, and alkyl; R¹³ is selected from the group consisting of H, alkyl, cycloalkyl,

alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and

heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more

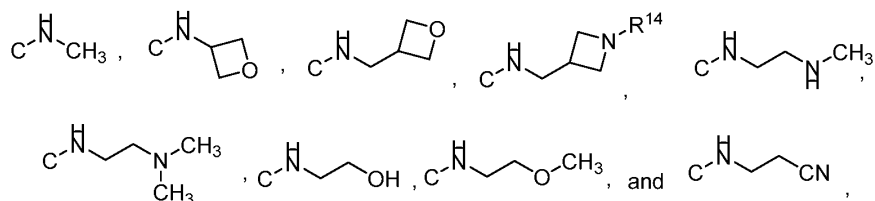
occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl,

haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano,

- cyanoalkyl, and heterocyclyl, and wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; A is selected from the group consisting of a substituted 5-membered heteroaryl, a substituted 6-membered heteroaryl, a pyridone, and a substituted aryl ring; L² is selected from the group consisting of a direct bond and C₁-C₆alkyl, wherein C₁-C₆alkyl is optionally substituted with (E²¹)_p; E² is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl, wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent 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, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and each p is independently 0, 1 or 2.
- 15 **[0116]** In some embodiments, L₂ is a direct bond. In some embodiments, L₂ is alkyl. In some embodiments, L₂ is C₁-C₆alkyl, wherein C₁-C₆alkyl is optionally substituted with (E²¹)_p.
- [0117]** In some embodiments, X₂ is N and X₃ is selected from the group consisting from CH, C-O-L₂-E₂, C-L₂-E₂, and C-N(R₂)-L₂-E₂.
- [0118]** In some embodiments, X₂ is CH and X₃ is selected from the group consisting from N, C-O-L₂-E₂, C-L₂-E₂, and C-N(R₂)-L₂-E₂.
- 20 **[0119]** In some embodiments, X₂ is selected from the group consisting of CH, C-O-L₂-E₂, C-L₂-E₂, and C-N(R₂)-L₂-E₂, and X₃ is N.
- [0120]** In some embodiments, X₂ is selected from the group consisting of CH, C-O-L₂-E₂, C-L₂-E₂, and C-N(R₂)-L₂-E₂, and X₃ is CH.
- 25 **[0121]** In some embodiments, X₂ is selected from the group consisting of N and CH, and X₃ is C-N(R₂)-L₂-E₂.
- [0122]** In some embodiments, X₂ is N and X₃ is C-N(R₂)-L₂-E₂.
- [0123]** In some embodiments, X₂ is CH and X₃ is C-N(R₂)-L₂-E₂.
- [0124]** In some embodiments, X₂ is C-O-L₂-E₂ and X₃ is C-N(R₂)-L₂-E₂.
- 30 **[0125]** In some embodiments, X₂ is C-L₂-E₂ and X₃ is C-N(R₂)-L₂-E₂.
- [0126]** In some embodiments, X₃ is C-N(R₂)-L₂-E₂.
- [0127]** In some embodiments, X₂ is N and X₃ is CCH₃.
- [0128]** In some embodiments, X₂ is N and X₃ is CN(H)CH₃.

[0129] In some embodiments, X2 is CH and X3 is N.

[0130] In some embodiments, X3 is selected from the group consisting of



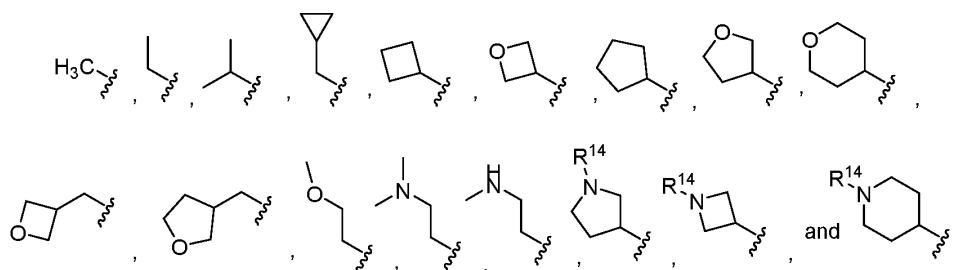
wherein R^{14} is independently selected from the group consisting of H, alkyl, alkoxyalkyl, haloalkyl, hydroxyalkyl, and cyanoalkyl.

[0131] In some embodiments, R1 is H.

[0132] In some embodiments, R1 is methyl.

[0133] In some embodiments, R1 is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, and heterocyclalkyl.

10 [0134] In some embodiments, the R1 is selected from the group consisting of:

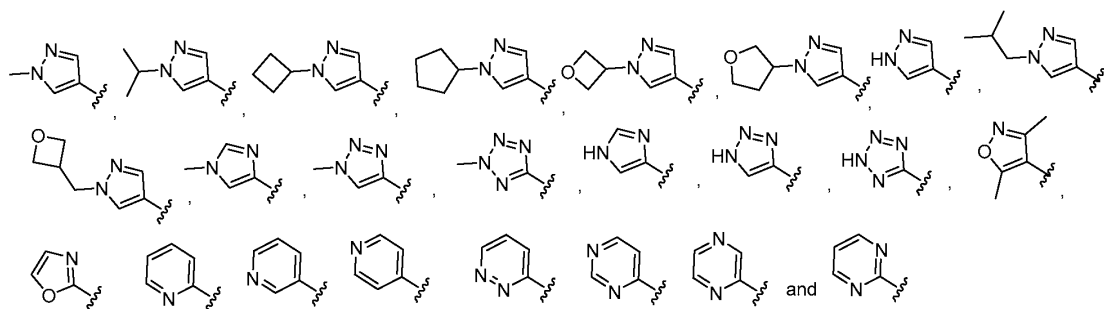


wherein each occurrence of R^{14} is independently selected from the group consisting of H, alkyl, alkoxyalkyl, haloalkyl, hydroxyalkyl, and cyanoalkyl.

[0135] In some embodiments, R1 is selected from the group consisting of aryl and heteroaryl,

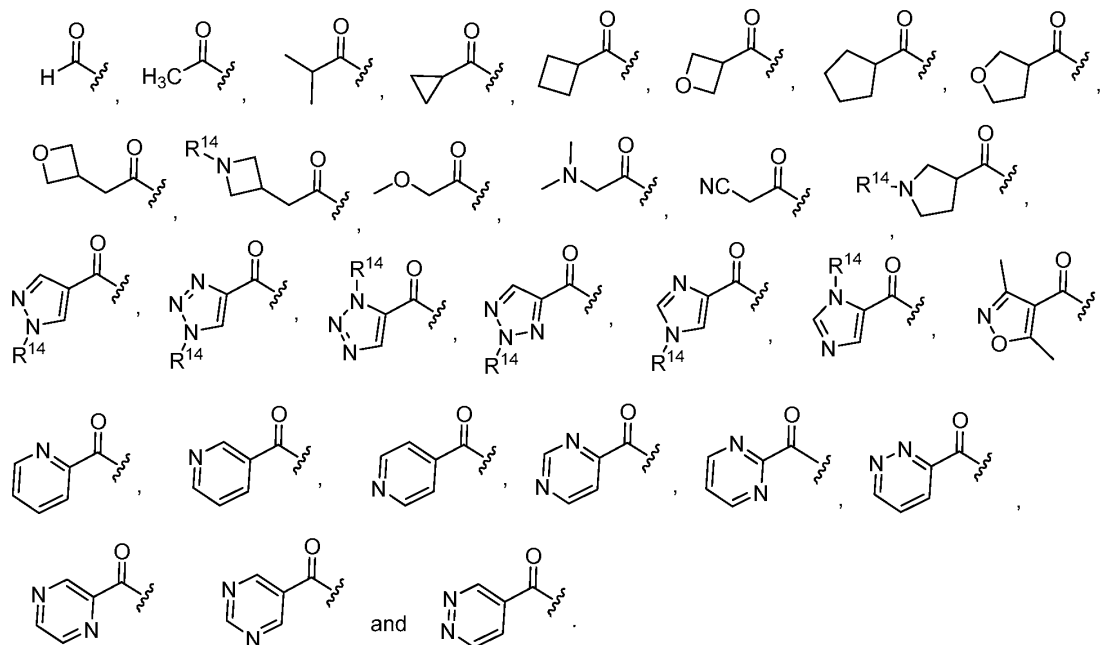
15 wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl.

[0136] In some embodiments, the R1 is selected from the group consisting of:



[0137] In some embodiments, R1 is selected from the group consisting of (C=O)R13, wherein R13 is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl.

[0138] In some embodiments, the R1 is selected from the group consisting of:

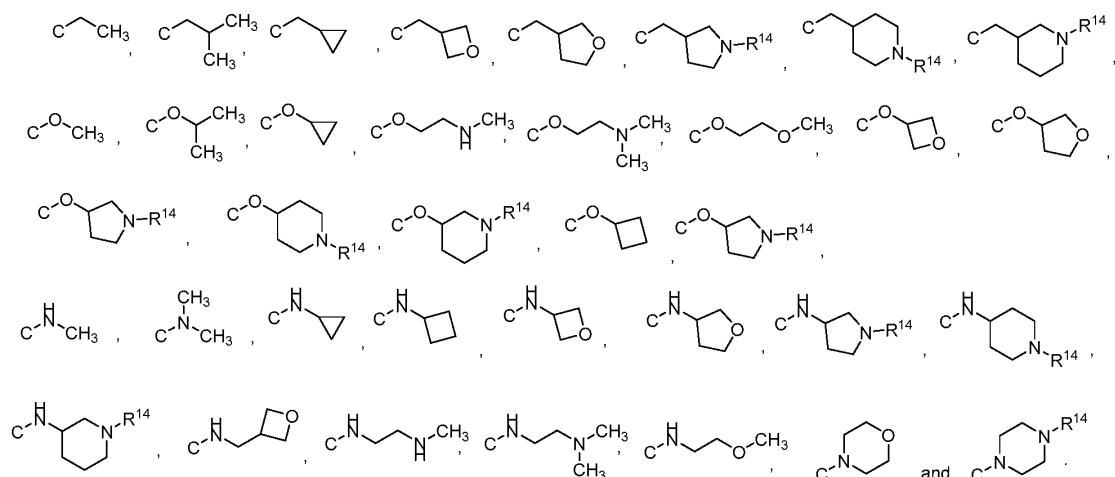


wherein each occurrence of R^{14} is independently selected from the group consisting of H, alkyl, alkoxyalkyl, haloalkyl, hydroxyalkyl, and cyanoalkyl.

[0139] In some embodiments, X1 is N.

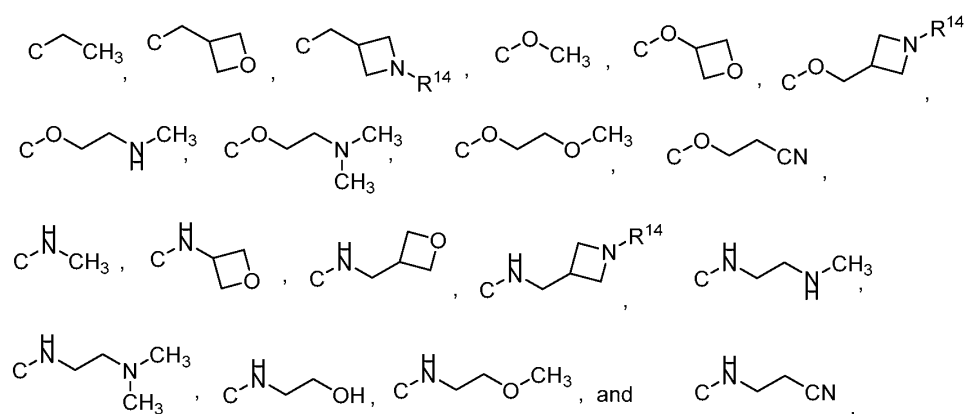
[0140] In some embodiments, X1 is CH.

5 [0141] In some embodiments, X2 is selected from the group consisting of:



wherein each occurrence of R^{14} is independently selected from the group consisting of H, alkyl, alkoxyalkyl, haloalkyl, hydroxyalkyl, and cyanoalkyl.

[0142] In some embodiments, X^3 is selected from the group consisting of:



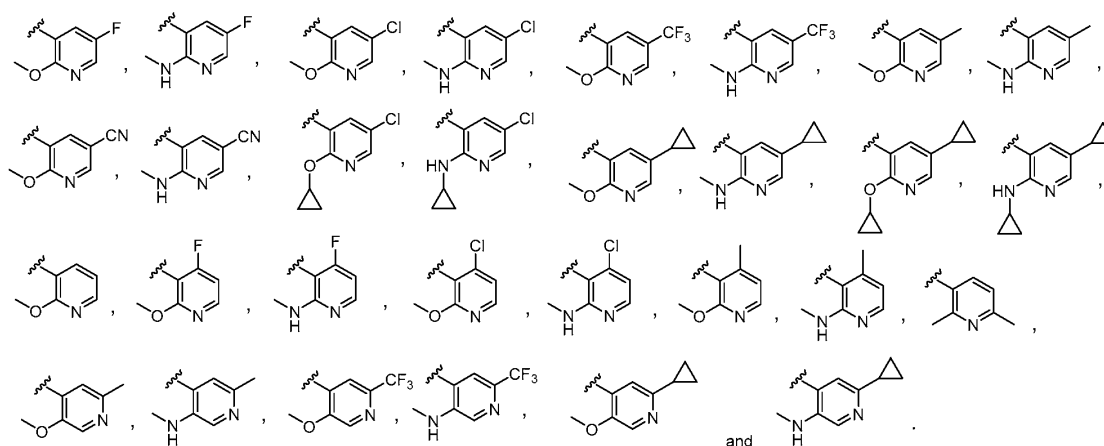
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wherein each occurrence of R^{14} is independently selected from the group consisting of H, alkyl, alkoxyalkyl, haloalkyl, hydroxyalkyl, and cyanoalkyl.

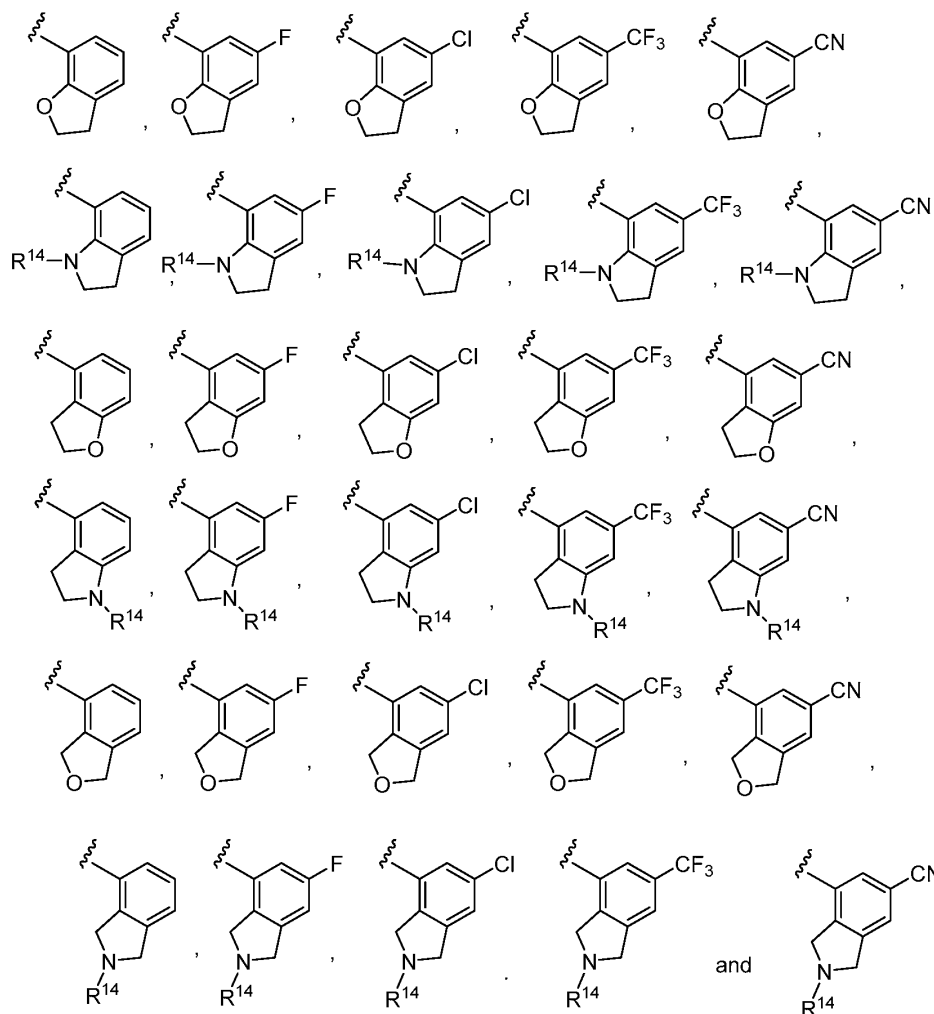
[0143] In some embodiments X4 is selected from the group consisting of N and CR3.

[0144] In some embodiments X10 is selected from the group consisting of N and CR5.

- [0145] In some embodiments X11 is selected from the group consisting of N and CR7.
- [0146] In some embodiments, R3 is selected from the group consisting of H, alkyl, and halogen.
- [0147] In some embodiments, R3 is selected from the group consisting of H, C1-C3alkyl, and halogen. In some embodiments, R3 is C1-C3alkyl.
- 5 [0148] In some embodiments, R3 is selected from the group consisting of H, methyl, and F. In some embodiments, R3 is H. In some embodiments, R3 is F. In some embodiments, R3 is Cl. In some embodiments, R3 is methyl.
- [0149] In some embodiments, X4 is CH.
- [0150] In some embodiments, R4 and R5 are each independently selected from the group
- 10 consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, and CN.
- [0151] In some embodiments, R4 is F, and R5, R6 and R7 are each H.
- [0152] In some embodiments, R6 is F, and R4, R5 and R7 are each H.
- [0153] In some embodiments, R4 and R5 are each F, and R6 and R7 are each H.
- [0154] In some embodiments, R5 and R6 are each F, and R4 and R7 are each H.
- 15 [0155] In some embodiments, R4 and R6 are each F, and R5 and R7 are each H.
- [0156] In some embodiments, R4 and R6 are each H, and R5 and R7 are each F.
- [0157] In some embodiments, A or B is selected from the group consisting of:

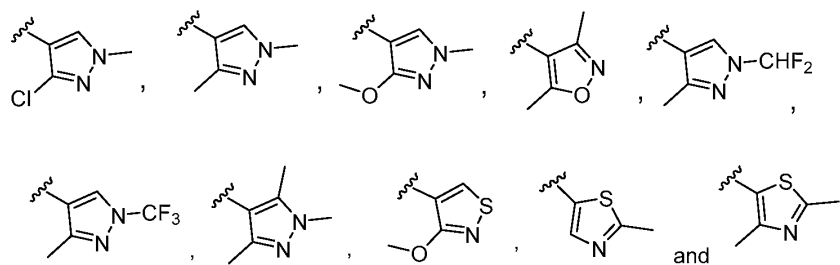


[0160] In some embodiments, A is selected from the group consisting of:



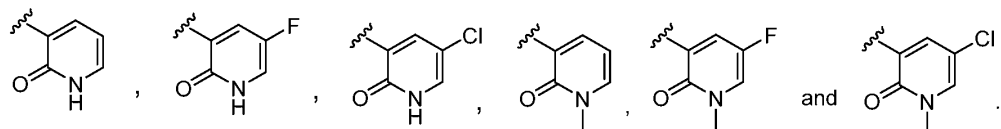
wherein each occurrence of R¹⁴ is independently selected from the group consisting of H, alkyl, alkoxyalkyl, haloalkyl, hydroxyalkyl, and cyanoalkyl.

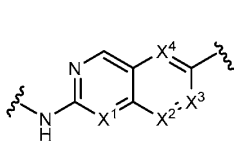
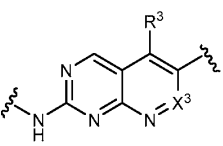
5 [0161] In some embodiments, A or B is selected from the group consisting of:

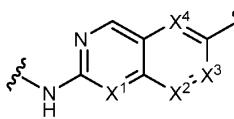
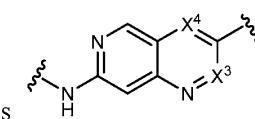


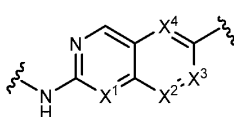
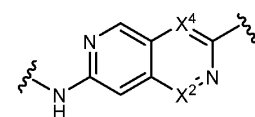
[0162] In some embodiments, A is an optionally substituted pyridone.

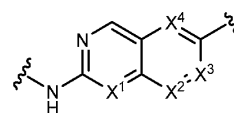
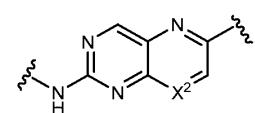
[0163] In some embodiments, A is selected from the group consisting of:

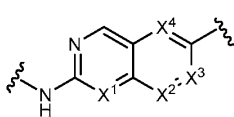
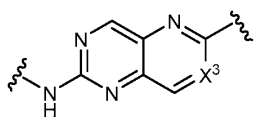


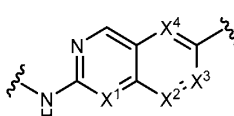
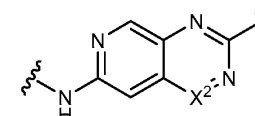
[0164] In some embodiments,  is , wherein X³ is
5 selected from the group consisting of CH, C-L²-E², C-O-L²-E², and C-N(R²)-L²-E².

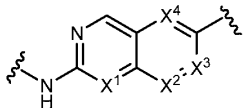
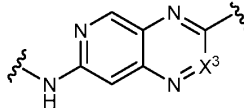
[0165] In some embodiments,  is , wherein X³ is
selected from the group consisting of CH, C-L²-E², C-O-L²-E², and C-N(R²)-L²-E² wherein X⁴ is N
or CR³.

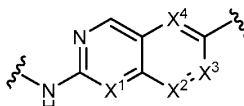
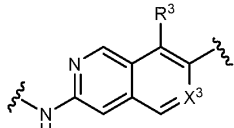
[0166] In some embodiments,  is , wherein X² is
10 selected from the group consisting of CH, C-L²-E², C-O-L²-E², and C-N(R²)-L²-E², wherein X⁴ is N
or CR³.

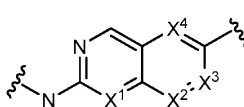
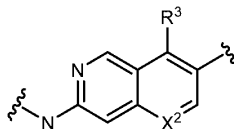
[0167] In some embodiments,  is , wherein X² is
selected from the group consisting of CH, C-L²-E², C-O-L²-E², and C-N(R²)-L²-E².

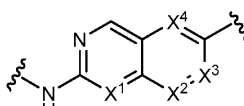
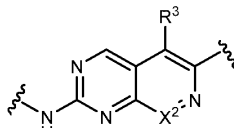
[0168] In some embodiments,  is , wherein X³ is
15 selected from the group consisting of CH, C-L²-E², C-O-L²-E², and C-N(R²)-L²-E².

[0169] In some embodiments,  is , wherein X² is
CH, C-L²-E², C-O-L²-E², and C-N(R²)-L²-E², wherein E² is not F.

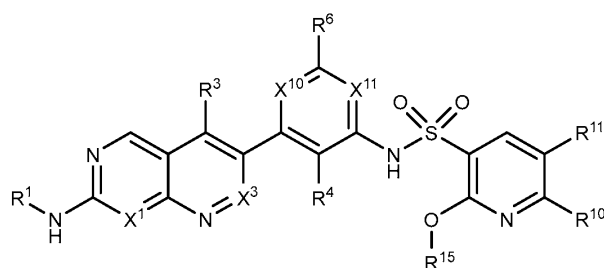
[0170] In some embodiments,  is , wherein X³ is CH, C-L²-E², C-O-L²-E², and C-N(R²)-L²-E², wherein E² is not F.

[0171] In some embodiments,  is , wherein X³ is CH, C-L²-E², C-O-L²-E², and C-N(R²)-L²-E².

5 [0172] In some embodiments,  is , wherein X³ is CH, C-L²-E², C-O-L²-E², and C-N(R²)-L²-E².

[0173] In some embodiments,  is , wherein X² is CH, C-L²-E², C-O-L²-E², and C-N(R²)-L²-E².

10 [0174] In one embodiment, described herein is a compound represented by Formula I-R:

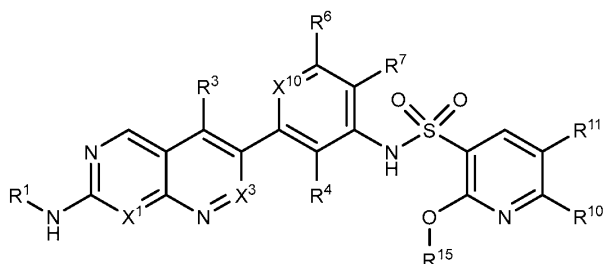


Formula I-R

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein: X¹ is selected from the group consisting of CH and N; X³ is selected from the group consisting of C-O-L²-E², C-L²-E², and C-N(R²)-L²-E²; X¹⁰ is selected from the group consisting of CR⁵ and N; X¹¹ is selected from the group consisting of CR⁷ and N; R¹ is selected from the group consisting of alkyl, (C=O)R¹³, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of

haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; R² is selected from the group consisting of H and alkyl; R³ is selected from the group consisting of H, alkyl, and halogen; R⁴ and R⁵ are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN; R⁶ is selected from the group consisting of halogen, H, and alkyl; R⁷ is selected from the group consisting of H and F; R¹⁰ and R¹¹ are each independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl; R¹³ is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; R¹⁵ is selected from the group consisting of alkyl, cycloalkyl, and heterocyclyl; L² is selected from the group consisting of a direct bond and C₁-C₆alkyl, wherein C₁-C₆alkyl is optionally substituted with (E²¹)_p; E² is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl, wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent 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, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen, and each p is independently 0, 1 or 2.

[0175] In one embodiment, described herein is a compound represented by Formula I-S:

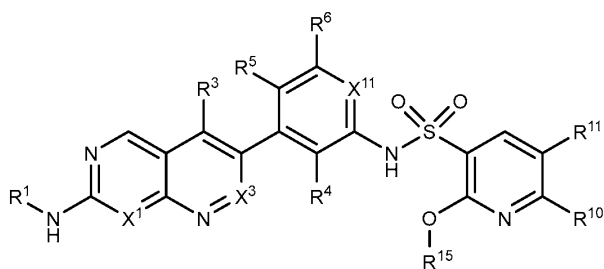


Formula I-S

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein: X¹ is
 5 selected from the group consisting of CH and N; X³ is selected from the group consisting of C-O-L²-
 E², C-L²-E², and C-N(R²)-L²-E²; X¹⁰ is selected from the group consisting of CR⁵ and N; R¹ is
 selected from the group consisting of alkyl, (C=O)R¹³, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl,
 aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of
 aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent
 10 independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen,
 amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and
 wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent
 independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine,
 aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl,
 15 and sulfonyl; R² is selected from the group consisting of H and alkyl; R³ is selected from the group
 consisting of H, alkyl, and halogen; R⁴ and R⁵ are each independently selected from the group
 consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN; R⁶ is selected from the
 group consisting of halogen, H, and alkyl; R⁷ is selected from the group consisting of H and F; R¹⁰
 and R¹¹ are each independently selected from the group consisting of hydroxyalkyl,
 20 hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl,
 aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl,
 haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxy carbonyl, and heterocyclylalkyl; R¹³ is
 selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl,
 aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of
 25 aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent
 independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen,
 amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and
 wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent

independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; R^{15} is selected from the group consisting of alkyl, cycloalkyl, and heterocyclyl; L^2 is selected from the group consisting of a direct bond and C_1 - C_6 alkyl, wherein C_1 - C_6 alkyl is optionally substituted with $(E^{21})_p$; E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl, wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent 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, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen, and each p is independently 0, 1 or 2.

[0176] In one embodiment, described herein is a compound represented by Formula I-T:

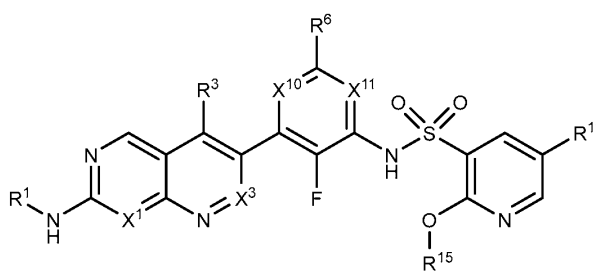


Formula I-T

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein: X^1 is selected from the group consisting of CH and N; X^3 is selected from the group consisting of $C-O-L^2-E^2$, $C-L^2-E^2$, and $C-N(R^2)-L^2-E^2$; R^1 is selected from the group consisting of alkyl, $(C=O)R^{13}$, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; R^2 is selected from the group consisting of H and alkyl; R^3 is selected from the group consisting of H, alkyl, and halogen; R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN; R^6 is selected from the group consisting of halogen, H, and alkyl; R^7 is selected from the group

consisting of H and F; R^{10} and R^{11} are each independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxyalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxyalkyl, and heterocyclylalkyl; R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; R^{15} is selected from the group consisting of alkyl, cycloalkyl, and heterocyclyl; L^2 is selected from the group consisting of a direct bond and C_1 - C_6 alkyl, wherein C_1 - C_6 alkyl is optionally substituted with $(E^{21})_p$; E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl, wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent 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, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen, and each p is independently 0, 1 or 2.

[0177] In one embodiment, described herein is a compound represented by Formula I-U:

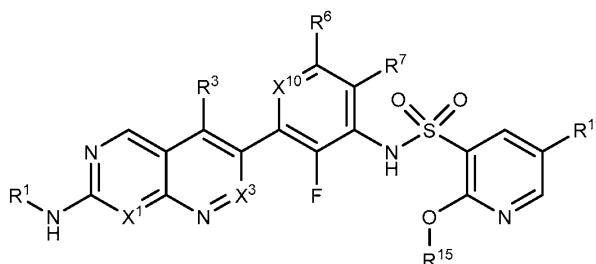


Formula I-U

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein: X^1 is selected from the group consisting of CH and N; X^3 is selected from the group consisting of $C-O-L^2$, E^2 , $C-L^2-E^2$, and $C-N(R^2)-L^2-E^2$; X^{10} is selected from the group consisting of CR^5 and N; X^{11} is

selected from the group consisting of CR⁷ and N; R¹ is selected from the group consisting of alkyl, (C=O)R¹³, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; R² is selected from the group consisting of H and alkyl; R³ is selected from the group consisting of H, alkyl, and halogen; R⁵ is selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN; R⁶ is selected from the group consisting of halogen, H, and alkyl; R⁷ is selected from the group consisting of H and F; R¹¹ is selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxyalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxyalkyl, and heterocyclylalkyl; R¹³ is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; R¹⁵ is selected from the group consisting of alkyl, cycloalkyl, and heterocyclyl; L² is selected from the group consisting of a direct bond and C₁-C₆alkyl, wherein C₁-C₆alkyl is optionally substituted with (E²¹)_p; E² is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl, wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent 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, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen, and each p is independently 0, 1 or 2.

[0178] In one embodiment, described herein is a compound represented by Formula I-V:

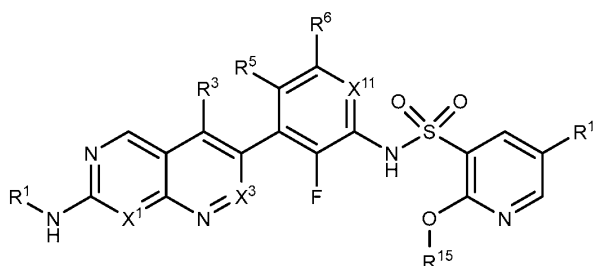


Formula I-V

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein: X¹ is
 5 selected from the group consisting of CH and N; X³ is selected from the group consisting of C-O-L²-
 E², C-L²-E², and C-N(R²)-L²-E²; X¹⁰ is selected from the group consisting of CR⁵ and N; R¹ is
 selected from the group consisting of alkyl, (C=O)R¹³, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl,
 aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of
 aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent
 10 independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen,
 amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and
 wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent
 independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine,
 aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl,
 15 and sulfonyl; R² is selected from the group consisting of H and alkyl; R³ is selected from the group
 consisting of H, alkyl, and halogen; R⁵ is selected from the group consisting of halogen, H, alkoxy,
 alkylamino, amino, alkyl, haloalkyl and CN; R⁶ is selected from the group consisting of halogen, H,
 and alkyl; R⁷ is selected from the group consisting of H and F; R¹¹ is selected from the group
 consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl,
 20 aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl,
 alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and
 heterocyclylalkyl; R¹³ is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl,
 cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,
 wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a
 25 substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy,
 halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and
 heterocyclyl, and wherein heterocyclyl is optionally substituted with one or more occurrences of a
 substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide,

amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; R^{15} is selected from the group consisting of alkyl, cycloalkyl, and heterocyclyl; L^2 is selected from the group consisting of a direct bond and C_1 - C_6 alkyl, wherein C_1 - C_6 alkyl is optionally substituted with $(E^{21})_p$; E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl, wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent 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, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen, and each p is independently 0, 1 or 2.

[0179] In one embodiment, described herein is a compound represented by Formula I-W:

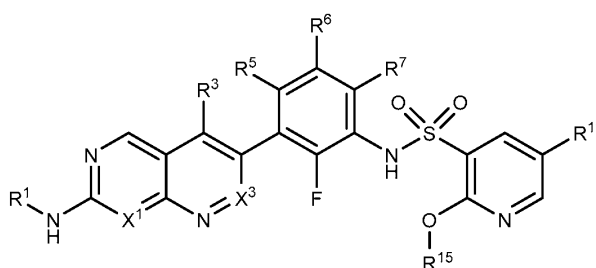


Formula 1-W

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein: X^1 is selected from the group consisting of CH and N; X^3 is selected from the group consisting of $C-O-L^2-E^2$, $C-L^2-E^2$, and $C-N(R^2)-L^2-E^2$; X^{11} is selected from the group consisting of CR^7 and N; R^1 is selected from the group consisting of alkyl, $(C=O)R^{13}$, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; R^2 is selected from the group consisting of H and alkyl; R^3 is selected from the group consisting of H, alkyl, and halogen; R^5 is selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN; R^6 is selected from the group consisting of halogen, H,

and alkyl; R^7 is selected from the group consisting of H and F; R^{11} is selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxyalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxyalkyl, and heterocyclalkyl; R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; R^{15} is selected from the group consisting of alkyl, cycloalkyl, and heterocyclyl; L^2 is selected from the group consisting of a direct bond and C_1 - C_6 alkyl, wherein C_1 - C_6 alkyl is optionally substituted with $(E^{21})_p$; E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl, wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent 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, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen, and each p is independently 0, 1 or 2.

[0180] In one embodiment, described herein is a compound represented by Formula I-X:

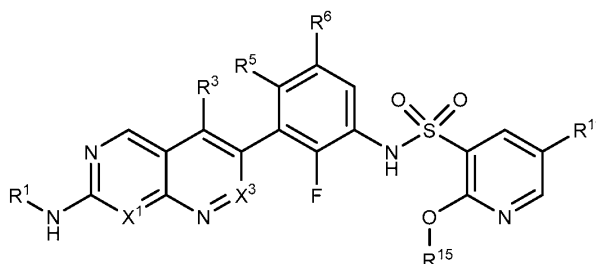


Formula I-X

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein: X^1 is selected from the group consisting of CH and N; X^3 is selected from the group consisting of $C-O-L^2-E^2$, $C-L^2-E^2$, and $C-N(R^2)-L^2-E^2$; R^1 is selected from the group consisting of alkyl, $(C=O)R^{13}$,

cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; R² is selected from the group consisting of H and alkyl; R³ is selected from the group consisting of H, alkyl, and halogen; R⁵ is independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN; R⁶ is selected from the group consisting of halogen, H, and alkyl; R⁷ is selected from the group consisting of H and F; R¹¹ is selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxy carbonyl, and heterocyclalkyl; R¹³ is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; R¹⁵ is selected from the group consisting of alkyl, cycloalkyl, and heterocyclyl; L² is selected from the group consisting of a direct bond and C₁-C₆alkyl, wherein C₁-C₆alkyl is optionally substituted with (E²¹)_p; E² is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl, wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent 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, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen, and each p is independently 0, 1 or 2.

[0181] In one embodiment, described herein is a represented by Formula I-Y:

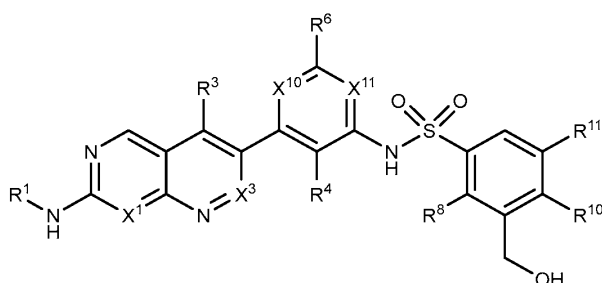


Formula I-Y

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein: X¹ is
 5 selected from the group consisting of CH and N; X³ is selected from the group consisting of C-O-L²-
 E², C-L²-E², and C-N(R²)-L²-E²; R¹ is selected from the group consisting of alkyl, (C=O)R¹³,
 cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclalkyl, aryl,
 heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one
 or more occurrences of a substituent independently selected from the group consisting of haloalkyl,
 10 alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano,
 cyanoalkyl, and heterocyclyl, and wherein heterocyclyl is optionally substituted with one or more
 occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy,
 alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl,
 15 oxo, cyano, cyanoalkyl, and sulfonyl; R² is selected from the group consisting of H and alkyl; R³ is
 selected from the group consisting of H, alkyl, and halogen; R⁵ is independently selected from the
 group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN; R⁶ is selected
 from the group consisting of halogen, H, and alkyl; R¹¹ is selected from the group consisting of
 hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl,
 aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl,
 20 alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxy carbonyl, and
 heterocyclalkyl; R¹³ is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl,
 cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclalkyl, aryl, heteroaryl, and heteroarylalkyl,
 wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a
 substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy,
 25 halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and
 heterocyclyl, and wherein heterocyclyl is optionally substituted with one or more occurrences of a
 substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide,
 amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano,

cyanoalkyl, and sulfonyl; R^{15} is selected from the group consisting of alkyl, cycloalkyl, and heterocyclyl; L^2 is selected from the group consisting of a direct bond and C_1 - C_6 alkyl, wherein C_1 - C_6 alkyl is optionally substituted with $(E^{21})_p$; E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl, wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent 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, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen, and each p is independently 0, 1 or 2.

[0182] In one embodiment, described herein is a compound represented by Formula I-Z:

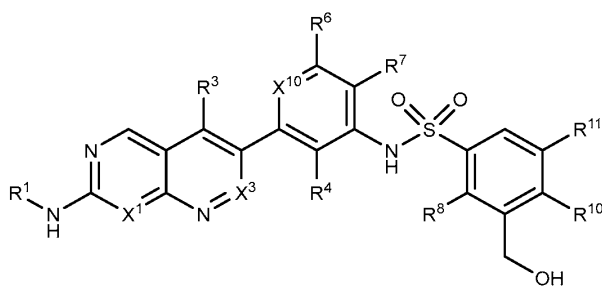


Formula I-Z

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein: X^1 is selected from the group consisting of CH and N; X^3 is selected from the group consisting of $C-O-L^2-E^2$, $C-L^2-E^2$, and $C-N(R^2)-L^2-E^2$; X^{10} is selected from the group consisting of CR^5 and N; X^{11} is selected from the group consisting of CR^7 and N; R^1 is selected from the group consisting of alkyl, $(C=O)R^{13}$, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; R^2 is selected from the group consisting of H and alkyl; R^3 is selected from the group consisting of H, alkyl, and halogen; R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN; R^6 is selected from the group consisting of halogen, H, and alkyl; R^7

is selected from the group consisting of H and F; R⁸ is selected from the group consisting of alkoxy, alkylamino, cycloalkoxy, cycloalkylamino, halogen, H, alkyl, haloalkoxy, haloalkyl, amide, alkoxycarbonyl, hydroxyalkyl, hydroxycycloalkyl, hydroxy, and CN; R¹⁰ and R¹¹ are each independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, 5 alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl; R¹³ is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, 10 alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, 15 oxo, cyano, cyanoalkyl, and sulfonyl; L² is selected from the group consisting of a direct bond and C₁-C₆alkyl, wherein C₁-C₆alkyl is optionally substituted with (E²¹)_p; E² is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl, wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, 20 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, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen, and each p is independently 0, 1 or 2.

[0183] In one embodiment, described herein is a compound represented by Formula I-AA:



Formula I-AA

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein: X¹ is selected from the group consisting of CH and N; X³ is selected from the group consisting of C-O-L²-

E^2 , $C-L^2-E^2$, and $C-N(R^2)-L^2-E^2$; X^{10} is selected from the group consisting of CR^5 and N ; R^1 is selected from the group consisting of alkyl, $(C=O)R^{13}$, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent

5 independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl,

10 and sulfonyl; R^2 is selected from the group consisting of H and alkyl; R^3 is selected from the group consisting of H , alkyl, and halogen; R^4 and R^5 are each independently selected from the group consisting of halogen, H , alkoxy, alkylamino, amino, alkyl, haloalkyl and CN ; R^6 is selected from the group consisting of halogen, H , and alkyl; R^7 is selected from the group consisting of H and F ; R^8 is selected from the group consisting of alkoxy, alkylamino, cycloalkoxy, cycloalkylamino, halogen, H ,

15 alkyl, haloalkoxy, haloalkyl, amide, alkoxycarbonyl, hydroxyalkyl, hydroxycycloalkyl, hydroxy, and CN ; R^{10} and R^{11} are each independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H , cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclalkyl; R^{13} is

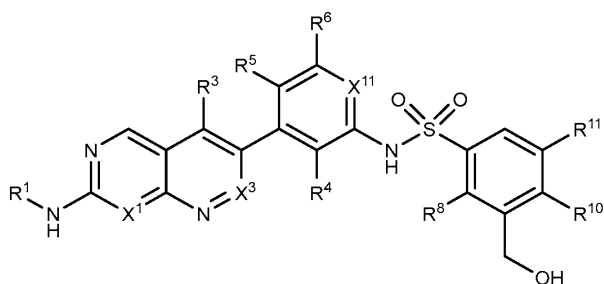
20 selected from the group consisting of H , alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

25 wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; L^2 is selected from the group consisting of a direct bond and C_1-C_6 alkyl, wherein C_1-C_6 alkyl is optionally substituted with $(E^{21})_p$; E^2 is selected from the group consisting of hydroxy,

30 alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H , alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl, wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent 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, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen, and each p is independently 0, 1 or 2.

[0184] In one embodiment, described herein is a compound represented by Formula I-AB:

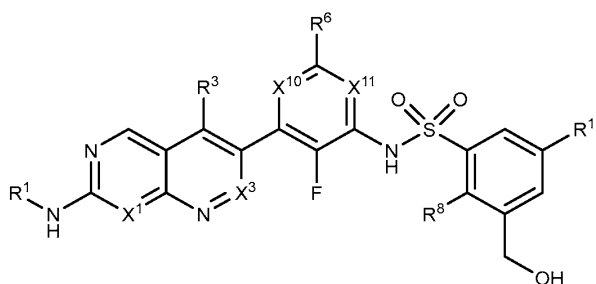


Formula I-AB

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein: X^1 is selected from the group consisting of CH and N; X^3 is selected from the group consisting of C-O-L²-E², C-L²-E², and C-N(R²)-L²-E²; X^{11} is selected from the group consisting of CR⁷ and N; R¹ is selected from the group consisting of alkyl, (C=O)R¹³, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; R² is selected from the group consisting of H and alkyl; R³ is selected from the group consisting of H, alkyl, and halogen; R⁴ and R⁵ are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN; R⁶ is selected from the group consisting of halogen, H, and alkyl; R⁷ is selected from the group consisting of H and F; R⁸ is selected from the group consisting of alkoxy, alkylamino, cycloalkoxy, cycloalkylamino, halogen, H, alkyl, haloalkoxy, haloalkyl, amide, alkoxycarbonyl, hydroxyalkyl, hydroxycycloalkyl, hydroxy, and CN; R¹¹ is selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl; R¹³ is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one

or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; L² is selected from the group consisting of a direct bond and C₁-C₆alkyl, wherein C₁-C₆alkyl is optionally substituted with (E²¹)_p; E² is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl, wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent 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, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen, and each p is independently 0, 1 or 2.

15 **[0185]** In one embodiment, described herein is a compound represented by Formula I-AC:

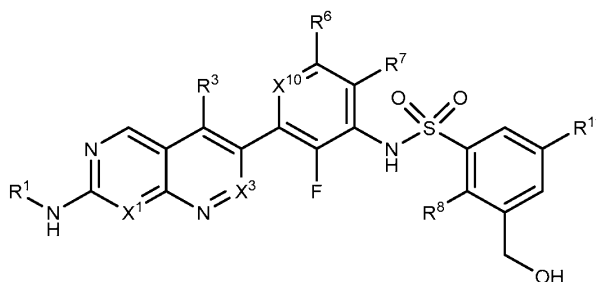


Formula 1-AC

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein: X¹ is selected from the group consisting of CH and N; X³ is selected from the group consisting of C-O-L²-E², C-L²-E², and C-N(R²)-L²-E²; X¹⁰ is selected from the group consisting of CR⁵ and N; X¹¹ is selected from the group consisting of CR⁷ and N; R¹ is selected from the group consisting of alkyl, (C=O)R¹³, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy,

halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; R² is selected from the group consisting of H and alkyl; R³ is selected from the group consisting of H, alkyl, and halogen; R⁵ is selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN; R⁶ is selected from the group consisting of halogen, H, and alkyl; R⁷ is selected from the group consisting of H and F; R⁸ is selected from the group consisting of alkoxy, alkylamino, cycloalkoxy, cycloalkylamino, halogen, H, alkyl, haloalkoxy, haloalkyl, amide, alkoxycarbonyl, hydroxyalkyl, hydroxycycloalkyl, hydroxy, and CN; R¹¹ is selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclalkyl; R¹³ is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; L² is selected from the group consisting of a direct bond and C₁-C₆alkyl, wherein C₁-C₆alkyl is optionally substituted with (E²¹)_p; E² is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl, wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent 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, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen, and each p is independently 0, 1 or 2.

[0186] In one embodiment, described herein is a compound represented by Formula I-AD:

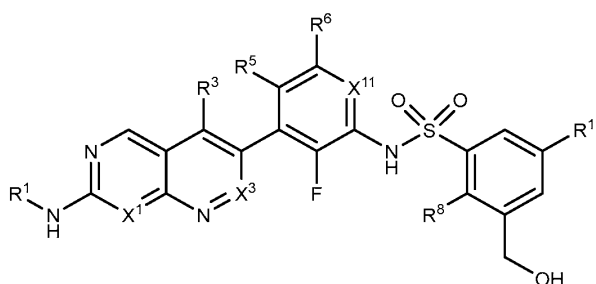


Formula 1-AD

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein: X^1 is
 5 selected from the group consisting of CH and N; X^3 is selected from the group consisting of C-O-L²-
 E², C-L²-E², and C-N(R²)-L²-E²; X^{10} is selected from the group consisting of CR⁵ and N; R¹ is
 selected from the group consisting of alkyl, (C=O)R¹³, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl,
 aminoalkyl, heterocyclyl, heterocyclalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of
 10 aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent
 independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen,
 amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and
 wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent
 independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine,
 aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl,
 15 and sulfonyl; R² is selected from the group consisting of H and alkyl; R³ is selected from the group
 consisting of H, alkyl, and halogen; R⁵ is selected from the group consisting of halogen, H, alkoxy,
 alkylamino, amino, alkyl, haloalkyl and CN; R⁶ is selected from the group consisting of halogen, H,
 and alkyl; R⁷ is selected from the group consisting of H and F; R⁸ is selected from the group
 consisting of alkoxy, alkylamino, cycloalkoxy, cycloalkylamino, halogen, H, alkyl, haloalkoxy,
 20 haloalkyl, amide, alkoxy carbonyl, hydroxyalkyl, hydroxycycloalkyl, hydroxy, and CN; R¹¹ is
 selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl,
 alkoxy cycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano,
 alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino,
 heterocyclyl, alkoxy carbonyl, and heterocyclalkyl; R¹³ is selected from the group consisting of H,
 25 alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclalkyl, aryl,
 heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one
 or more occurrences of a substituent independently selected from the group consisting of haloalkyl,
 alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano,

cyanoalkyl, and heterocyclyl, and wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; L^2 is selected from the group consisting of a direct bond and C₁-C₆alkyl, wherein C₁-C₆alkyl is optionally substituted with $(E^{21})_p$; E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl, wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent 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, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen, and each p is independently 0, 1 or 2.

[0187] In one embodiment, described herein is a compound represented by Formula I-AE:

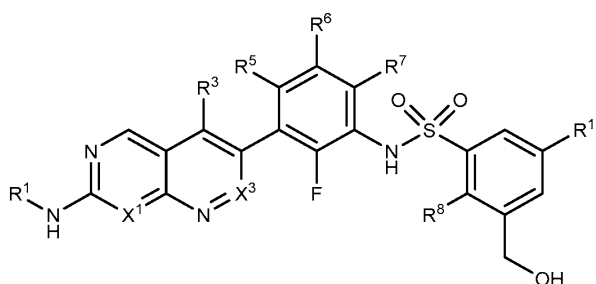


Formula I-AE

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein: X^1 is selected from the group consisting of CH and N; X^3 is selected from the group consisting of C-O- L^2 - E^2 , C- L^2 - E^2 , and C-N(R^2)- L^2 - E^2 ; X^{11} is selected from the group consisting of CR⁷ and N; R^1 is selected from the group consisting of alkyl, (C=O)R¹³, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; R^2 is selected from the group consisting of H and alkyl; R^3 is selected from the group consisting of H, alkyl, and halogen; R^5 is selected from the group consisting of halogen, H, alkoxy,

alkylamino, amino, alkyl, haloalkyl and CN; R⁶ is selected from the group consisting of halogen, H, and alkyl; R⁷ is selected from the group consisting of H and F; R⁸ is selected from the group consisting of alkoxy, alkylamino, cycloalkoxy, cycloalkylamino, halogen, H, alkyl, haloalkoxy, haloalkyl, amide, alkoxy carbonyl, hydroxyalkyl, hydroxycycloalkyl, hydroxy, and CN; R¹¹ is selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxy cycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxy carbonyl, and heterocyclylalkyl; R¹³ is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; L² is selected from the group consisting of a direct bond and C₁-C₆alkyl, wherein C₁-C₆alkyl is optionally substituted with (E²¹)_p; E² is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl, wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent 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, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen, and each p is independently 0, 1 or 2.

[0188] In one embodiment, described herein is a compound represented by Formula I-AF:

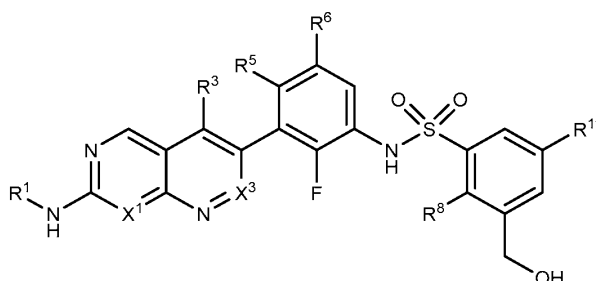


Formula 1-AF

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein: X^1 is selected from the group consisting of CH and N; X^3 is selected from the group consisting of C-O-L²-E², C-L²-E², and C-N(R²)-L²-E²; R¹ is selected from the group consisting of alkyl, (C=O)R¹³, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; R² is selected from the group consisting of H and alkyl; R³ is selected from the group consisting of H, alkyl, and halogen; R⁵ is selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN; R⁶ is selected from the group consisting of halogen, H, and alkyl; R⁷ is selected from the group consisting of H and F; R⁸ is selected from the group consisting of alkoxy, alkylamino, cycloalkoxy, cycloalkylamino, halogen, H, alkyl, haloalkoxy, haloalkyl, amide, alkoxy carbonyl, hydroxyalkyl, hydroxycycloalkyl, hydroxy, and CN; R¹¹ is selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxy cycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxy carbonyl, and heterocyclalkyl; R¹³ is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; L² is selected from the group consisting of a direct bond and C₁-C₆alkyl, wherein C₁-C₆alkyl is optionally substituted with (E²¹)_p; E² is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl, wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent 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, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen, and each p is independently 0, 1 or 2.

[0189] In one embodiment, described herein is a compound represented by Formula I-AG:

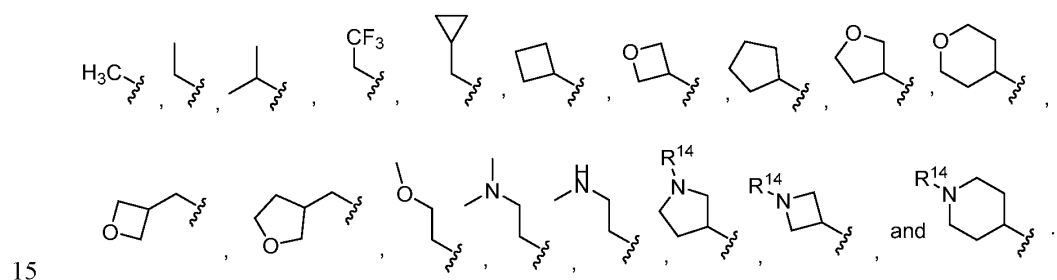


Formula 1-AG

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein: X^1 is selected from the group consisting of CH and N; X^3 is selected from the group consisting of C-O-L²-E², C-L²-E², and C-N(R²)-L²-E²; R^1 is selected from the group consisting of alkyl, (C=O)R¹³, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; R^2 is selected from the group consisting of H and alkyl; R^3 is selected from the group consisting of H, alkyl, and halogen; R^5 is selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN; R^6 is selected from the group consisting of halogen, H, and alkyl; R^8 is selected from the group consisting of alkoxy, alkylamino, cycloalkoxy, cycloalkylamino, halogen, H, alkyl, haloalkoxy, haloalkyl, amide, alkoxycarbonyl, hydroxyalkyl, hydroxycycloalkyl, hydroxy, and CN; R^{11} is selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclalkyl; R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy,

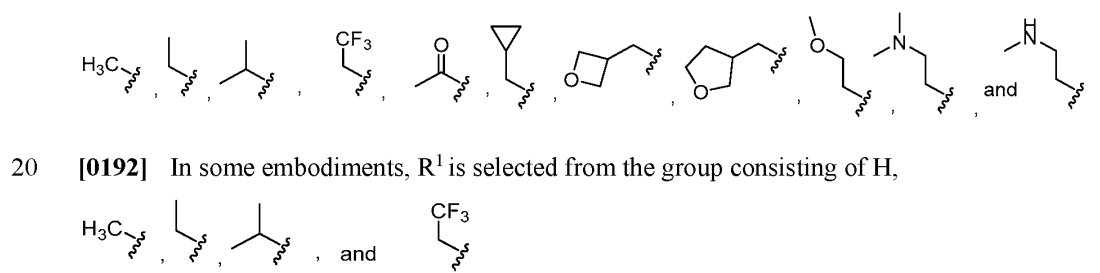
halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; L² is selected from the group consisting of a direct bond and C₁-C₆alkyl, wherein C₁-C₆alkyl is optionally substituted with (E²¹)_p; E² is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl, wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent 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, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen, and each p is independently 0, 1 or 2.

[0190] In some embodiments, R^1 is selected from the group consisting of

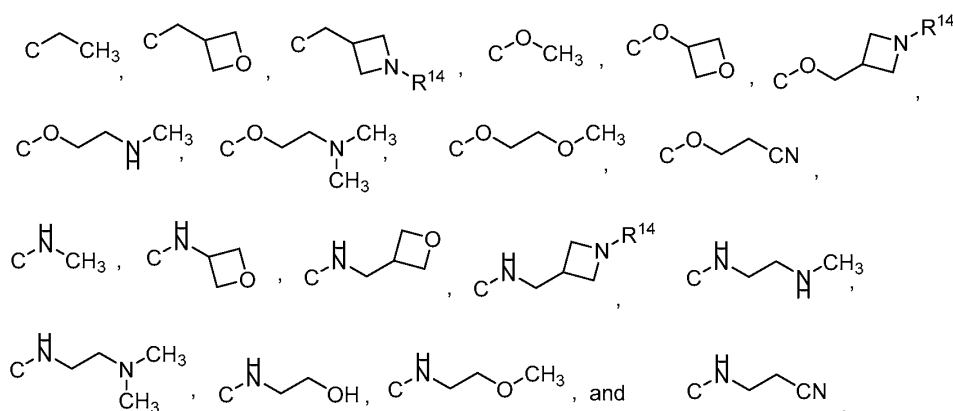


wherein each occurrence of R¹⁴ is independently selected from the group consisting of H, alkyl, alkoxyalkyl, haloalkyl, hydroxyalkyl, and cyanoalkyl.

[0191] In some embodiments, R^1 is selected from the group consisting of

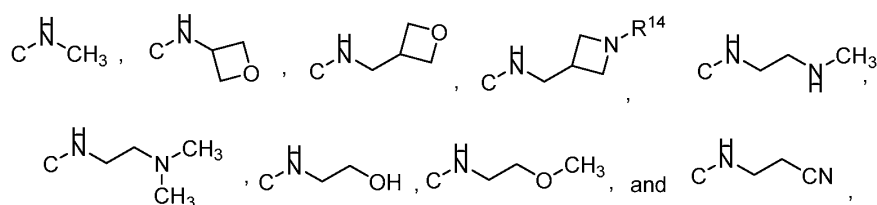


[0196] In some embodiments, X^3 is selected from the group consisting of:



wherein each occurrence of R^{14} is independently selected from the group consisting of H, alkyl, alkoxyalkyl, haloalkyl, hydroxyalkyl, and cyanoalkyl.

5 [0197] In some embodiments, X^3 is selected from the group consisting of



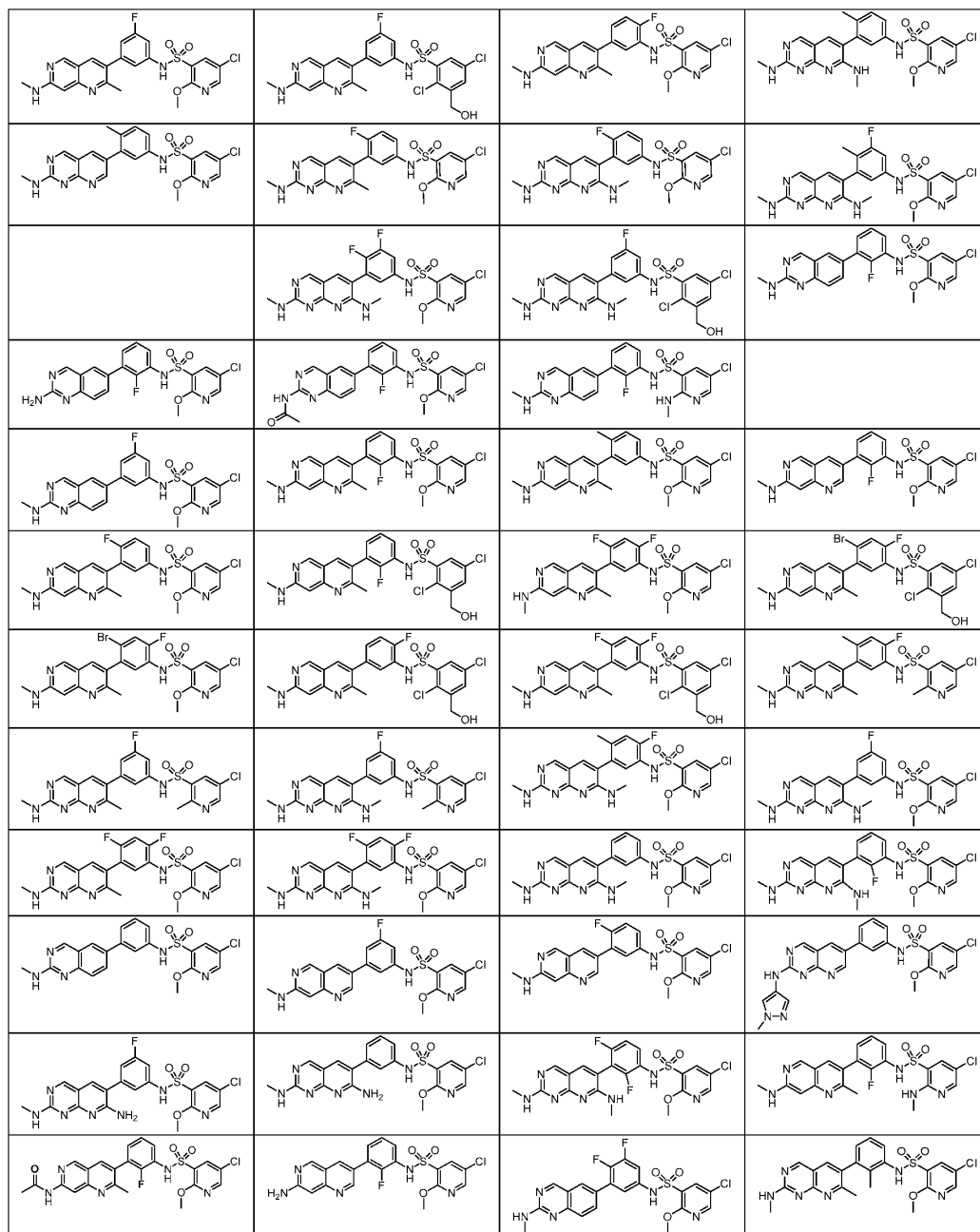
wherein each occurrence of R^{14} is independently selected from the group consisting of H, alkyl, alkoxyalkyl, haloalkyl, hydroxyalkyl, and cyanoalkyl.

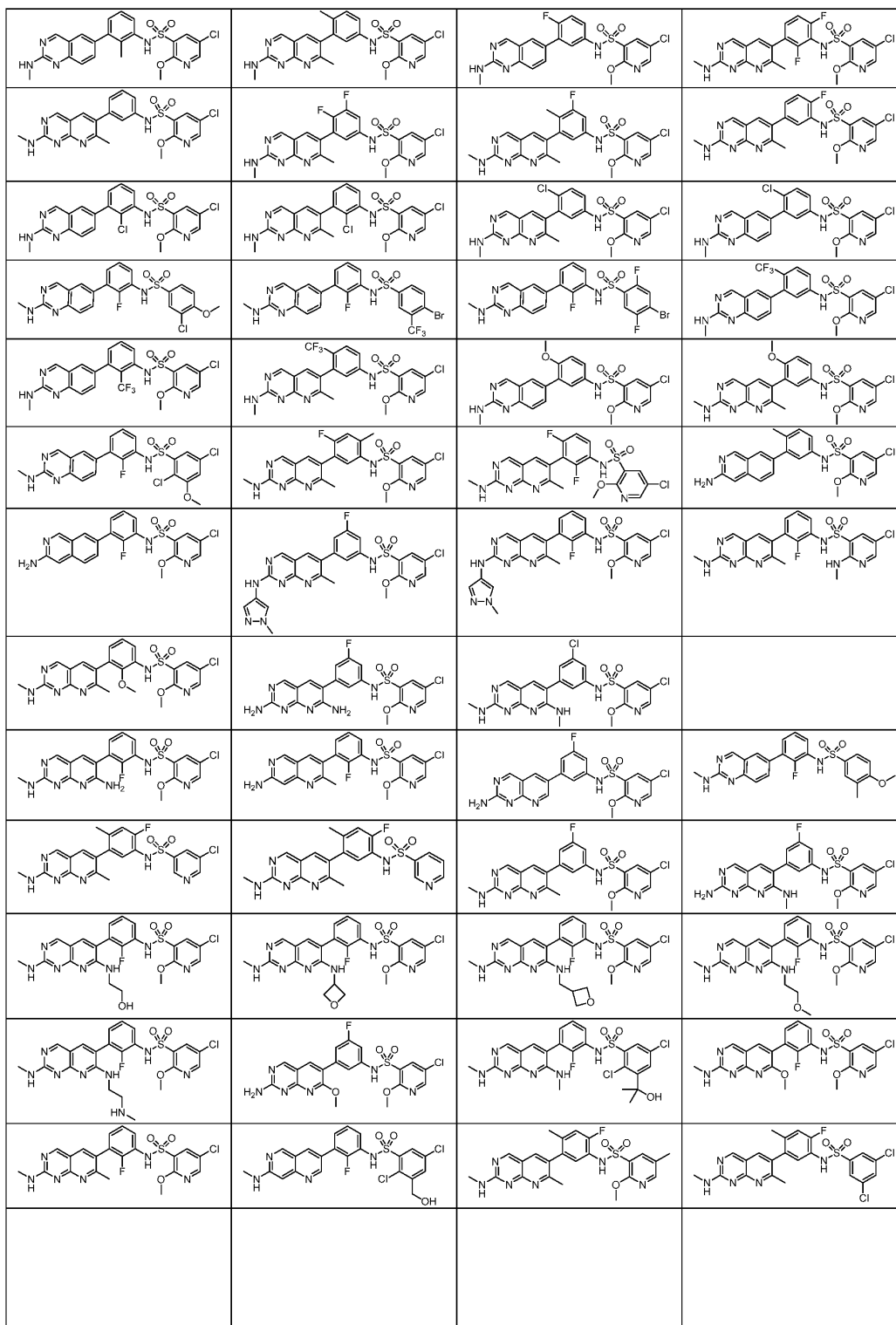
[0198] In some embodiments, X^{10} is N and X^{11} is CR^7 . In some embodiments, X^{10} and X^{11} are N.

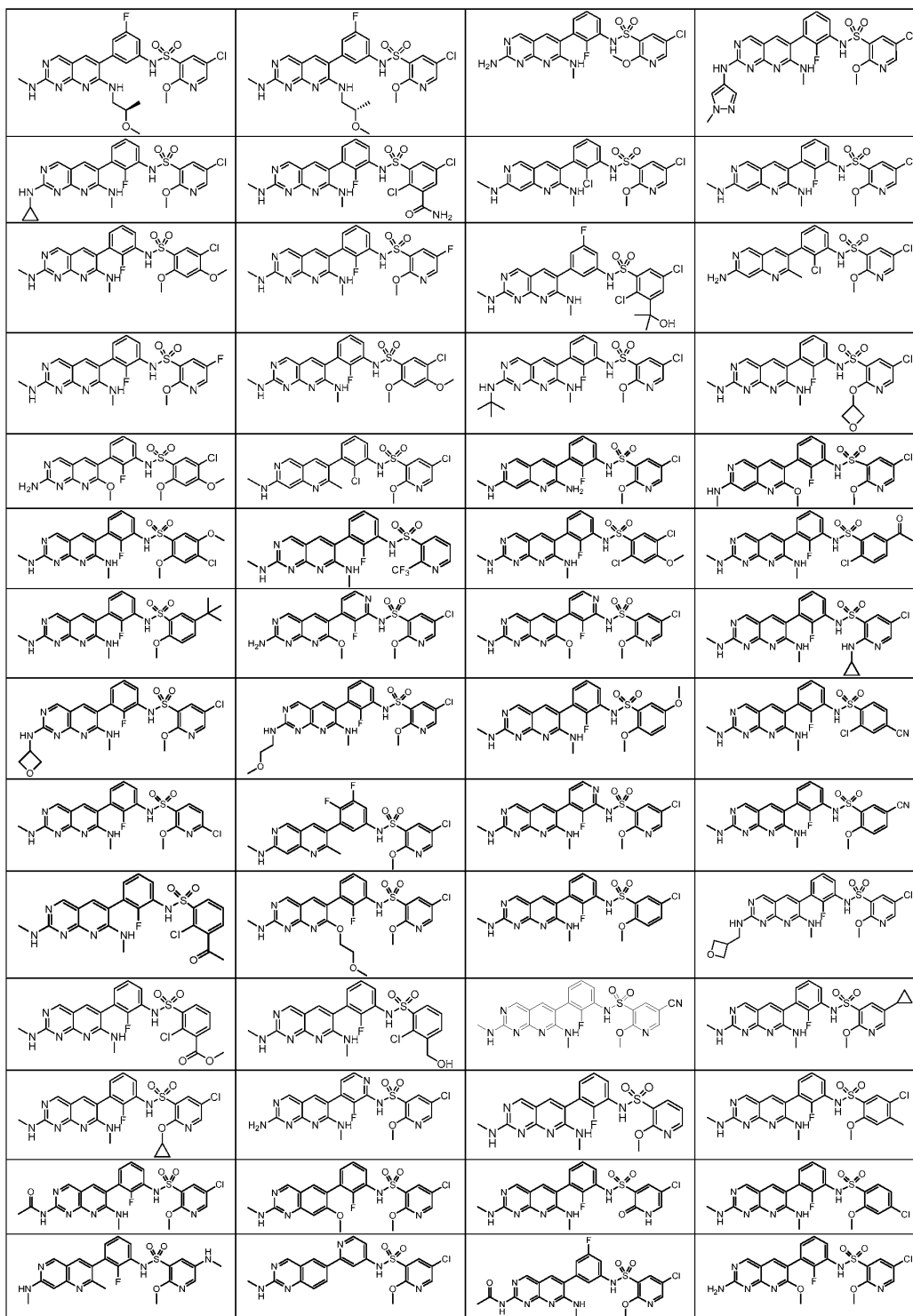
- 10 In some embodiments, X^{10} is CR^5 and X^{11} is N. In some embodiments, R^3 is H, C_1 - C_6 alkyl, and halogen. In some embodiments, R^3 is H. In some embodiments, R^3 is Me. In some embodiments, R^3 is F. In some embodiments, R^3 is Cl. In some embodiments, R^4 is selected from the group consisting of H, F, Cl, Me, OMe, CF_3 , and CN. In some embodiments, R^5 is selected from the group consisting of H, F, Cl, Me, OMe, CF_3 , and CN. In some embodiments, R^6 and R^7 are each
- 15 independently selected from the group consisting of H, F, Cl, Me. In some embodiments, R^4 , R^5 , R^6 , and R^7 are each independently H or F, and wherein at least one of R^4 , R^5 , R^6 , and R^7 is F. In some embodiments, R^6 is F; and R^4 , R^5 , and R^7 are each H. In some embodiments, R^4 is F; and R^5 , R^6 , and R^7 are each H. In some embodiments, R^4 and R^6 are each F; and R^5 and R^7 are each H. In some
- 20 embodiments, R^4 and R^5 are each F; and R^6 and R^7 are each H. In some embodiments, R^5 and R^6 are each F; and R^4 and R^7 are each H. In some embodiments, R^{15} is selected from the group consisting of C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, and C_3 - C_6 heterocyclyl. In some embodiments, R^{15} is cyclopropyl.

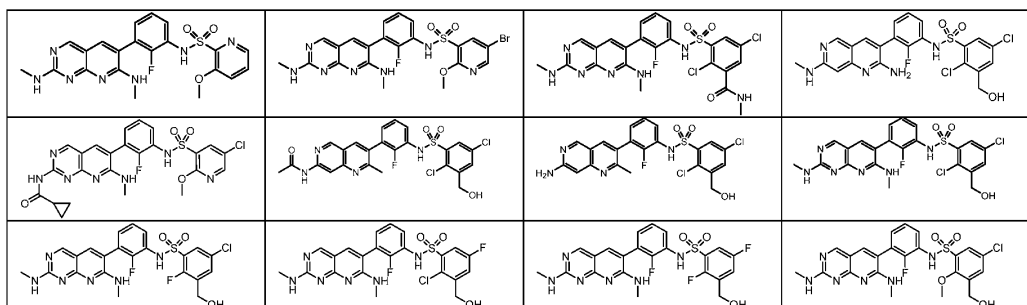
In some embodiments, R¹⁵ is Me. In some embodiments, R¹⁵ is oxetanyl. In some embodiments, R¹⁵ is oxetan-2-yl. In some embodiments, R¹⁵ is oxetan-3-yl.

[0199] In some embodiments, the compound is selected from the group consisting of:









and pharmaceutically acceptable salts, enantiomers, stereoisomers, and tautomers thereof.

Methods of Treatment

- 5 **[0200]** Compounds described herein, *e.g.*, compounds of Formula I as defined herein, can act as therapeutic agents for diseases driven by GCN2 or PERK kinase, and are useful in the treatment of diseases and disorders in patients in need thereof, such as cancer. Exemplary cancers include, but are not limited to, colorectal cancer, rectal cancer, anal cancer, familial colorectal cancer, hereditary nonpolyposis colorectal cancer, gastrointestinal stromal tumor, lung cancer (*e.g.*, non-small cell lung cancer, small cell lung cancer, malignant mesothelioma), mesothelioma, pancreatic cancer (*e.g.*,
10 pancreatic duct cancer, pancreatic endocrine tumor), pharyngeal cancer, laryngeal cancer, esophagus cancer, gastric cancer (*e.g.*, papillary adenocarcinoma, mucinous adenocarcinoma, adenosquamous carcinoma), duodenal cancer, small intestinal cancer, breast cancer (*e.g.*, invasive ductal carcinoma, ductal carcinoma in situ, inflammatory breast cancer), ovarian cancer (*e.g.*, ovarian epithelial carcinoma, extragonadal germ cell tumor, ovarian germ cell tumor, ovarian low malignant potential tumor), testis tumor, prostate cancer (*e.g.*, hormone-dependent prostate cancer, non-hormone dependent prostate cancer, castration-resistant prostate cancer), liver cancer (*e.g.*, hepatoma, primary liver cancer, extrahepatic bile duct cancer), thyroid cancer (*e.g.*, medullary thyroid carcinoma), renal cancer (*e.g.*, renal cell carcinoma (*e.g.*, clear cell renal cell carcinoma), transitional cell carcinoma of
20 renal pelvis and ureter), uterine cancer (*e.g.*, cervical cancer, uterine body cancer, uterus sarcoma), gestational choriocarcinoma, brain tumor (*e.g.*, medulloblastoma, glioma, pineal astrocytoma, pilocytic astrocytoma, diffuse astrocytoma, anaplastic astrocytoma, hypophyseal adenoma), retinoblastoma, skin cancer (*e.g.*, basal cell carcinoma, malignant melanoma, melanoma), sarcoma (*e.g.*, rhabdomyosarcoma, leiomyosarcoma, soft tissue sarcoma, spindle cell sarcoma, osteosarcoma),
25 fibrosarcoma, malignant bone tumor, urinary bladder cancer, hematologic cancer (*e.g.*, multiple myeloma, leukemia, acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), including blast crisis of chronic leukemia), malignant lymphoma, Hodgkin's disease, chronic

myeloproliferative disease), cancer of unknown primary nucleus], cancer growth inhibitor, cancer metastasis inhibitor, apoptosis promoter, and for the prophylaxis or treatment of precancerous lesion (e.g., bone marrow myelodysplastic syndrome).

[0201] Also described herein, in one embodiment, is a method of treating a disease caused by a dysregulation of an integrated stress response 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 Formula I described herein), or a pharmaceutically acceptable salt thereof, or of a pharmaceutical composition described herein. In some embodiments, the dysregulation of the integrated stress response and/or the unfolded protein response is caused by GCN2 kinase. In some embodiments, the dysregulation of the integrated stress response and/or the unfolded protein response is caused by PERK kinase. In some embodiments, the dysregulation of the integrated stress response is caused by GCN2 kinase. In some embodiments, the dysregulation of the unfolded protein response is caused by PERK kinase. In some embodiments, the dysregulation of the integrated stress response is caused by activation of a kinase selected from the group consisting of PERK kinase and GCN2 kinase. In some embodiments, the dysregulation of the integrated stress response is caused by activation of GCN2 kinase. In some embodiments, the dysregulation of the integrated stress response is caused by activation of PERK kinase.

[0202] Also described herein, in one embodiment, is a method of treating a disease caused by a dysregulation of an integrated stress response and/or an unfolded protein response 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 Formula I described herein), or a pharmaceutically acceptable salt thereof, or of a pharmaceutical composition described herein. In some embodiments, the dysregulation of the integrated stress response and/or the unfolded protein response is caused by activation of a kinase selected from the group consisting of PERK kinase and GCN2 kinase. In some embodiments, the dysregulation of the integrated stress response is caused by activation of GCN2 kinase. In some embodiments, the dysregulation of the unfolded protein response is caused by activation of PERK kinase.

[0203] In another embodiment, described herein is a method of modulating the activity of GCN2 kinase in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof, or of a pharmaceutical composition described herein.

[0204] In another embodiment, described herein is a method of activating GCN2 kinase in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a

compound described herein, or a pharmaceutically acceptable salt thereof, or of a pharmaceutical composition described herein.

[0205] In another embodiment, described herein is a method of modulating the activity of PERK kinase in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof, or of a pharmaceutical composition described herein.

[0206] In another embodiment, described herein is a method of activating PERK kinase in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof, or of a pharmaceutical composition described herein.

[0207] In another embodiment, described herein is a method of inhibiting GCN2 kinase and inhibiting PERK kinase in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof, or of a pharmaceutical composition described herein.

[0208] In another embodiment, described herein is a method of modulating the activity of GCN2 kinase in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof, or of a pharmaceutical composition described herein.

[0209] In another embodiment, described herein is a method of inhibiting the activity of PERK kinase in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof, or of a pharmaceutical composition described herein.

[0210] 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 Formula I described herein), or a pharmaceutically acceptable salt thereof, or of a pharmaceutical composition described herein. In some embodiments, the cancer is selected from the group consisting of colorectal cancer, lung cancer, mesothelioma, pancreatic cancer, pharyngeal cancer, laryngeal cancer, esophagus cancer, gastric, duodenal cancer, small intestinal cancer, breast cancer, ovarian cancer, testis tumor, prostate, liver cancer, thyroid cancer, renal cancer, uterine cancer, gestational choriocarcinoma, brain tumor, retinoblastoma, skin cancer, melanoma, sarcoma, fibrosarcoma, malignant bone tumor, urinary bladder cancer, hematologic cancer, leukemia, acute myeloid leukemia, acute lymphoblastic leukemia, and malignant lymphoma. In some embodiments, the cancer is selected from the group consisting of colorectal cancer, lung cancer, mesothelioma, pancreatic cancer, pharyngeal cancer, laryngeal cancer, esophagus cancer,

gastric, duodenal cancer, small intestinal cancer, breast cancer, ovarian cancer, testis tumor, prostate, liver cancer, thyroid cancer, renal cancer, uterine cancer, gestational choriocarcinoma, brain tumor, retinoblastoma, skin cancer, melanoma, sarcoma, fibrosarcoma, malignant bone tumor, urinary bladder cancer, hematologic cancer, leukemia, acute myeloid leukemia, acute lymphoblastic

5 leukemia, chronic lymphocytic leukemia, chronic myeloid leukemia, multiple myeloma, B-cell lymphoma, Follicular lymphoma, mantle cell lymphoma, diffuse large B cell lymphoma, T-cell lymphoma, erythroleukemia, histocytic lymphoma, waldenstrom macroglobulinemia, and malignant lymphoma. In some embodiments, the cancer is leukemia. In some embodiments, the cancer is acute myeloid leukemia. In some embodiments, the cancer is acute lymphoblastic leukemia. In

10 some embodiments, the cancer is fibrosarcoma. In some embodiments, the cancer is multiple myeloma. In some embodiments, the cancer is lymphoma. In some embodiments, the cancer is B-cell lymphoma. In some embodiments, the cancer is T cell lymphoma.

[0211] In an embodiment, described herein is a method of treating amyloidosis in a patient in need thereof, comprising administering to the patient a compound described herein, or pharmaceutically

15 acceptable salt thereof, or pharmaceutical composition described herein. In an embodiment, described herein is a method of treating light chain amyloidosis in a patient in need thereof, comprising administering to the patient a compound described herein, or pharmaceutically acceptable salt thereof, or pharmaceutical composition described herein.

[0212] In another embodiment, described herein is a method of treating a disease selected from a

20 GCN2 associated disease and a PERK associated disease, 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 Formula I described herein), or a pharmaceutically acceptable salt thereof, or of a pharmaceutical composition described herein. In some embodiments, the disease is a GCN2 associated disease. In some embodiments, the disease is a PERK associated disease. In some

25 embodiments, the disease is a cancer. In some embodiments, the cancer is selected from the group consisting of colorectal cancer, lung cancer, mesothelioma, pancreatic cancer, pharyngeal cancer, laryngeal cancer, esophagus cancer, gastric, duodenal cancer, small intestinal cancer, breast cancer, ovarian cancer, testis tumor, prostate, liver cancer, thyroid cancer, renal cancer, uterine cancer, gestational choriocarcinoma, brain tumor, retinoblastoma, skin cancer, melanoma, sarcoma,

30 fibrosarcoma, malignant bone tumor, urinary bladder cancer, hematologic cancer, leukemia, acute myeloid leukemia, acute lymphoblastic leukemia, and malignant lymphoma. In some embodiments, the cancer is selected from the group consisting of colorectal cancer, lung cancer, mesothelioma, pancreatic cancer, pharyngeal cancer, laryngeal cancer, esophagus cancer, gastric, duodenal cancer, small intestinal cancer, breast cancer, ovarian cancer, testis tumor, prostate, liver cancer, thyroid

cancer, renal cancer, uterine cancer, gestational choriocarcinoma, brain tumor, retinoblastoma, skin cancer, melanoma, sarcoma, fibrosarcoma, malignant bone tumor, urinary bladder cancer, hematologic cancer, leukemia, acute myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myeloid leukemia, multiple myeloma, B-cell lymphoma, Follicular lymphoma, mantle cell lymphoma, diffuse large B cell lymphoma, T-cell lymphoma, erythroleukemia, histocytic lymphoma, waldenstrom macroglobulinemia, and malignant lymphoma. In some embodiments, the cancer is leukemia. In some embodiments, the cancer is acute myeloid leukemia. In some embodiments, the cancer is acute lymphoblastic leukemia. In some embodiments, the cancer is fibrosarcoma. In some embodiments, the cancer is multiple myeloma.

10 In some embodiments, the cancer is lymphoma. In some embodiments, the cancer is B-cell lymphoma. In some embodiments, the cancer is T cell lymphoma. In some embodiments, the disease is amyloidosis. In some embodiments, the disease is light chain amyloidosis.

[0213] In another embodiment, described herein is a method of treating a disease selected from a GCN2 associated disease and a PERK associated disease, in a patient in need thereof, comprising

15 administering to the patient a therapeutically effective amount of a compound described herein (e.g., a compound of Formula I described herein), or a pharmaceutically acceptable salt thereof, and a therapeutically effective amount of one or more therapeutic agents. In some embodiments, the disease is a GCN2 associated disease. In some embodiments, the disease is a PERK associated disease. In some embodiments, the disease is a cancer. In some embodiments, the cancer is selected

20 from the group consisting of colorectal cancer, lung cancer, mesothelioma, pancreatic cancer, pharyngeal cancer, laryngeal cancer, esophagus cancer, gastric, duodenal cancer, small intestinal cancer, breast cancer, ovarian cancer, testis tumor, prostate, liver cancer, thyroid cancer, renal cancer, uterine cancer, gestational choriocarcinoma, brain tumor, retinoblastoma, skin cancer, melanoma, sarcoma, fibrosarcoma, malignant bone tumor, urinary bladder cancer, hematologic cancer, leukemia, acute myeloid leukemia, acute lymphoblastic leukemia, and malignant lymphoma.

25 In some embodiments, the cancer is selected from the group consisting of colorectal cancer, lung cancer, mesothelioma, pancreatic cancer, pharyngeal cancer, laryngeal cancer, esophagus cancer, gastric, duodenal cancer, small intestinal cancer, breast cancer, ovarian cancer, testis tumor, prostate, liver cancer, thyroid cancer, renal cancer, uterine cancer, gestational choriocarcinoma, brain tumor,

30 retinoblastoma, skin cancer, melanoma, sarcoma, fibrosarcoma, malignant bone tumor, urinary bladder cancer, hematologic cancer, leukemia, acute myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myeloid leukemia, multiple myeloma, B-cell lymphoma, Follicular lymphoma, mantle cell lymphoma, diffuse large B cell lymphoma, T-cell lymphoma, erythroleukemia, histocytic lymphoma, waldenstrom macroglobulinemia, and malignant

lymphoma. In some embodiments, the cancer is leukemia. In some embodiments, leukemia is acute myeloid leukemia. In some embodiments, leukemia is acute lymphoblastic leukemia. In some embodiments, the cancer is fibrosarcoma. In some embodiments, the cancer is multiple myeloma. In some embodiments, the cancer is lymphoma. In some embodiments, the cancer is B-cell lymphoma. In some embodiments, the cancer is T cell lymphoma. In some embodiments, the disease is amyloidosis. In some embodiments, the disease is light chain amyloidosis. In some embodiments, the one or more therapeutic agents is selected from the group consisting of L-asparaginase, pegylated asparaginase, a PERK inhibitor, a mTOR inhibitor, an immunomodulatory agent, a MAPK pathway inhibitor, a MEK inhibitor, an ERK inhibitor, and a Ras inhibitor. In some

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embodiments, the one or more therapeutic agents is selected from the group consisting of an IMiD agent, a proteasome inhibitor, a steroid, an anti-CD38 agent, an anti-CD20 agent, a Bcl-2 inhibitor, a PI3K inhibitor, a Bi-specific antibody, a nucleoside analog, a BTK inhibitor, a DNA alkylating agent, an EZH2 inhibitor, an anthracycline, a topoisomerase inhibitor, a platin, a tyrosine kinase inhibitor, an HDAC inhibitor, a nuclear export inhibitor, an anti-microtubule agent L-asparaginase, pegylated asparaginase, a PERK inhibitor, a mTOR inhibitor, an immunomodulatory agent, a MAPK pathway inhibitor, a MEK inhibitor, an ERK inhibitor, and a Ras inhibitor. In some embodiments, the one or more therapeutic agents is selected from the group consisting of L-asparaginase, pegaspargase, calaspargase pegol – mnkl, bortezomib, carfilzomib, ixazomib, thalidomide, pomalidomide, lenalidomide, dexamethasone, prednisone, daratumumab, daratumumab / hyaluronidase, isatuximab, rituximab, obinutuzumab, venetoclax, idelalisib, copanlisib, duvelisib, umbralisib, gemcitabine, cytarabine, ibrutinib, acalabrutinib, zanubrutinib, bendamustine, cyclophosphamide, tazemetostat, doxorubicin, daunorubicin, etoposide, oxaloplatin, carboplatin, cisplatinbosutinib, dasatinib, imatinib, nilotinib, ponatinib, panobinostat, selinexor, vincristine, JZP-458, eryaspase, PF745 (JZP-341), asparaginase *Erwinia chrysanthemi* (crisantaspase), *Escherichia coli* asparaginase (colaspase), an anti-PD1 agent, an anti-PDL1 agent, and an anti-CTLA4 agent.

[0214] In an embodiment, described herein is a compound described herein, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition described herein, for use in treating a disease caused by a dysregulation of an integrated stress response and/or the unfolded protein response in a patient in need thereof. In some embodiments, the dysregulation of the integrated stress response and/or the unfolded protein response is caused by a kinase selected from the group consisting of PERK kinase and GCN2 kinase. In some embodiments, the dysregulation of the integrated stress response and/or the unfolded protein response is caused by GCN2 kinase. In some embodiments, the dysregulation of the integrated stress response and/or the unfolded protein response is caused by PERK kinase. In some embodiments, the dysregulation of the integrated stress

response is caused by GCN2 kinase. In some embodiments, the dysregulation of the unfolded protein response is caused by PERK kinase. In some embodiments, the dysregulation of the integrated stress response is caused by activation of a kinase selected from the group consisting of PERK kinase and GCN2 kinase. In some embodiments, the dysregulation of the integrated stress response is caused by activation of GCN2 kinase. In some embodiments, the dysregulation of the integrated stress response is caused by activation of PERK kinase. In an embodiment, described herein is a compound described herein, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition described herein, for use in modulating the activity of GCN2 kinase in a patient in need thereof. In an embodiment, described herein is a compound described herein, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition described herein, for use in activating GCN2 kinase in a patient in need thereof. In an embodiment, described herein is a compound described herein, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition described herein, for use in modulating the activity of PERK kinase in a patient in need thereof. In an embodiment, described herein is a compound described herein, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition described herein, for use in activating PERK kinase in a patient in need thereof.

[0215] In an embodiment, described herein is a compound described herein, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition described herein, for use in inhibiting GCN2 kinase and inhibiting PERK kinase in a patient in need thereof. In an embodiment, described herein is a compound described herein, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition described herein, for use in modulating the activity of GCN2 kinase in a patient in need thereof. In another embodiment, described herein is a compound described herein, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition described herein, for use in inhibiting the activity of PERK kinase in a patient in need thereof.

[0216] In an embodiment, described herein is a compound described herein, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition described herein, for use in treating a cancer in a patient in need thereof. In some embodiments, the cancer is selected from the group consisting of colorectal cancer, lung cancer, mesothelioma, pancreatic cancer, pharyngeal cancer, laryngeal cancer, esophagus cancer, gastric, duodenal cancer, small intestinal cancer, breast cancer, ovarian cancer, testis tumor, prostate, liver cancer, thyroid cancer, renal cancer, uterine cancer, gestational choriocarcinoma, brain tumor, retinoblastoma, skin cancer, melanoma, sarcoma, fibrosarcoma, malignant bone tumor, urinary bladder cancer, hematologic cancer, leukemia, acute myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myeloid leukemia, multiple myeloma, B-cell lymphoma, follicular lymphoma, mantle cell lymphoma, diffuse

large B cell lymphoma, T-cell lymphoma, erythroleukemia, histiocytic lymphoma, waldenstrom macroglobulinemia, and malignant lymphoma. In some embodiments, the cancer is leukemia. In some embodiments, the cancer is acute myeloid leukemia. In some embodiments, the cancer is acute lymphoblastic leukemia. In some embodiments, the cancer is fibrosarcoma. In some embodiments, the cancer is multiple myeloma. In some embodiments, the cancer is lymphoma. In some embodiments, the cancer is B-cell lymphoma. In some embodiments, the cancer is T cell lymphoma.

[0217] In an embodiment, described herein is a compound described herein, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition described herein, for use in treating amyloidosis in a patient in need thereof. In an embodiment, described herein is a compound described herein, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition described herein, for use in treating light chain amyloidosis in a patient in need thereof.

[0218] In an embodiment, described herein is a compound described herein, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition described herein, for use in treating a disease selected from a GCN2 associated disease and a PERK associated disease, in a patient in need thereof. In some embodiments, the disease is a GCN2 associated disease. In some embodiments, the disease is a PERK associated disease. In some embodiments, the disease is a cancer. In some embodiments, the cancer is selected from the group consisting of colorectal cancer, lung cancer, mesothelioma, pancreatic cancer, pharyngeal cancer, laryngeal cancer, esophagus cancer, gastric, duodenal cancer, small intestinal cancer, breast cancer, ovarian cancer, testis tumor, prostate, liver cancer, thyroid cancer, renal cancer, uterine cancer, gestational choriocarcinoma, brain tumor, retinoblastoma, skin cancer, melanoma, sarcoma, fibrosarcoma, malignant bone tumor, urinary bladder cancer, hematologic cancer, leukemia, acute myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myeloid leukemia, multiple myeloma, B-cell lymphoma, follicular lymphoma, mantle cell lymphoma, diffuse large B cell lymphoma, T-cell lymphoma, erythroleukemia, histiocytic lymphoma, waldenstrom macroglobulinemia, and malignant lymphoma. In some embodiments, the cancer is leukemia. In some embodiments, the cancer is acute myeloid leukemia. In some embodiments, the cancer is acute lymphoblastic leukemia. In some embodiments, the cancer is fibrosarcoma. In some embodiments, the cancer is multiple myeloma. In some embodiments, the cancer is lymphoma. In some embodiments, the cancer is B-cell lymphoma. In some embodiments, the cancer is T cell lymphoma. In some embodiments, the disease is amyloidosis. In some embodiments, the disease is light chain amyloidosis.

[0219] In an embodiment, described herein is a compound described herein, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition described herein, for use in treating a disease selected from a GCN2 associated disease and a PERK associated disease, in a patient in need

thereof. In some embodiments, the disease is a GCN2 associated disease. In some embodiments, the disease is a PERK associated disease. In some embodiments, the disease is a cancer. In some embodiments, the cancer is selected from the group consisting of colorectal cancer, lung cancer, mesothelioma, pancreatic cancer, pharyngeal cancer, laryngeal cancer, esophagus cancer, gastric, duodenal cancer, small intestinal cancer, breast cancer, ovarian cancer, testis tumor, prostate, liver cancer, thyroid cancer, renal cancer, uterine cancer, gestational choriocarcinoma, brain tumor, retinoblastoma, skin cancer, melanoma, sarcoma, fibrosarcoma, malignant bone tumor, urinary bladder cancer, hematologic cancer, leukemia, acute myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myeloid leukemia, multiple myeloma, B-cell lymphoma, follicular lymphoma, mantle cell lymphoma, diffuse large B cell lymphoma, T-cell lymphoma, erythroleukemia, histocytic lymphoma, waldenstrom macroglobulinemia, and malignant lymphoma. In some embodiments, the cancer is leukemia. In some embodiments, leukemia is acute myeloid leukemia. In some embodiments, leukemia is acute lymphoblastic leukemia. In some embodiments, the cancer is fibrosarcoma. In some embodiments, the cancer is multiple myeloma.

In some embodiments, the cancer is lymphoma. In some embodiments, the cancer is B-cell lymphoma. In some embodiments, the cancer is T cell lymphoma. In some embodiments, the disease is amyloidosis. In some embodiments, the disease is light chain amyloidosis. In some embodiments, the one or more therapeutic agents is selected from the group consisting of an IMiD agent, a proteasome inhibitor, a steroid, an anti-CD38 agent, an anti-CD20 agent, a Bcl-2 inhibitor, a PI3K inhibitor, a Bi-specific antibody, a nucleoside analog, a BTK inhibitor, a DNA alkylating agent, an EZH2 inhibitor, an anthracycline, a topoisomerase inhibitor, a platin, a tyrosine kinase inhibitor, an HDAC inhibitor, a nuclear export inhibitor, an anti-microtubule agent, L-asparaginase, pegylated asparaginase, a PERK inhibitor, a mTOR inhibitor, an immunomodulatory agent, a MAPK pathway inhibitor, a MEK inhibitor, an ERK inhibitor, and a Ras inhibitor. In some embodiments, the one or more therapeutic agents is selected from the group consisting of bortezomib, carfilzomib, ixazomib, thalidomide, pomalidomide, lenalidomide, dexamethasone, prednisone, daratumumab, daratumumab / hyaluronidase, isatuximab, rituximab, obinutuzumab, venetoclax, idelalisib, copanlisib, duvelisib, umbralisib, gemcitabine, cytarabine, ibrutinib, acalabrutinib, zanubrutinib, bendamustine, cyclophosphamide, tazemetostat, doxorubicin, daunorubicin, etoposide, oxaloplatin, carboplatin, cisplatinbosutinib, dasatinib, imatinib, nilotinib, ponatinib, panobinostat, selinexor, vincristine, L-asparaginase, pegaspargase, calaspargase pegol-mnkl, JZP-458, eryaspase, PF745 (JZP-341), asparaginase *Erwinia chrysanthemi* (crisantaspase), *Escherichia coli* asparaginase (colaspase), anti-PD1, anti-PDL1, and anti-CTLA4..

[0220] 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.

[0221] 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

[0222] Compounds described herein, *e.g.*, a compound of Formula I as defined 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 Formula I as defined herein, one or more additional therapeutic agents, and a pharmaceutically acceptable excipient. In some embodiments, a compound of Formula I as defined herein, and one additional therapeutic agent is administered. In some embodiments, a compound of Formula I as defined herein, and two additional therapeutic agents are administered. In some embodiments, a compound of Formula I as defined 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 Formula I as defined 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 Formula I as one therapeutic agent and one or more additional therapeutic agents such as a chemotherapeutic

agent. For example, a compound of Formula I as defined 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.

[0223] 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.

[0224] Combination therapy can also include two or more administrations of one or more of the agents used in the combination using different routes of administration. Each of the one or more of the agents may be independently 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.

[0225] In some embodiments, the compounds of Formula I as described herein, are combined with asparaginase (ASNase, L-asparaginase) or its derivatives. In some embodiments, asparaginase is obtained from *Erwinia chrysanthemi* and is known as crisantaspase or asparaginase *Erwinia chrysanthemi*. Asparaginase *Erwinia chrysanthemi* is sold under the trademarks Erwinaze® or Erwinase®. In some embodiments, asparaginase is obtained from *Escherichia coli* and is known as colaspase. Colaspase is sold under the trademarks Elspar®, Leunase®, Kidrolase®, or Spectrila® (recombinant *E. coli* asparaginase). Pegylated derivatives of colaspase are pegaspargase, sold under the trademark Oncaspar®, and calaspargase pegol – mnkl, sold under the trademark Asparlas®. Other asparaginase products currently in preclinical or clinical development include JZP-458 (recombinant *Erwinia* asparaginase), PF745 (JZP-341), eryaspase (GRASPA®), and Xoncane.

[0226] In some embodiments, the compounds of Formula I as defined 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.

[0227] 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.

[0228] Exemplary MEK inhibitors include, but are not limited to, trametinib, selumetinib, cobimetinib, binimetinib, and pharmaceutically acceptable salts thereof. Exemplary ERK inhibitors include, but are not limited to, include, but are not limited to, ulixertinib, SCH772984, LY3214996, raxoxertinib, 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.

[0229] 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.

[0230] The compounds of Formula I as 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, pomalidomide, bortezomib, carfilzomib, ixazomib, daratumumab, daratumumab / hyaluronidase, isatuximab, dexamethasone, and antibody-drug-conjugates (ADCs).

[0231] 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 nab-paclitaxel, eribulin, docetaxel, ixabepilone, vincristine, auristatins, or maytansinoids), vinorelbine, DNA-alkylating agents (including cisplatin, carboplatin, oxaliplatin, cyclophosphamide, ifosfamide, temozolomide), DNA intercalating agents or DNA topoisomerase inhibitors (including 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.

[0232] 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,

[0233] 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.

[0234] In some embodiments, the additional therapeutic agents can be anti-angiogenic agents including bevacizumab, aflibercept, and AMG386.

[0235] In some embodiments, the additional therapeutic agents can be antibody-drug-conjugates (ADCs) including DM1, DM4, MMAE, MMAF, or camptothecin payloads, brentuximab vedotin and
5 trastuzumab emtansine, radiotherapy, therapeutic vaccines including but not limited to sipuleucel-T.

[0236] In some embodiments, the additional therapeutic agent can be an autophagy inhibitor including ULK inhibitors, VPS34 inhibitors, PIKfyve inhibitors, PPT1 inhibitors, or lysosomal blocking agents. In some embodiments, the additional therapeutic agent can be DCC-3116, SAR405, SB02024, hydroxychloroquine, chloroquine, apilimod, MRT403, and LYS05.

10 [0237] In some embodiments, the additional therapeutic agent is selected from a luteinizing hormone-releasing hormone (LHRH) analog, including goserelin and leuprolide.

[0238] 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-

15 258, GSK461364, AZD 1152, enzastaurin, vandetanib, ARQ-197, MK-0457, MLN8054, PHA-739358, R-763, AT-9263, pemetrexed, erlotinib, dasatanib, 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
20 1001, IPdR1 KRX-0402, lucanthone, LY 317615, neuradiab, vitespan, Rta 744, alanosine (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]-,

25 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
30 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, ionafarnib, BMS-214662, tipifarnib; amifostine, NVP-LAQ824, suberoyl analide 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, gleevac, 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-mecaptopurine, deoxycoformycin, 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, pibendoxifene, 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-779450, 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

[0239] 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.

[0240] 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.

[0241] 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.

[0242] 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 a 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.

10 **[0243]** 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
15 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.

[0244] Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. Liquid
20 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,
25 tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, cyclodextrins and mixtures thereof.

[0245] Suspensions, in addition to the subject composition, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters,
30 microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

[0246] 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.

[0247] 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.

[0248] 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.

[0249] 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.

[0250] 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, Pluronic, 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.

[0251] 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.

[0252] 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.

[0253] In another embodiment, provided are enteral pharmaceutical formulations including a disclosed compound and 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.

[0254] 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.

[0255] 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.

5 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

10 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.

[0256] 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

15 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

20 second compound can consist of several tablets or capsules and vice versa. The memory aid should reflect this.

EXAMPLES

[0257] The compounds described herein can be prepared in a number of ways based on the teachings contained herein and disclosures of synthetic procedures in the art. In the description of

25 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

30 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.

[0258] The following abbreviations are used in this disclosure and have the following definitions:

“AcOH” is acetic acid, “ADP” is adenosine diphosphate, “AgNO₃” is silver nitrate, “ASNase” is Asparaginase, “Boc” is *t*-butylcarbonate, “CDI” is carbodiimidazole, “conc.” is concentrated, “Cs₂CO₃” is cesium carbonate, “CuI” is copper (I) iodide, “DBU” is 1,8-diazabicyclo[5.4.0]undec-7-ene, “DCC” is *N,N'*-Dicyclohexylcarbodiimide, “DCE” is dichloroethane, “DCM” is dichloromethane, “DIAD” is diisopropyl azodicarboxylate, “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, “DMSO” is dimethylsulfoxide, “EDTA” is ethylenediaminetetraacetic acid, “ESI” is electrospray ionization, “EtOAc” is ethyl acetate, “EtOH” is ethanol, “GST” is glutathione S-transferase, “h” is hour or hours, “HBTU” is (2-*(1H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate, “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, “KOAc” is potassium acetate, “K₃PO₄” is potassium phosphate, “NaBH₄” is sodium borohydride, “LAH” is lithium aluminum hydride, “LiOH” is lithium hydroxide, “MeCN” is acetonitrile, “MeOH” is methanol, “Me₄tBuXPhos” is di-*tert*-butyl(2',4',6'-triisopropyl-3,4,5,6-tetramethyl-[1,1'-biphenyl]-2-yl)phosphine, “MgSO₄” is magnesium sulfate, “MHz” is megahertz, “min” is minute or minutes, “MnO₂” is manganese (IV) oxide, “MS” is mass spectrometry, “NADH” is nicotinamide adenine dinucleotide, “Na” is sodium, “NaH” is sodium hydride, “NaHCO₃” is sodium bicarbonate, “NaNO₂” is sodium nitrite, “NaOMe” is sodium methoxide, “Na₂SO₄” is sodium sulfate, “NBS” is *N*-bromosuccinimide, “NCS” is *N*-chlorosuccinimide, “NH₄Cl” is ammonium chloride, “NH₂OH” is hydroxylamine, “NMP” is *N*-methyl-2-pyrrolidone, “NMR” is nuclear magnetic resonance, “PBS” is phosphate buffered saline, “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), “Pd(dppf)Cl₂” is 1,1-bis(diphenylphosphino)ferrocene-palladium(II)dichloride, “prep-HPLC” is preparative high performance liquid chromatography, “PCl₃” is phosphorus trichloride, “Ph₃P” is triphenylphosphine, “PhPOCl₂” is phenylphosphonic dichloride, “PMB” is *para*-methoxybenzyl, “POCl₃” is phosphorus oxychloride, “PyBOP” is benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate, “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, “satd.” is saturated, “SDS” is sodium dodecyl sulfate, “SFC” is supercritical fluid chromatography, “S_NAr” is nucleophilic aromatic substitution, “SOCl₂” is thionyl chloride, “T₃P” is *n*-propanephosphonic acid anhydride, “TEA” is triethylamine, “TFA” is trifluoroacetic acid, “THF” is tetrahydrofuran, “Xantphos” is 4,5-bis(diphenylphosphino)-

9,9-dimethylxanthene, “X-Phos” is 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl and “ZnCl₂” is zinc chloride.

[0259] In the Examples below and corresponding Figures, “Compound 16” refers to the compound depicted as Example 16 in Table I below.

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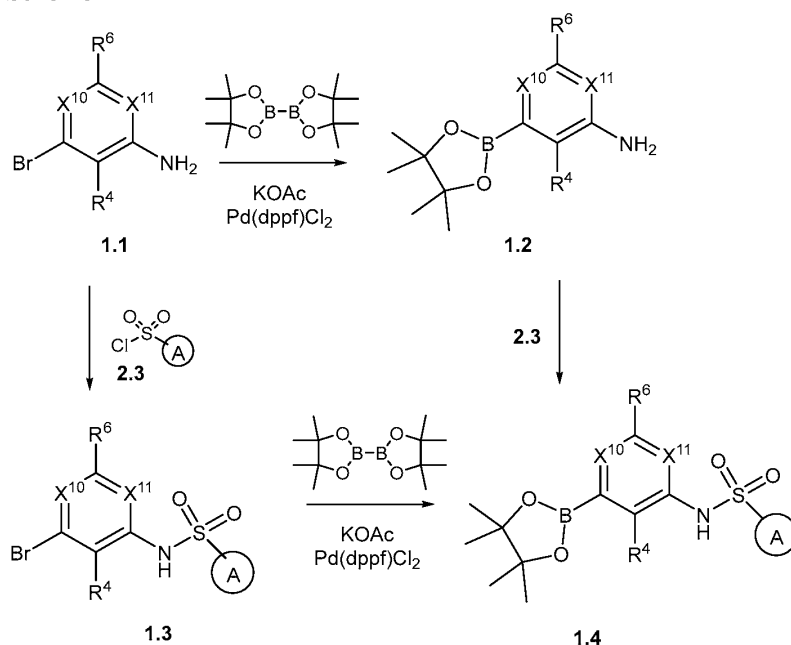
General Chemistry

[0260] Exemplary compounds described herein are available by the general synthetic methods illustrated in the Schemes below, intermediate preparations, and the accompanying Examples.

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Synthetic Schemes

Scheme 1



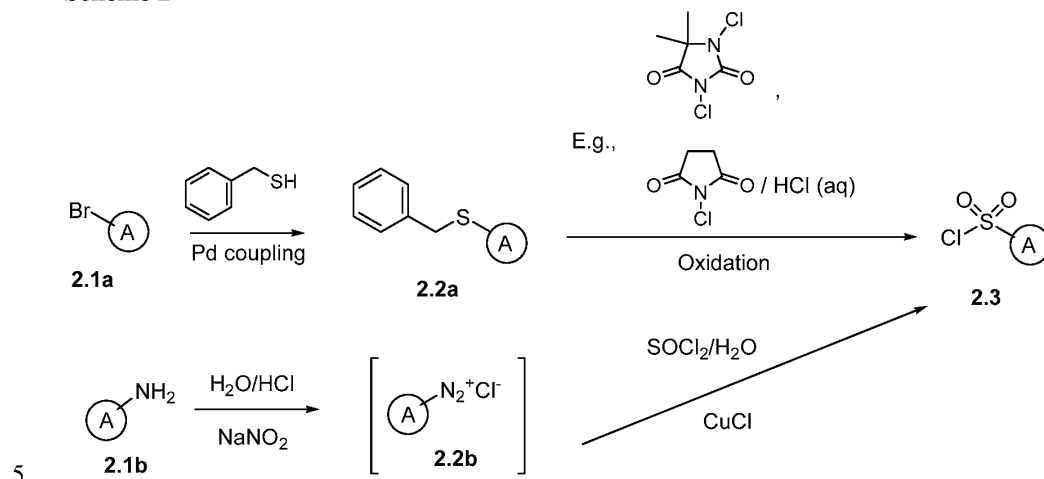
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[0261] Scheme 1 illustrates an exemplary preparation of boronates **1.4**. Compounds **1.1** (commercially available, synthesized as described in WO2013134298 or synthesized by those skilled in the art) react with bis(pinacolato)diboron by borylation reaction known to those skilled in the art (palladium-mediated reaction conducted using palladium catalysts such as Pd(dppf)Cl₂, a suitable base such as KOAc in a suitable solvent such as 1,4-dioxane at elevated temperature) to obtain compounds **1.2** which are reacted with sulfonyl chlorides **2.3** (see scheme 2) to give compounds **1.4**. Alternatively, compounds **1.1** react with sulfonyl chlorides **2.3** to afford the sulfonamides **1.3** which

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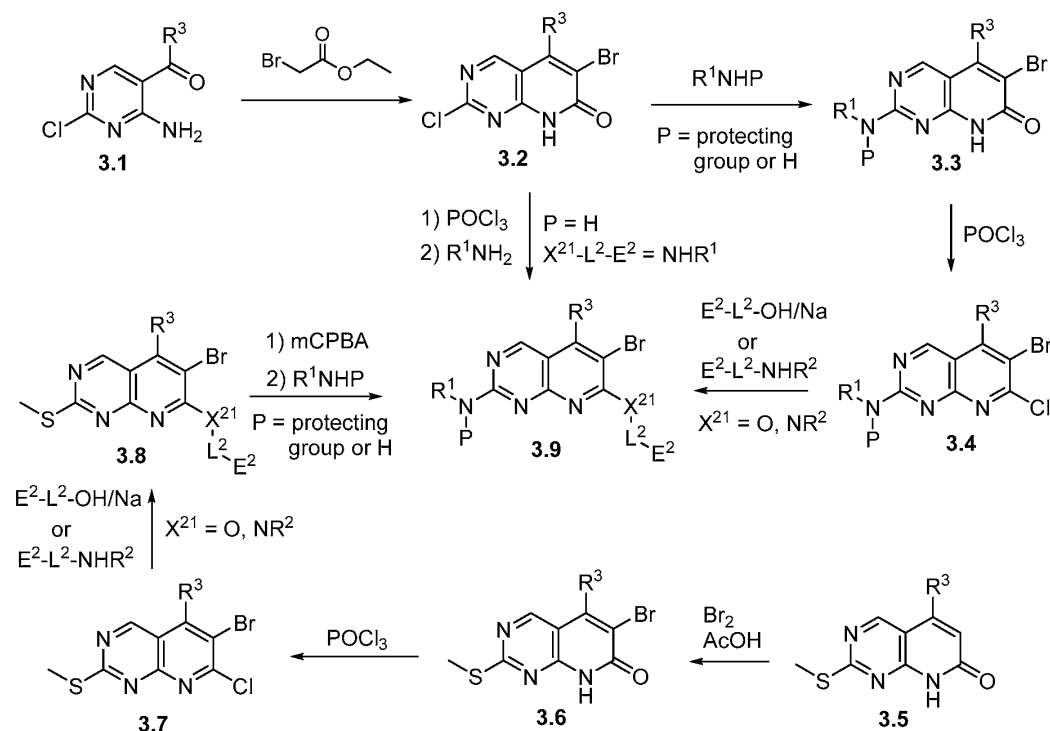
are converted to the boronates **1.4** under the borylation reaction conditions known to those skilled in the art.

Scheme 2



[0262] Scheme 2 illustrates an exemplary preparation of sulfonyl chlorides **2.3**. Bromides **2.1a** (ring A: substituted aryl, five or six-membered heteroaryl, commercially available or synthesized by those skilled in the art) are converted to thio-ethers **2.2a** by a Pd catalyzed coupling reaction (for example, using Pd₂(dba)₃, XantPhos, phenylmethanethiol in the presence of a base, such as DIEA in a solvent such as toluene, and at elevated temperature). A smooth oxidation of thio-ethers **2.2a** (e.g., by combination of NCS and dilute HCl, 1,3-dichloro-5,5-dimethylhydantoin) affords the corresponding sulfonyl chlorides **2.3** according to general reaction conditions reported in *Synthesis*, 2006, 24, 4131-4134 and *Bioorg. Med. Chem.*, 2017, 25, 3447-3460. Alternatively, sulfonyl chlorides **2.3** can be prepared from amines **2.1b** (ring A: substituted aryl, five or six-membered heteroaryl, commercially available or synthesized by those skilled in the art) by diazotization, followed by Cu-mediated chlorination of the resulting intermediate (according to general reaction conditions reported in *Org. Proc. Res. Dev.*, 2009, 5, 875-879).

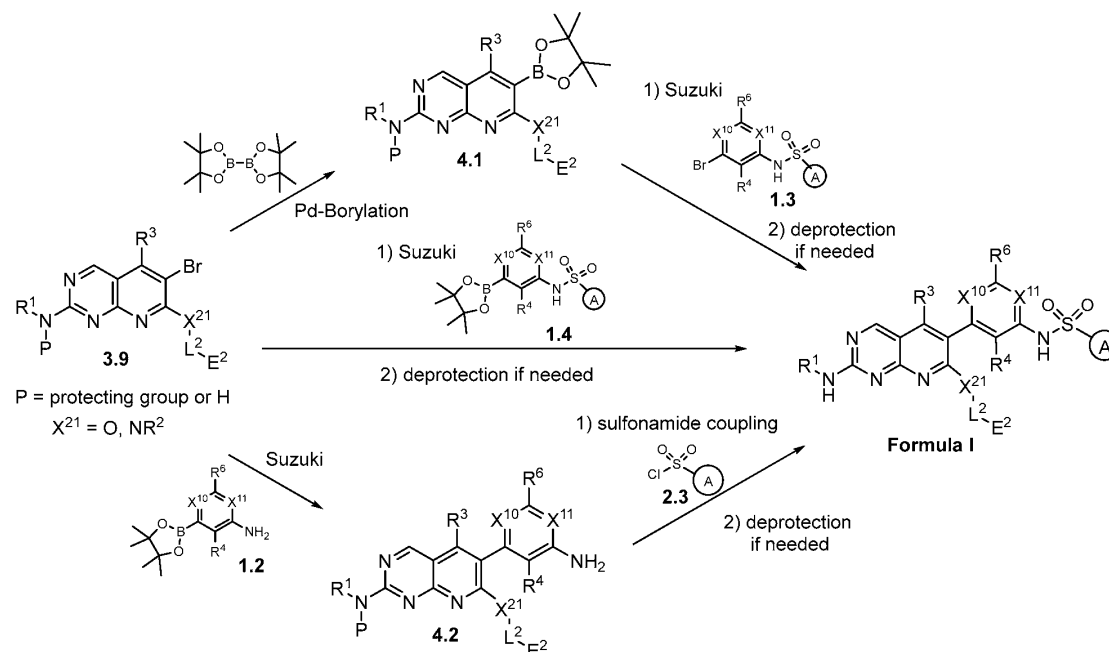
Scheme 3



- 5 **[0263]** Scheme 3 illustrates an exemplary preparation of intermediates **3.9** ($X^{21} = O, NR^2$). Compounds **3.1** (commercially available or synthesized by those skilled in the art) react with ethyl 2-bromoacetate in the presence of a base such as piperidine to afford the pyridopyrimidinones **3.2**. Compounds **3.2** react with amines R^1NHP ($P =$ protecting group or H) in the presence of base such as DIEA in a polar aprotic solvent such NMP at elevated temperature to afford **3.3**. Compounds **3.3** react with $POCl_3$ to afford **3.4** which are converted to the intermediates **3.9** ($X^{21} = O, NR^2$) by reaction with either alkoxides (E^2-L^2-OH/Na) or amines ($E^2-L^2-NHR^2$). In another embodiment, pyridopyrimidinones **3.2** react with $POCl_3$, followed by substitution reaction of the resulting intermediate with amines (R^1NH_2) to provide intermediates **3.9** ($X^{21}-L^2-E^2 = NHR^1$). Alternatively, intermediates **3.9** can be prepared from compounds **3.5** according to general reaction conditions reported in WO2018153373, CN105481858, and CN105968108. Bromination of **3.5** with bromine in AcOH affords bromides **3.6** which are converted to the chlorides **3.7** by treatment with $POCl_3$. Intermediates **3.7** are then converted to compounds **3.8** ($X^{21} = O, NR^2$) by reaction with alkoxides (E^2-L^2-OH/Na) or amines ($E^2-L^2-NHR^2$). Conversion of compounds **3.8** to the intermediates **3.9** is conducted in a two-step process including: (i) Thioether oxidation in the presence of an oxidant such

as mCPBA in a suitable solvent such as DCM at rt to obtain the corresponding sulfoxides and (ii) condensation of the sulfoxides with amines R^1NHP (P = protecting group or H).

Scheme 4

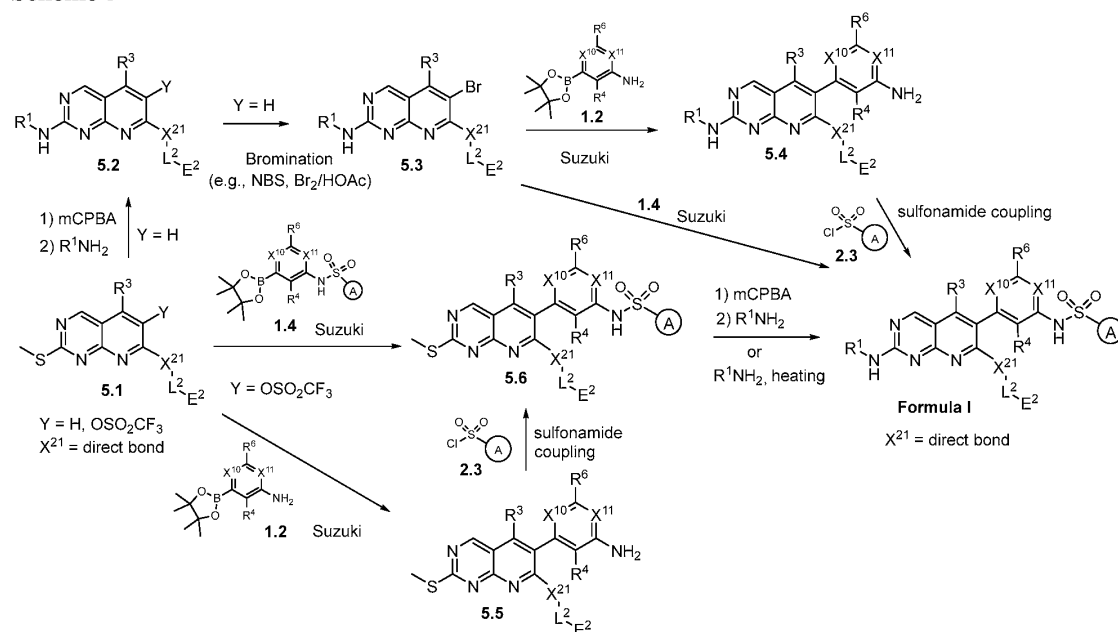


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[0264] Scheme 4 illustrates an exemplary preparation of compounds of Formula I. Condensation of intermediates **3.9** (prepared as described in Scheme 3, $X^{21} = O, NR^2$) with boronates **1.4** in the presence of a Pd catalyst such as $Pd(PPh_3)_4$ or $Pd(dppf)Cl_2$ affords compounds of Formula I.

Alternatively, **3.9** reacts with bis(pinacolato)diboron under palladium-mediated borylation reaction conditions to afford the boronate intermediates **4.1**. The boronates **4.1** react with bromides **1.3** to afford compounds of Formula I by Suzuki reaction known to those skill in the art. In another embodiment, **3.9** react with boronates **1.2** under Pd catalyzed coupling conditions (Suzuki reaction) to provide compounds **4.2**. Anilines **4.2** react with sulfonyl chlorides **2.3** in the presence of base such as pyridine to afford compounds of Formula I. In instances, where compounds of Formula I contain a nitrogen protecting group P , such as Boc or PMB, the protecting group can be removed under acidic conditions (TFA or HCl in 1,4-dioxane) to afford the corresponding amines (compounds of Formula I).

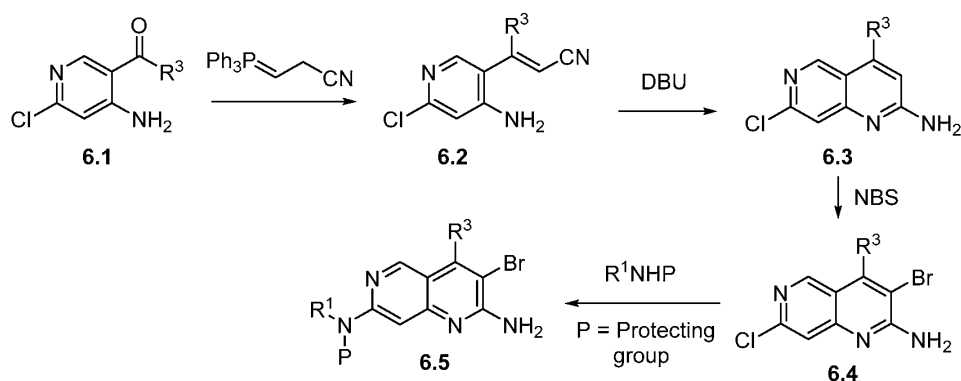
Scheme 5



[0265] Scheme 5 illustrates an exemplary preparation of compounds of Formula I. Suzuki reaction of **5.1** ($Y = OSO_2CF_3$, $X^{21} = \text{direct bond}$, synthesized as described in WO2013134243, WO2013029084 and *J. Med. Chem.*, 2015, 58, 4165-4179) with boronates **1.2** in the presence of a Pd catalyst such as $Pd(PPh_3)_4$ or $Pd(dppf)Cl_2$ affords anilines **5.5**. In a similar manner, compounds **5.1** ($Y = OSO_2CF_3$, $X^{21} = \text{direct bond}$) react with boronates **1.4** under Pd catalyzed coupling conditions (Suzuki reaction) to provide compounds **5.6**. Alternatively, **5.6** can be prepared by sulfonamide coupling reaction of anilines **5.5** with sulfonyl chlorides **2.3**. Conversion of compounds **5.6** to compounds of Formula I is conducted in a two-step process including: (i) thioether oxidation in the presence of an oxidant such as mCPBA in a suitable solvent such as DCM at rt to obtain the corresponding sulfoxides and (ii) condensation of the sulfoxides with amines R^1NH_2 . Alternatively, compounds of Formula I can be obtained by direct substitution reaction of **5.6** with amines R^1NH_2 at elevated temperature.

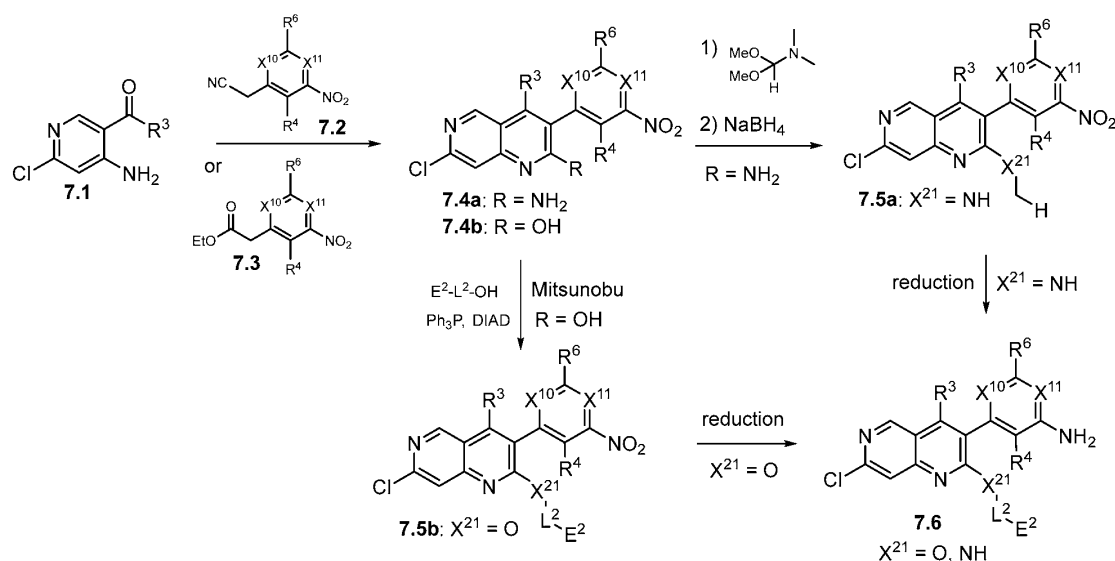
[0266] In another embodiment, oxidation of compounds **5.1** ($Y = H$, $X^{21} = \text{direct bond}$, commercially available or synthesized as described in WO2013134243, WO2013029084 and *J. Med. Chem.*, 2015, 58, 4165-4179) with mCPBA, followed by substitution reaction of the resulting intermediate with amines R^1NH_2 , typically performed in an aprotic solvent at temperatures ranging from rt to $150^\circ C$, affords compounds **5.2**. Bromination of **5.2** (e.g., with NBS or $Br_2/HOAc$) affords bromides **5.3** ($X^{21} = \text{direct bond}$) according to general reaction conditions reported in

WO2013134243, WO2013029084 and J. Med. Chem., 2015, 58, 4165-4179. Pd-catalyzed coupling reaction (Suzuki reaction) of compounds 5.3 with boronates 1.2 in the presence of a Pd catalyst such as Pd(PPh₃)₄ or Pd(dppf)Cl₂ affords compounds 5.4 which are reacted with sulfonyl chlorides 2.3 to obtain the corresponding sulfonamides (compounds of Formula I). Alternatively, compounds of Formula I can be directly prepared from 5.3 with boronates 1.4 by Suzuki reaction.

Scheme 6

10 [0267] Scheme 6 illustrates an exemplary preparation of intermediates 6.5. Compounds 6.1
 (commercially available or synthesized by those skilled in the art) react with 3-(triphenyl-15-
 phosphanylidene)propanenitrile under Wittig reaction conditions to those skilled in the art to afford
 compounds 6.2. DBU-promoted cyclization of compounds 6.2 at elevated temperature under
 microwave irradiation affords the 1,6-naphthyridin-2-amines 6.3. Bromination of 6.3 with NBS
 15 affords intermediates 6.4 which are converted to compounds 6.5 by substitution reaction with amines
 R¹NHP at elevated temperature.

Scheme 7

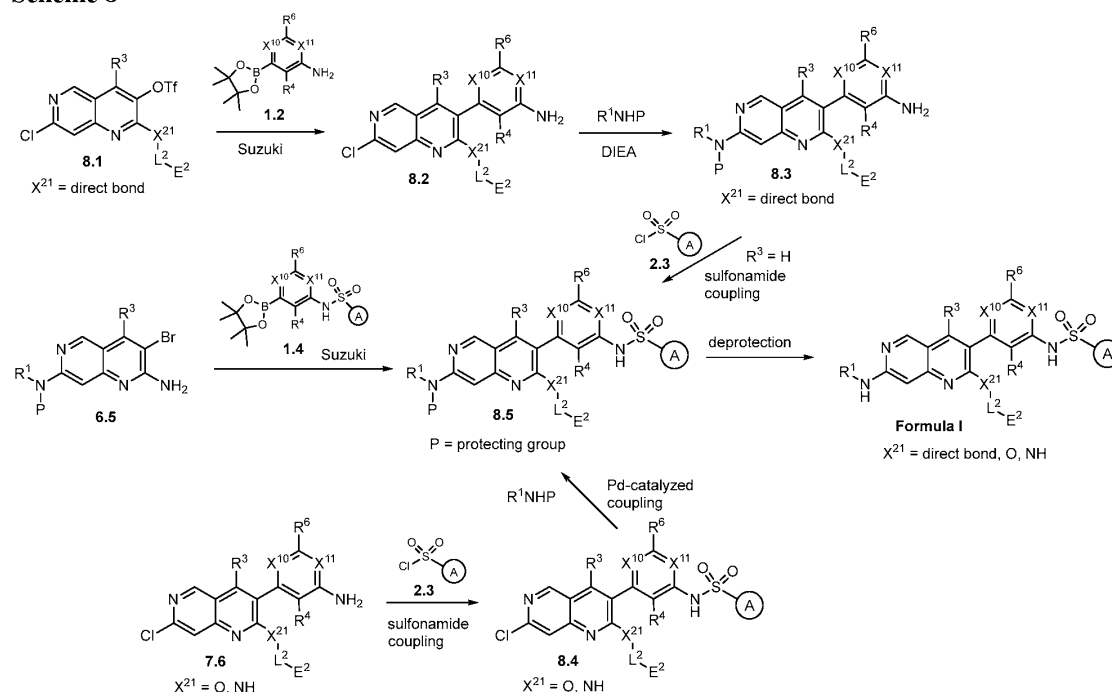


[0268] Scheme 7 illustrates an exemplary preparation of intermediates 7.6 (X²¹ = O, NH).

Compounds 7.1 (commercially available or synthesized by those skilled in the art) react with

- 5 phenylacetonitriles 7.2 (commercially available or synthesized by those skilled in the art) in the presence of a suitable base such as sodium alkoxide and in a protic solvent such as 2-ethoxyethanol at elevated temperature to obtain 7.4a (R = NH₂). Intermediates 7.4a (R = NH₂) react with DMF-dimethyl acetal, followed by NaBH₄ reduction to afford 7.5a (X²¹ = NH) according to general reaction conditions reported in *Synlett*, 2001, 5, 643-645. The reduction of the nitro substituent of
- 10 compounds 7.5a under mild reducing conditions such as zinc or iron metal with ammonium chloride affords the aniline derivatives 7.6. In another embodiment, compounds 7.1 react with esters 7.3 (commercially available or synthesized by those skilled in the art) in the presence of a base such as piperidine, in a protic solvent such as EtOH at elevated temperature to afford 7.4b (R = OH). Intermediates 7.4b react with alcohols (E²-L²-OH) under standard Mitsunobu conditions (conducted
- 15 for example in the presence of Ph₃P and DIAD) to provide the ethers 7.5b (X²¹ = O), which are converted to the compounds 7.6 via reduction of the nitro functional group of 7.5b to the corresponding anilines in the presence of zinc or iron with ammonium chloride.

Scheme 8



[0269] Scheme 8 illustrates an exemplary preparation of compounds of Formula I. Anilines **8.3** are prepared in 2 steps from triflates **8.1** (X^{21} = direct bond) according to general reaction conditions reported in WO2013134298 and WO2018229629. Suzuki reaction of triflates **8.1** (synthesized as described in *J. Med. Chem.*, 2015, 58, 4165-4179) with boronates **1.2** affords **8.2**. Chlorides **8.2** react with R^1NHP (P = protecting group) in the presence of a base such as DIEA at elevated temperature to afford compounds **8.3**, which are converted to sulfonamides **8.5** by reaction with sulfonyl chlorides **2.3**. In another embodiment, compounds **8.5** are prepared by Suzuki coupling reaction of bromides **6.5** (see preparation of intermediates **6.5** described in scheme 6) with boronates **1.4**. Alternatively, anilines **7.6** (X^{21} = O, NH, see preparation of intermediates **7.6** described in scheme 7) react with sulfonyl chlorides **2.3** to afford sulfonamides **8.4**, which are converted to compounds **8.5** by reaction with amines R^1NHP (P = protecting group) in the presence of a palladium catalyst such as $Pd_2(dba)_3$ or $Pd(OAc)_2$, and a metal coordinating group such as XantPhos, or *tert*-butyl XPhos, in the presence of a base such as Cs_2CO_3 , in a suitable solvent such as 1,4-dioxane to afford intermediates **8.5**. Deprotection of **8.5** provides compounds of Formula I. In instances, where compounds contain a nitrogen protecting group P, such as Boc or PMB, the protecting group can be removed under acidic conditions (TFA or HCl in 1,4-dioxane) to afford the corresponding amines (compounds of Formula I).

9.1a $\xrightarrow{\text{Guanidine carbonate}}$ **9.2a** $\xrightarrow{\text{Sandmeyer}}$ **9.3a**

$X^1 = \text{Cl, I}$
 $X^1 = \text{N}$ $\downarrow$ R^1NH_2

9.4a: $X^1 = \text{N}$
9.4b: $X^1 = \text{CH}$
9.4c: $X^1 = \text{CH, N}$ and $\text{R}^1 = (\text{CO})\text{R}^{13}$

9.1b $\xrightarrow[3) (\text{CF}_3\text{SO}_2)_2\text{O}]{1) \text{EtOOC-O-CO-OEt, 2) H}_2\text{SO}_4}$ **9.2b** $\xrightarrow{\text{R}^1\text{NH}_2}$ **9.4a-c**

$X^{21} = \text{direct bond, O, NH}$

9.2b $\xrightarrow{(\text{R}^{13}\text{CO})_2\text{O}}$ **9.4a-c**

9.2c $\xrightarrow{\text{Suzuki}}$ **9.5a-c**

$X^1 = \text{CH, N}$
 $X^3 = \text{CH}$ and $\text{R}^3 = \text{H}$

9.4a-c $\xrightarrow{\text{Suzuki}}$ **Formula I**

Formula I: $X^{21} = \text{direct bond, O, NH}$

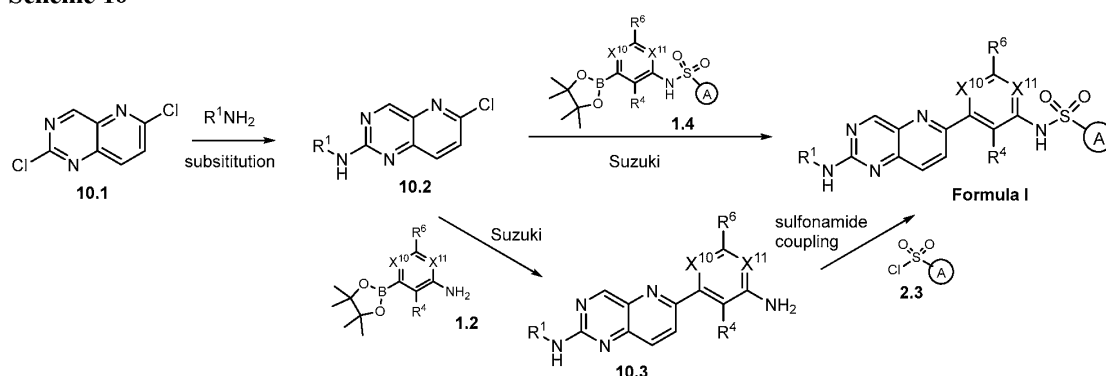
9.1b $\xrightarrow[3) (\text{CF}_3\text{SO}_2)_2\text{O}]{1) \text{EtOOC-O-CO-OEt, 2) H}_2\text{SO}_4}$ **9.2b** + regioisomer of **9.2b**

$\text{R}^3 = \text{H}$

[0270] Scheme 9 illustrates an exemplary preparation of compounds of Formula I. Aldehydes **9.1a** (commercially available or synthesized by those skilled in the art, X²¹ = direct bond, O, NH) react with guanidine carbonate in the presence of a base such as DIEA, in a polar solvent such as NMP at elevated temperature to afford 6-bromoquinazolin-2-amines **9.2a**. Compounds **9.2a** convert to **9.3a** (X = Cl, I) using Sandmeyer reaction conditions known to those skilled in the art (for example, X = I: isoamyl nitrite, CuI and CH₂I₂). S_NAr reaction of **9.3a** (X=Cl or I) with amines R¹NH₂ at elevated temperature affords **9.4a** (X¹ = N, according to general reaction conditions reported in WO2018046739, WO2006039718 US20090197862 and *J. Med. Chem.*, 2006, 49, 5671-5686). In another embodiment, primary amines **9.1b** (commercially available or synthesized by those skilled in the art, X²¹ = direct bond, O, NH) react with ethyl 2,2-dimethoxyacetate in the presence of a base such as DIEA at elevated temperature, followed by acid-mediated cyclization and triflation with trifluoromethyl sulfonic anhydride to afford triflates **9.2b**. When R³ is H, any resulting regioisomers of **9.2b** can be separated by a suitable method such as SFC purification, crystallization or chromatography. Triflates **9.2b** reacted with amines R¹NH₂ via S_NAr reaction at elevated temperature to afford **9.4b** (X¹ = CH) according to general reaction conditions reported in *ACS Med. Chem. Lett.*, 2015, 6, 31-36. Commercially available **9.2c** (X¹ = N, X³ = CH and R³ = H: 6-

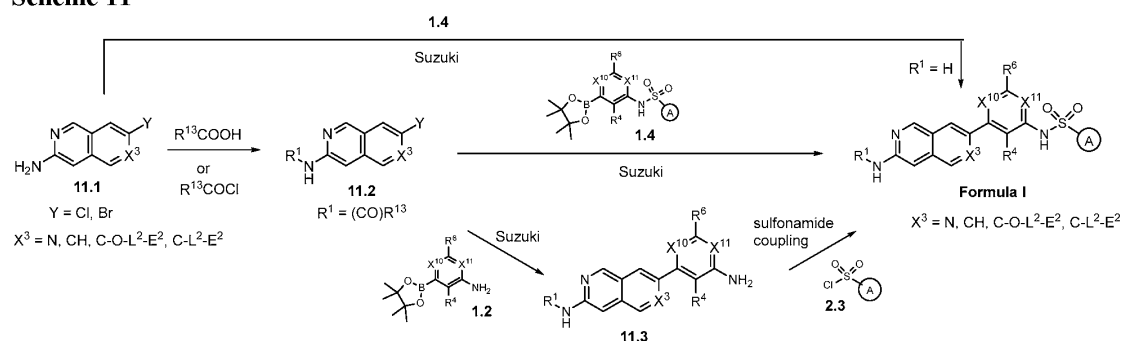
bromoquinazolin-2-amine and $X^1 = \text{CH}$, $X^3 = \text{CH}$ and $R^3 = \text{H}$: 7-bromoisoquinolin-3-amine) reacts with an acid anhydride $((R^{13}(\text{CO}))_2\text{O})$ at elevated temperature to afford acetamides **9.4c** ($X^1 = \text{N}$ or CH ; $R^1 = (\text{CO})R^{13}$). Palladium-catalyzed coupling of **9.4a**, **9.4b** and **9.4c** with boronates **1.2** under Suzuki reaction conditions affords the intermediates **9.5a**, **9.5b** and **9.5c**, respectively. Coupling of amines **9.5a**, **9.5b** and **9.5c** with sulfonyl chlorides **2.3** under reaction conditions known to those skilled in the art affords compounds of Formula **I**. Alternatively, compounds of Formula **I** can be prepared from **9.2c**, **9.4a**, **9.4b** and **9.4c** with boronates **1.4** by palladium-catalyzed coupling reaction (Suzuki reaction).

Scheme 10



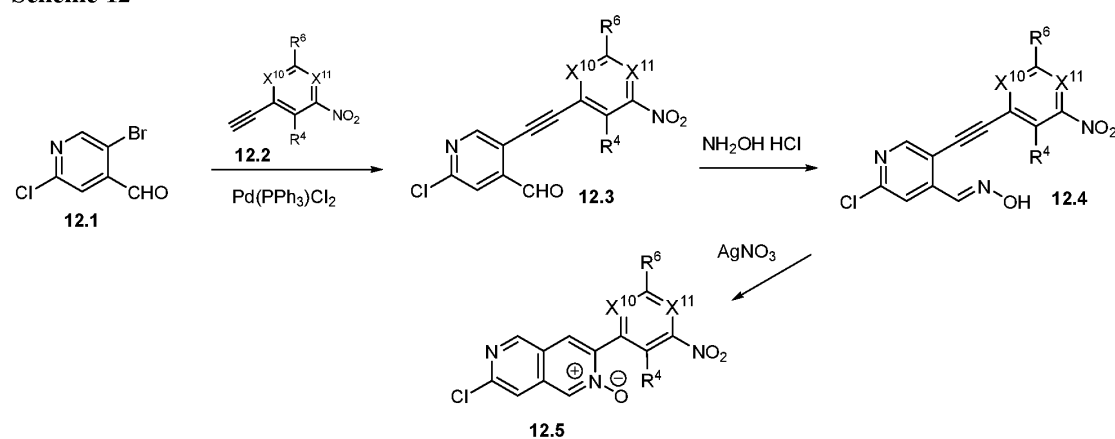
[0271] Compounds of Formula **I** may be prepared as described in Scheme 10. Commercially available 2,6-dichloropyrido[3,2-d]pyrimidine (**10.1**) reacts with amines $R^1\text{NH}_2$ (commercially available or synthesized by those skilled in the art) in the presence of a base such as DIEA to afford intermediates **10.2**. Palladium-catalyzed coupling reaction (Suzuki reaction) of chlorides **10.2** with boronates **1.2** affords anilines **10.3**. Anilines **10.3** react with sulfonyl chlorides **2.3** to provide compounds of Formula **I**. Alternatively, compounds of Formula **I** can be directly prepared from chlorides **10.2** with boronates **1.4** under Suzuki reaction conditions.

Scheme 11



- [0272] Compounds of Formula I may be prepared as described in Scheme 11. Amines **11.1** (commercially available or synthesized by those skilled in the art) react with boronates **1.4** under palladium-mediated Suzuki coupling conditions to afford compounds of Formula I ($\text{R}^1 = \text{H}$). In another embodiment, amines **11.1** react with carboxylic acids R^{13}COOH under amide coupling conditions (for example, HATU and DMAP in the presence of DIEA) or acyl chlorides R^{13}COCl in the presence of base such as pyridine to afford **11.2**. Intermediates **11.2** react with boronates **1.2** under Suzuki reaction conditions to afford compounds **11.3**, which are converted to compounds of Formula I via reaction with sulfonyl chlorides **2.3**. Alternatively, compounds of Formula I can be directly prepared from **11.2** with boronates **1.4** under Suzuki reaction conditions.

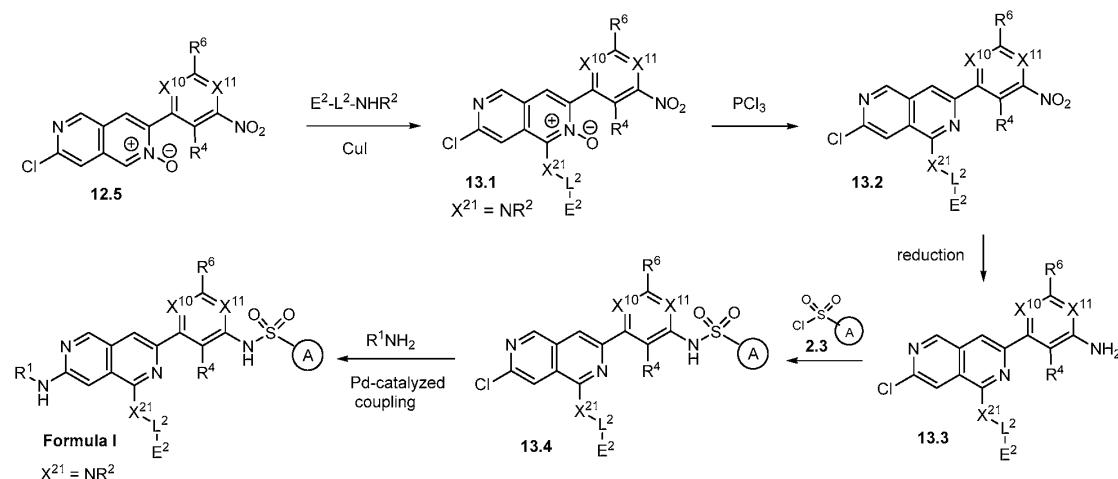
Scheme 12



- [0273] Intermediates of formula **12.5** may be prepared as described in Scheme 12. Commercially available 5-bromo-2-chloroisonicotinaldehyde (**12.1**) reacts with 3-nitrophenylacetylenes **12.2** (commercially available or synthesized by those skilled in the art) under Pd/Cu-catalyzed Sonogashira cross-coupling reaction conditions (for example, in the presence of a palladium catalyst such as $\text{Pd(PPh}_3)_2\text{Cl}_2$, in the presence of a Cu (I) catalyst such as CuCl or CuI , in the presence of a

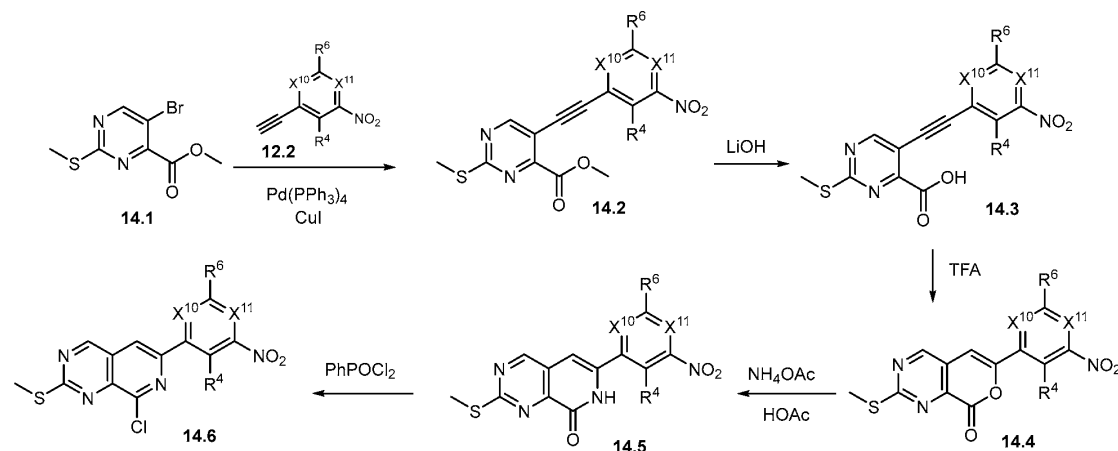
base such as triethylamine, in a suitable solvent such as DMF/THF at temperatures ranging from rt to 120 °C) to afford the acetylenes **12.3**. Intermediates **12.3** react with hydroxylamine hydrochloride in the presence of a suitable base such as NaOAc to afford oximes **12.4**. N-oxides **12.5** are prepared by electrophilic metal-catalyzed cyclization of **12.4** with AgNO₃ according to synthetic procedure reported in US20190270742.

Scheme 13



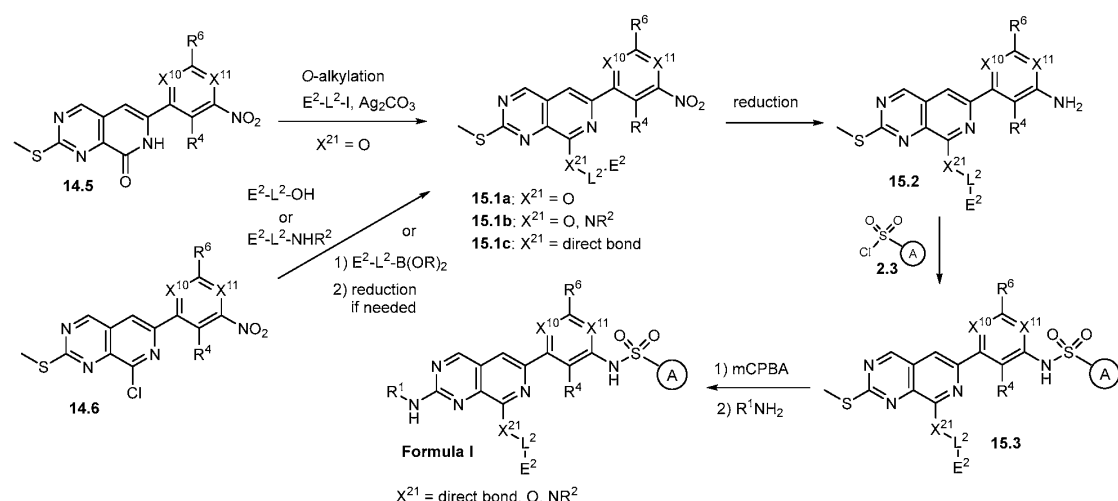
- [0274]** Compounds of Formula I may be prepared as described in Scheme 13. Copper-catalyzed direct amination of N-oxides **12.5** (see preparation of **12.5** illustrated in Scheme 12) reacts with amines $E^2-L^2-NHR^2$ in the presence of a catalyst such as CuI in an aprotic solvent such as toluene at elevated temperature (according to general reaction conditions reported in *J. Org. Chem.*, 2017, 82, 8933-8942) to afford **13.1** ($X^{21} = NR^2$). Conversion of N-oxides **13.1** to compounds **13.2** is conducted in the presence of PCl_3 according to synthetic procedures reported in US20190270742. Nitro reduction of **13.2** under mild reducing conditions (reaction conducted in the presence of a metal such as zinc or iron with ammonium chloride) affords anilines **13.3**, which are converted to the corresponding sulfonamides **13.4** by reaction with sulfonyl chlorides **2.3**. Finally, Pd-catalyzed coupling reaction known to those skill in the art (Buchwald reaction) of **13.4** with R^1NH_2 affords compounds of Formula I.

Scheme 14



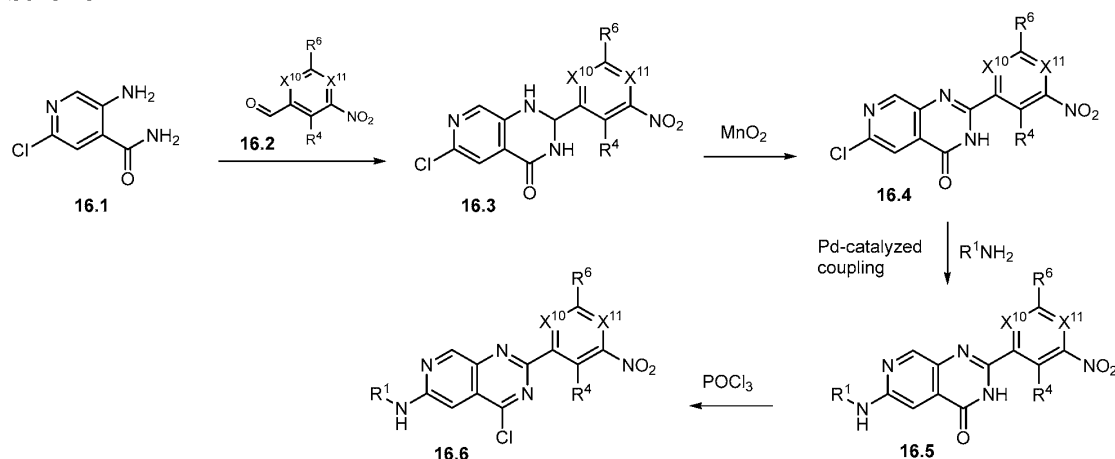
[0275] Intermediates of formula **14.6** may be prepared as described in Scheme 14. Commercially available methyl 5-bromo-2-(methylthio)pyrimidine-4-carboxylate (**14.1**) reacts with 3-nitrophenylacetylenes **12.2** (commercially available or synthesized by those skilled in the art) under Pd/Cu-catalyzed conditions known to those skill in the art (Sonogashira Reaction) to afford **14.2**. Hydrolysis of esters **14.2** with LiOH (aq) affords the corresponding acids **14.3**. Acid-promoted intramolecular cyclization of acids **14.3** affords **14.4** according to general reaction conditions reported in *Org. Lett.*, 2006, 8, 5517-5520. Intermediates **14.4** are converted to **14.5** under NH₄OAc in glacial acetic acid at elevated temperature. Compounds **14.5** react with PhPOCl₂ to afford intermediates **14.6** according to general reaction conditions reported in WO2018113584.

Scheme 15



[0276] Compounds of Formula **I** may be prepared as described in Scheme 15. *O*-alkylation of **14.5** (see preparation of **14.5** illustrated in Scheme 14) with alkylating reagents E^2L^2-I in the presence of Ag_2CO_3 affords **15.1a** ($X^{21} = O$) according to general reaction conditions reported in WO2018113584. Alternatively, chlorides **14.6** react with alcohols (E^2-L^2-OH) or amines ($E^2-L^2-NHR^2$) by substitution reaction in the presence of a base such as DIEA, in polar aprotic solvents such as NMP at elevated temperature to afford **15.1b** ($X^{21} = O, NR^2$) according to general reaction conditions reported in WO2014037750. Alternatively, chlorides **14.6** (prepared in scheme 14) react with boronic acids or boronates $E^2-L^2-B(OR)_2$ (commercially available or synthesized by those skilled in the art) under Pd-catalyzed coupling conditions (Suzuki reaction) to afford **15.1c** ($X^{21} =$ direct bond). Nitro reduction of **15.1a**, **15.1b** and **15.1c** under by palladium catalyzed hydrogenation or mild reducing conditions (zinc or iron metal with ammonium chloride) affords anilines **15.2**. When **15.1c** contains double or triple bonds at the L^2-E^2 , these moieties along with the nitro group can be fully reduced under palladium catalyzed hydrogenation conditions to afford **15.2**. Anilines **15.2** react with sulfonyl chlorides **2.3** to obtain sulfonamides **15.3** under sulfonamide coupling conditions known to those skilled in the art. Finally, compounds of Formula **I** can be prepared by oxidation of **15.3** with mCPBA, followed by S_NAr reaction of the resulting intermediate with amines R^1NH_2 .

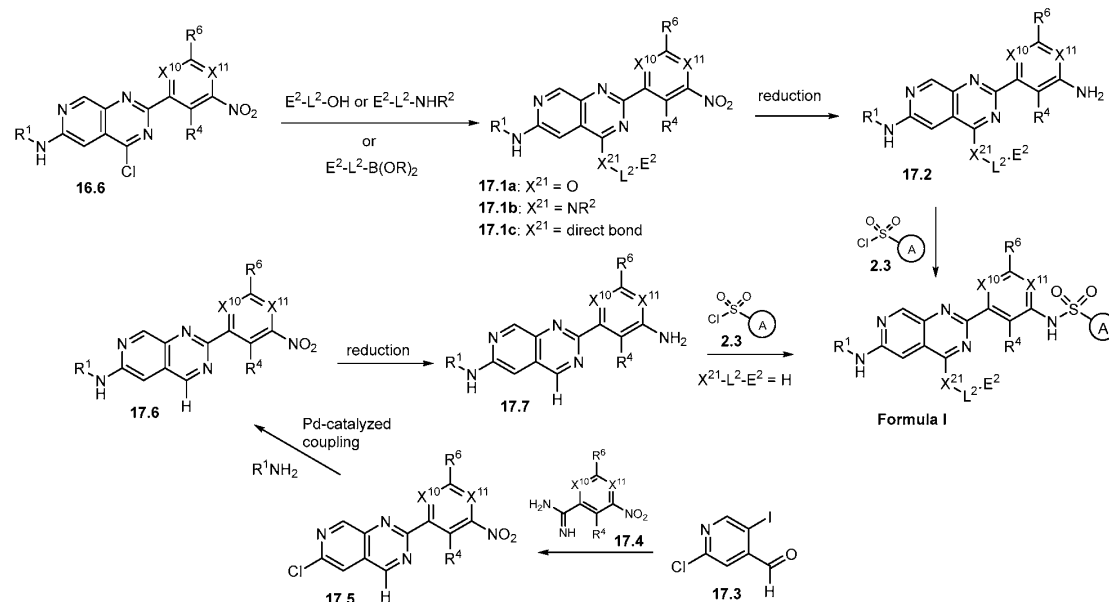
20 Scheme 16



[0277] Intermediates of formula **16.6** may be prepared as described in Scheme 16. Commercially available 5-amino-2-chloroisonicotinamide (**16.1**) reacts with 3-nitro-aldehydes **16.2** (commercially available or synthesized by those skilled in the art) to afford **16.3**. Oxidation of **16.3** with an oxidant such as MnO_2 affords **16.4** according to general reaction conditions reported in WO2018113584.

Intermediates **16.4** react with amines R^1NH_2 under Pd-catalyzed coupling reaction known to those skill in the art (Buchwald reaction) to afford **16.5** which can be reacted with $POCl_3$ to afford intermediates chlorides **16.6**.

5 Scheme 17



- [0278] Compounds of Formula I may be prepared as described in Scheme 17. Chlorides **16.6** (prepared as described in Scheme 16) react with alcohols (E^2-L^2-OH) or amines ($E^2-L^2-NHR^2$) by substitution reaction to afford **17.1a** ($X^{21} = O$) or **17.1b** ($X^{21} = NR^2$). Alternatively, **17.1c** ($X^{21} = \text{direct bond}$) can be prepared from **16.6** by Pd-coupling reaction (Suzuki reaction) with either boronic acids or boronates ($E^2-L^2-B(OR)_2$). Nitro-reduction of **17.1a**, **17.1b** and **17.1c** via palladium catalyzed hydrogenation or mild reducing conditions (zinc or iron metal with ammonium chloride) affords anilines **17.2**. When **17.1c** contains double or triple bonds at the L^2-E^2 , these moieties along with the nitro group can be fully reduced under palladium catalyzed hydrogenation conditions to afford **17.2**. Finally, anilines **17.2** react with sulfonyl chlorides **2.3** under sulfonamide coupling conditions to afford compounds of Formula I. In another embodiment, ligand-free copper-catalyzed Ullmann reaction of commercially available 2-chloro-5-iodoisonicotinaldehyde (**17.3**) with various benzimidamides **17.4** (commercially available or synthesized by those skilled in the art) affords **17.5** ($X^{21}-L^2-E^2 = H$) according to general reaction conditions reported in *Tetrahedron Lett.*, 2010, 51, 785-760. Pyridopyrimidines **17.5** react with amines R^1NH_2 by Pd-catalyzed coupling reaction known to those skill in the art (Buchwald reaction) to afford **17.6**. Nitro-reduction of **17.6** via

palladium catalyzed hydrogenation or mild reducing conditions (zinc or iron metal with ammonium chloride) affords anilines **17.7**. Sulfonamide coupling reaction of anilines **17.7** with sulfonyl chlorides **2.3** affords compounds of Formula **I**.

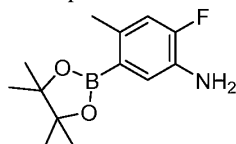
5 Preparation of Intermediates and Final compounds.

[0279] 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

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Example **A1**: 2-fluoro-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline



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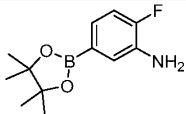
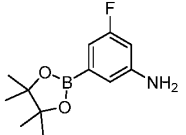
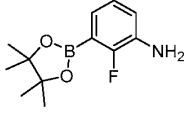
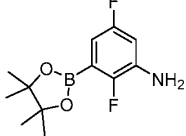
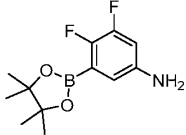
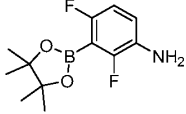
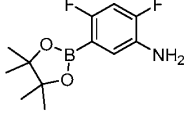
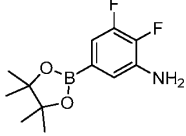
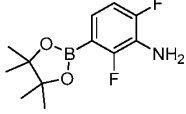
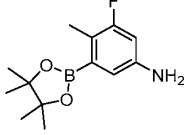
[0280] A mixture of potassium acetate (14.4 g, 147 mmol), 5-bromo-2-fluoro-4-methylaniline (10.0 g, 49 mmol), and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (17.4 g, 69 mmol) in 1,4-dioxane (150 mL) was degassed with Ar for 10 min. PdCl₂(dppf) (1.79 g, 2.5 mmol) was added and the reaction mixture was heated at 110 °C for 6 h. The reaction was cooled to rt and filtered through a pad of celite. The filtrate was removed under reduced pressure and the residue was purified by silica gel column chromatography (0 to 50% EtOAc/hexanes and 1% EtOAc/DCM) to obtain 2-fluoro-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (6.2 g, 50% yield) as a tan solid. ¹H NMR (500 MHz, DMSO-d₆): δ 7.12 (d, J = 10.4 Hz, 1H), 6.78 (d, J = 12.8 Hz, 1H), 4.86 (s, 2H), 2.29 (s, 3H), 1.26 (s, 12H); MS (ESI) m/z: 252.2 (M+H⁺).

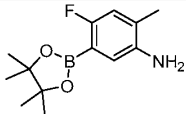
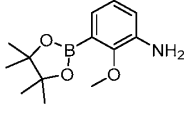
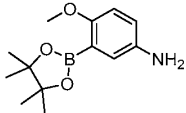
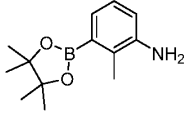
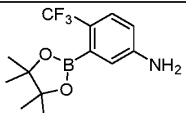
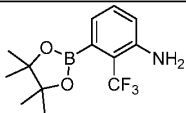
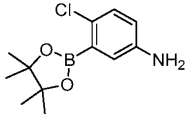
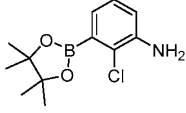
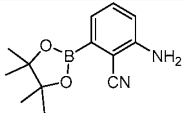
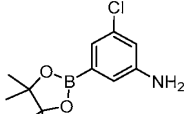
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[0281] Using the General Method A above, the following Intermediates of Table A were prepared.

Table A.

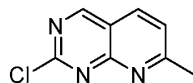
Ex No	Product	Yield (%)	¹ H NMR (400 or 500 MHz, DMSO-d ₆): δ	MS (m/z: M+H ⁺)
A2		96	No Data	234.2
A3		61	6.85 (m, 1H), 6.78 (m, 1H), 6.65 (m, 1H), 4.90 (brs, 2H), 1.27 (s, 12H).	238.1

A4		62	7.13 (d, J = 9.8 Hz, 1H), 6.94 (m, 2H), 6.82 (t, J = 6.3 Hz, 1H), 5.09 (s, 2H), 1.24 (s, 12H).	238.1
A5		88	6.77 (d, J = 2.0 Hz, 1H), 6.42 (m, 2H), 5.42 (s, 2H), 1.27 (s, 12H).	238.2
A6		78	6.86 (m, 2H), 6.76 (d, J = 6.8 Hz, 1H), 5.02 (s, 2H), 1.28 (s, 12H).	238.2
A7		crude	No Data	256.2
A8		36	6.59 (m, 2H), 5.20 (brs, 2H), 1.28 (s, 12H).	256.1
A9		33	No Data	256.2
A10		93	7.09 (m, 1H), 6.94 (m, 1H), 5.00 (s, 2H), 1.28 (s, 12H).	256.2
A11		crude	7.1.3 (d, J = 9.8 Hz, 1H), 6.94 (m, 1H), 6.82 (m, 1H), 5.09 (s, 2H), 1.24 (s, 12H).	238.1
A12		61	6.88 (t, J = 8.8 Hz, 1H), 6.77 (m, 1H), 5.10 (brs, 2H), 1.28 (s, 12H).	256.0
A13		65	6.74 (d, J = 2.4 Hz, 1H), 6.37 (dd, J = 2.4 and 12.4 Hz, 1H), 5.10 (brs, 2H), 2.18 (d, J = 2.0 Hz, 3H), 1.28 (s, 12H).	252.1

A14		40	6.88 (d, J = 7.8 Hz, 1H), 6.71 (m, 1H), 4.7 (brs, 2H), 2.05 (s, 3H), 1.26 (s, 12H).	252.3
A15		81	6.80 (d, J = 4.6 Hz, 2H), 6.75 (m, 1H), 4.80 (s, 2H), 3.65 (s, 3H), 1.29 (s, 12H).	250.2
A16		38	6.84 (d, J = 2.8 Hz, 1H), 6.66 (d, J = 8.8 Hz, 1H), 6.61 (m, 1H), 4.6 (brs, 2H), 3.59 (s, 3H), 1.25 (s, 12H).	250.1
A17		76	6.86 (m, 2H), 6.71 (m, 1H), 4.7 (brs, 2H), 2.20 (s, 3H), 1.28 (s, 12H).	234.2
A18		60	7.31 (d, J = 8.4 Hz, 1H), 6.83 (d, J = 2.4 Hz, 1H), 6.64 (dd, J = 1.6 and 8.4 Hz, 1H), 5.80 (brs, 2H), 1.28 (s, 12H).	288.1
A19		62	7.22 (t, J = 8.0 Hz, 1H), 6.84 (d, J = 8.0 Hz, 1H), 6.57 (d, J = 6.8 Hz, 1H), 5.50 (brs, 2H), 1.27 (s, 12H).	287.8
A20		46	6.99 (d, J = 8.8 Hz, 1H), 6.87 (d, J = 2.8 Hz, 1H), 6.60 (dd, J = 3.2 and 8.8 Hz, 1H), 5.20 (brs, 2H), 1.28 (s, 12H).	254.0
A21		43	6.99 (t, J = 7.6 Hz, 1H), 6.86 (d, J = 6.4 Hz, 1H), 6.77 (d, J = 6.8 Hz, 1H), 5.25 (brs, 2H), 1.28 (s, 12H).	254.1
A22		78	7.29 (m, 1H), 6.92 (m, 2H), 5.93 (s, 2H), 1.30 (s, 12H).	245.2
A23		42	6.85 (d, J = 1.2 Hz, 1H), 6.69 (s, 1H), 6.67 (m, 1H), 5.41 (brs, 2H), 1.27 (s, 12H)	No Data

General Method B: Condensation

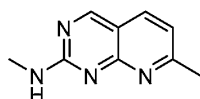
Example **B1**: 7-methyl-2-(methylthio)pyrido[2,3-d]pyrimidine



- 5 **[0282]** A solution of 4-amino-2-(methylthio)pyrimidine-5-carbaldehyde (3.0 g, 18 mmol) in acetone (50 mL) was treated with K₂CO₃ (3.1 g, 22 mmol). The reaction was heated to 65 °C overnight. The reaction was filtered while hot, the filtrate was cooled to rt and the solvent was evaporated. The residue was recrystallized from water. The solids were filtered and rinsed with
- 10 hexanes (20 mL) to obtain 7-methyl-2-(methylthio)pyrido[2,3-d]pyrimidine (3.1 g, 93% yield) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.40 (s, 1H), 8.42 (d, *J* = 8.2 Hz, 1H), 7.55 (d, *J* = 8.2 Hz, 1H), 2.71 (s, 3H), 2.63 (s, 3H).

General Method C: Substitution

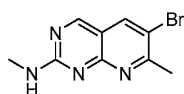
- 15 Example **B2**: N,7-dimethylpyrido[2,3-d]pyrimidin-2-amine



- [0283]** A solution of 7-methyl-2-(methylthio)pyrido[2,3-d]pyrimidine (**B1**, 1.00 g, 0.52 mmol) in N-methylamine (33% in ethanol, 8 mL) was heated in a sealed tube at 80 °C overnight. The reaction was cooled to rt and then concentrated under reduced pressure to obtain N,7-dimethylpyrido[2,3-
- 20 d]pyrimidin-2-amine (0.62 g, 68% yield) as an orange solid. The material was used without further purification for the next reaction. MS (ESI) *m/z*: 175.2 (M+H⁺).

General Method D: Halogenation (Br or I)

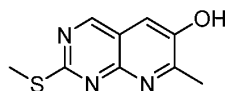
Example **B3**: 6-bromo-N,7-dimethylpyrido[2,3-d]pyrimidin-2-amine



- 25 **[0284]** A solution of N,7-dimethylpyrido[2,3-d]pyrimidin-2-amine (**B2**, 0.62 g, 0.36 mmol) in DCM (7.5 mL) was added NBS (0.67 g, 0.38 mmol) portion wise at rt. The reaction mixture was stirred at rt overnight. The reaction mixture was cooled to 0 °C and stirred for 15 min. The solids were filtered and rinsed with cold DCM (15 mL) to obtain 6-bromo-N,7-dimethylpyrido[2,3-
- 30 d]pyrimidin-2-amine (0.48 g, 53% yield). ¹H NMR (500 MHz, DMSO-*d*₆): δ 9.07 (s, 1H), 8.47 (s, 1H), 7.84 (s, 1H), 2.90 (d, *J* = 4.7 Hz, 3H), 2.68 (s, 3H); MS (ESI) *m/z*: 253.0 (M+H⁺) and 255.0.

General Method E: Condensation

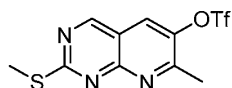
Example **B4**: 7-methyl-2-(methylthio)pyrido[2,3-d]pyrimidin-6-ol



- [0285] A suspension of 4-amino-2-(methylthio)pyrimidine-5-carbaldehyde (45 g, 266 mmol) in water (600 mL) was treated with NaOH (21 g, 530 mmol). 1-Hydroxypropan-2-one (23 g, 319 mmol) was added and then the reaction mixture was heated to 55 °C for 4 h. The reaction was cooled to 0 °C and conc-HCl was added dropwise to pH ~3-4 under the same conditions. The reaction was stirred at 0 °C for 30 min, then the solids were filtered to obtain 7-methyl-2-(methylthio)pyrido[2,3-d]pyrimidin-6-ol (51 g, 93% yield) as a yellow solid. ¹H NMR (500 MHz, DMSO-d₆): δ 10.8 (s, 1H), 9.28 (s, 1H), 7.53 (s, 1H), 2.57 (s, 3H), 2.56 (s, 3H); MS (ESI) m/z: 208.2 (M+H⁺).

General Method F: Activation

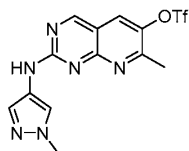
Example **B5**: 7-methyl-2-(methylthio)pyrido[2,3-d]pyrimidin-6-yl trifluoromethanesulfonate



- [0286] A suspension of 7-methyl-2-(methylthio)pyrido[2,3-d]pyrimidin-6-ol (**B4**, 20 g, 97 mmol) and DIEA (37 g, 290 mmol) in DCM (500 mL) was stirred at 0 °C. A solution of 1,1,1-trifluoro-N-phenyl-N-((trifluoromethyl)sulfonyl)methanesulfonamide (34 g, 97 mmol) in DCM (130 mL) was added slowly. The reaction mixture was slowly warmed to rt over 3 h. The reaction mixture was quenched with sat'd NaHCO₃ (aq, 500 mL) and then the solution was filtered through a pad of celite. The filtrate was extracted with DCM (3 x 100 mL) and the combined organics were washed with water (2 x 20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was suspended in hexanes and the solids were filtered to obtain 7-methyl-2-(methylthio)pyrido[2,3-d]pyrimidin-6-yl trifluoromethanesulfonate (23 g, 70% yield) as a yellow-brown solid. ¹H NMR (500 MHz, DMSO-d₆): δ 9.55 (s, 1H), 8.77 (s, 1H), 2.75 (s, 3H), 2.65 (s, 3H); MS (ESI) m/z: 340.0 (M+H⁺).

General Method G: Oxidation and Substitution

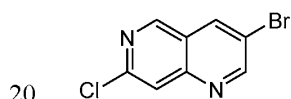
Example **B6**: 7-methyl-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrido[2,3-d]pyrimidin-6-yl trifluoromethanesulfonate



- 5 **[0287]** A solution of 7-methyl-2-(methylthio)pyrido[2,3-d]pyrimidin-6-yl trifluoromethanesulfonate (**B5**, 1.0 g, 2.9 mmol) in THF (50 mL) was cooled to 0 °C. mCPBA (0.51 g, 2.9 mmol) was added portion-wise and the reaction mixture was stirred under the same conditions for 1 h. 1-Methyl-1H-pyrazol-4-amine (0.29 g, 2.9 mmol) and DIEA (1.0 mL, 5.9 mmol) were added and the reaction mixture was stirred at rt overnight. The reaction was quenched with water (50 mL)
- 10 and extracted with DCM (3 x 50 mL). The combined organic extracts were washed with sat'd NaHCO₃ (2 x 50 mL), brine (2 x 50 mL), then dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to obtain 7-methyl-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrido[2,3-d]pyrimidin-6-yl trifluoromethanesulfonate (0.81 g, 71% yield) as a brown solid. NMR (500 MHz, DMSO-d₆): δ 10.3 (s, 1H), 9.33 (s, 1H), 8.49 (s, 1H), 8.20 (s, 1H), 7.64 (s, 1H), 3.88 (s, 3H), 2.67 (s, 3H); MS
- 15 (ESI) m/z: 389.0 (M+H⁺).

General Method H: Condensation under tris(((trifluoromethyl)sulfonyl)oxy)ytterbium as a catalyst

Example **B7**: 3-bromo-7-chloro-1,6-naphthyridine

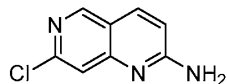


- [0288]** A mixture of 4-amino-6-chloronicotinaldehyde (2.2 g, 14 mmol) and 2-bromo-1,1-dimethoxyethane (3.3 mL, 28 mmol) in DCE (50 mL) was treated with tris(((trifluoromethyl)sulfonyl)oxy)ytterbium (0.55 g, 0.89 mmol). The reaction mixture was heated
- 25 at 100 °C for 12 h. The reaction mixture was cooled to rt and concentrated under reduced pressure. The crude was purified by silica gel column chromatography (0 to 100% EtOAc/hexanes) to afford 3-bromo-7-chloro-1,6-naphthyridine (2.7 g, 79% yield) as a yellow solid. MS (ESI) m/z: 243.0 (M+H⁺) and 245.0.

30

General Method I: Wittig Reaction and Cyclization

Example **B8**: 7-chloro-1,6-naphthyridin-2-amine

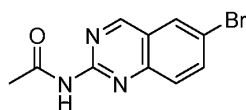


- 5 **[0289]** A solution of 4-amino-6-chloronicotinaldehyde (0.5 g, 3.2 mmol) and (triphenylphosphoranylidene)acetonitrile (0.97 g, 3.2 mmol) in THF (5 mL) was stirred at rt overnight. The reaction mixture was concentrated and the solid residue was suspended in EtOAc (5 mL). The solids were filtered to obtain (E)-3-(4-amino-6-chloropyridin-3-yl)acrylonitrile (0.51 g, 89% yield). A mixture of (E)-3-(4-amino-6-chloropyridin-3-yl)acrylonitrile (0.51 g, 2.9 mmol) and
- 10 DBU (0.85 mL, 5.7 mmol) was heated to 170 °C for 5 h in microwave. The reaction mixture was cooled to rt and quenched with sat'd NaHCO₃ (aq, 10 mL). The solution was extracted with EtOAc (3 x 10 mL). The combined organics were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford 7-chloro-1,6-naphthyridin-2-amine (0.24 g, 47% yield). MS (ESI) m/z: 180.0 (M+H⁺).

15

General Method J: Amide Coupling

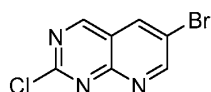
Example **B9**: N-(6-bromoquinazolin-2-yl)acetamide



- [0290]** A solution of 6-bromoquinazolin-2-amine (0.20 g, 0.89 mmol) in acetic anhydride (5 mL) was heated to 140 °C for 45 min. The reaction mixture was cooled to rt and the solids were filtered, washed with water and dried under vacuum overnight to obtain N-(6-bromoquinazolin-2-yl)acetamide (0.09 g, 38% yield). MS (ESI) m/z: 266.0 (M+H⁺) and 268.0.
- 20

General Method K: Reaction with POCl₃

- 25 Example **B12**: 6-bromo-2-chloropyrido[2,3-d]pyrimidine

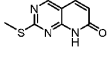
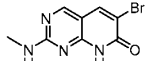
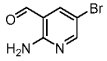
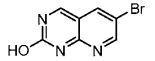
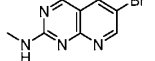
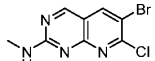
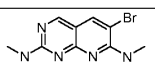
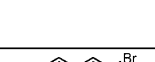
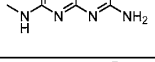
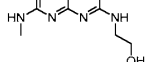
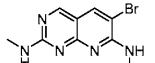
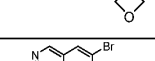


- [0291]** 6-Bromopyrido[2,3-d]pyrimidin-2-ol (**B11**, 5.0 g, 22 mmol) was treated with POCl₃ (31 mL) and the reaction was heated to 100 °C overnight. The reaction was cooled to rt and concentrated under reduced pressure. Ice (~200-300 g) was added to the remaining residue and the solution was
- 30 extracted with EtOAc (3 x 250 mL). The combined organics were washed with sat'd NaHCO₃(aq,

100 mL). The organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to afford 6-bromo-2-chloropyrido[2,3-d]pyrimidine (4.5 g, 83% yield) as a yellow solid. MS (ESI) m/z: 244.0 (M+H⁺) and 246.0.

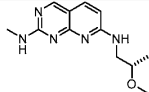
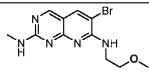
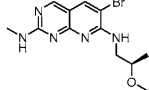
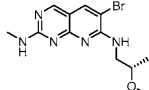
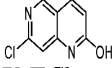
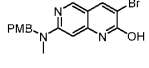
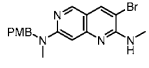
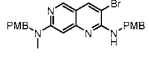
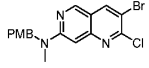
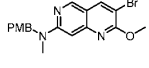
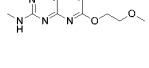
- 5 [0292] Using the General Methods B-K above, the following Intermediates of Table B were prepared.

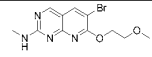
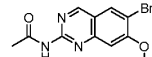
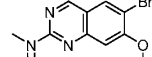
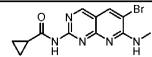
Table B.

Ex No	SM	Product	Method	Yield (%)	¹ H NMR (400 or 500 MHz, DMSO-d ₆): δ	MS (m/z: M+H ⁺)
B10			C & D	crude	12.3 (brs, 1H), 8.55 (brs, 1H), 8.25 (brs, 1H), 7.80 (brs, 1H), 2.86 (brs, 3H).	255.0 257.0
B11			B	89	No Data	226.0 228.0
B13	B12		C	82	9.13 (s, 1H), 8.90 (t, J = 2.8 Hz, 1H), 8.52 (t, J = 2.6 Hz, 1H), 2.89 (m, 3H).	239.0 241.0
B14	B10		K	93	9.18 (s, 1H), 8.68 (s, 1H), 8.19 (brm, 1H), 2.89 (d, J = 4.4 Hz, 3H).	275.0
B15	B14		C	94	8.61 (s, 1H), 8.12 (s, 1H), 7.34 (s, 1H), 7.25 (s, 1H), 2.95 (d, J = 4.5 Hz, 3H), 2.85 (d, J = 4.7 Hz, 3H).	268.0 270.0
B16	B14		C	99	8.62 (s, 1H), 8.15 (s, 1H), 7.36 (s, 1H), 7.20 (brs, 2H), 2.85 (m, 3H).	254.0 256.0
B17	B14		C	crude	No Data	298.0 300.0
B18	B14		C	29	No Data	310.0 312.0
B19	B14		C	73	No Data	324.0 326.0
B20	B14		C	88	No Data	311.0 313.0

B21	B11		C	83	No Data	305.0 307.0
B22			B	88	10.9 (s, 1H), 9.02 (s, 1H), 7.78 (s, 1H), 7.55 (s, 1H), 2.55 (s, 3H).	195.1
B23	B22		F	90	No Data	327.0
B24			C	77	No Data	238.0 240.0
B25			B	58	9.63 (d, J = 0.8 Hz, 1H), 9.24 (d, J = 2.4 Hz, 1H), 9.00 (dd, J = 0.9 and 2.4 Hz, 1H), 8.14 (s, 1H).	242.8 245.0
B26	B25		C	61	No Data	238.0 240.0
B27			H	61	9.22 (s, 1H), 8.94 (s, 1H), 8.01 (s, 1H), 2.82 (s, 3H).	257.0 258.8
B28	B27		C	18	No Data	358.0 360.0
B29	B27		C	23	8.94 (s, 1H), 8.51 (s, 1H), 7.17 (d, J = 8.3 Hz, 2H), 6.87 (d, J = 8.3 Hz, 2H), 6.71 (s, 1H), 4.86 (s, 2H), 3.71 (s, 3H), 3.09 (s, 3H), 2.67 (s, 3H).	372.0 374.0
B30	B8		D	69	No Data	258.0 260.0 262.0
B31	B30		C	14	No Data	373.0 375.0
B32	B14		C	57	No Data	269.0 271.0
B33	B25		C	50	No Data	344.0 346.0
B34	B10		C	92	9.17 (s, 1H), 8.91 (d, J = 2.7 Hz, 1H), 8.52 (d, J = 2.7 Hz, 1H), 7.44 (s, 2H).	225.0 227.0

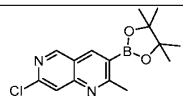
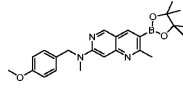
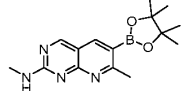
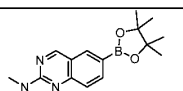
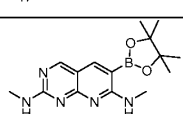
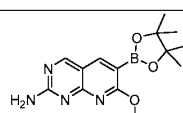
B35	B14		C	79	No Data	312.2 314.2
B36	B5		G	77	9.20 (s, 1H), 8.40 (s, 1H), 8.0 (brs, 1H), 2.90 (d, J = 4.8 Hz, 3H), 2.61 (s, 3H).	323.2
B37	 Cl	 H ₂ N	C & D	36	No Data	239.9
B38	 H ₂ N	 H ₂ N	K, C & D	53	8.62 (s, 1H), 8.10 (s, 1H), 7.2 (brs, 1H), 6.8 (brs, 2H), 2.91 (d, J = 4.8 Hz, 3H).	254.1
B39	 H ₂ N	 H ₂ N	K, C & D	52	9.09 (s, 1H), 8.59 (s, 1H), 7.7 (brs, 2H), 4.06 (s, 3H).	255.2 257.2
B40	B38	 H ₂ N	J	27	12.4 (brs, 1H), 8.6 (brs, 1H), 7.92 (d, J = 9.2 Hz, 1H), 6.65 (d, J = 10.8 Hz, 1H), 3.11 (s, 3H), 1.79 (s, 3H).	295.9
B41	 F Guanidine carbonate	 H ₂ N	B	63	8.92 (s, 1H), 8.06 (s, 1H), 6.89 (s, 1H), 6.84 (brs, 2H), 3.94 (s, 3H).	254.2
B42	 Cl ethyl acrylate	 Cl	I	54	12.7 (s, 1H), 8.95 (s, 1H), 7.98 (d, J = 9.6 Hz, 1H), 6.65 (d, J = 9.2 Hz, 1H).	179.9
B43	B42	 H ₂ N	K	62	9.75 (s, 1H), 8.77 (d, J = 8.4 Hz, 1H), 7.93 (d, J = 8.8 Hz, 1H).	200.2
B44	B43	 H ₂ N	C	67	8.53 (s, 1H), 7.62 (m, 2H), 7.05 (br s, 1H), 6.45 (d, J = 8.8 Hz, 1H), 3.56 (m, 2H), 3.50 (m, 2H), 3.29 (s, 3H), 2.84 (d, J = 4.4 Hz, 3H).	233.9
B45	B43	 H ₂ N	C	49	8.53 (s, 1H), 7.61 (d, J = 8.8 Hz, 1H), 7.53 (brs, 1H), 7.05 (brs, 1H), 6.50 (d, J = 8.8 Hz, 1H), 3.48- 3.55 (m, 2H), 3.40 (m, 1H), 3.28 (s, 3H), 2.84 (d, J = 4.4 Hz, 3H), 1.18 (d, J = 6.0 Hz, 3H).	248.0

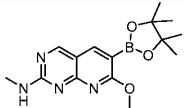
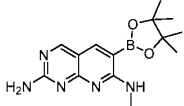
B46	B43		C	64	8.53 (s, 1H), 7.61 (d, J = 8.4 Hz, 1H), 7.52 (brs, 1H), 7.03 (brs, 1H), 6.50 (d, J = 8.4 Hz, 1H), 3.48-3.57 (m, 2H), 3.40 (m, 1H), 3.29 (s, 3H), 2.84 (d, J = 4.8 Hz, 3H), 1.12 (d, J = 6.0 Hz, 3H).	248.1
B47	B44		D	37	No Data	311.9
B48	B45		D	60	8.61 (s, 1H), 8.15 (s, 1H), 7.35 (brs, 1H), 6.80 (brs, 1H), 3.64 (m, 1H), 3.47-3.60 (m, 2H), 3.25 (s, 3H), 2.84 (s, 3H), 1.11 (d, J = 5.6 Hz, 3H).	326.0
B49	B46		D	62	8.61 (s, 1H), 8.15 (s, 1H), 7.36 (brs, 1H), 6.79 (brs, 1H), 3.64 (m, 1H), 3.52 (m, 2H), 3.29 (s, 3H), 2.84 (s, 3H), 1.11 (d, J = 5.6 Hz, 3H).	325.9
B50	 PMBCl Pyridinium tribromide		C & D	76	12.17 (1H, s), 8.52 (1H, s), 8.39 (1H, s), 7.20 (2H, d, J = 8.4 Hz), 6.90-6.92 (2H, m), 6.40 (1H, s), 4.76 (2H, s), 3.73 (3H, s), 3.13 (3H, s).	387.2 389.2
B51	B50 BOP CH ₃ NH ₂		F & C	76	8.52 (s, 1H), 8.17 (s, 1H), 7.13 (d, J = 8.4 Hz, 2H), 7.01 (q, J = 4.6 Hz, 1H), 6.86 (d, J = 8.4 Hz, 2H), 6.36 (s, 1H), 4.80 (s, 2H), 3.70 (s, 3H), 3.02 (s, 3H), 2.92 (d, J = 4.6 Hz, 3H).	387.2 389.2
B52	B50 BOP PMBNH ₂		F & C	78	No Data	493.2 495.2
B53	B50		K	95	No Data	392.0
B54	B53 NaOCH ₃		C	67	No Data	388.0 390.0
B55	B43		C	52	8.97 (s, 1H), 8.05 (d, J = 8.8 Hz, 1H), 7.56 (brs, 1H), 6.67 (d, J = 8.4 Hz,	235.0

					1H), 4.50 (t, J = 4.8 Hz, 2H), 3.70 (t, J = 4.8 Hz, 2H), 3.32 (s, 3H), 2.87 (d, J = 4.4 Hz, 3H).	
B56	B55		D	61	8.99 (s, 1H), 8.45 (s, 1H), 7.75 (brs, 1H), 4.56 (s, 2H), 3.72 (br s, 2H), 3.33 (s, 3H), 2.87 (br s, 3H).	312.9
B57	B41		J	88	10.6 (s, 1H), 9.26 (s, 1H), 8.36 (s, 1H), 7.24 (s, 1H), 4.03 (s, 3H), 2.27 (s, 3H).	296.1
B58	B57 MeI K ₂ CO ₃		Methylation & hydrolysis	35	8.89 (brs, 1H), 8.06 (s, 1H), 7.40 (brs, 1H), 6.98 (br s, 1H), 3.96 (s, 3H), 2.86 (d, J = 4.8 Hz, 3H).	268.1
B59	B38		J	49	No Data	322.0 324.0

[0293] Using the General Method A above, the following Intermediates of Table C were prepared.

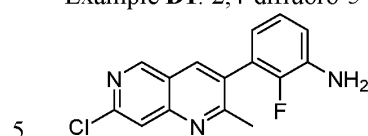
Table C.

Ex No	Product	Yield (%)	¹ H NMR (400 or 500 MHz, DMSO-d ₆): δ	MS (m/z: M+H ⁺)
C1		72	No Data	305.2
C2		10	No Data	420.2
C3		28	No Data	219.0 (boronic acid)
C4		60	No Data	286.2
C5		87	8.57 (s, 1H), 7.86 (s, 1H), 7.24 (brs, 1H), 7.13 (brs, 1H), 2.95 (d, J = 4.7 Hz, 3H), 2.84 (d, J = 4.6 Hz, 3H), 1.21 (s, 12 H).	234.2
C6		crude	No Data	303.3

C7		crude	No Data	317.0
C8		crude	No Data	301.9

General Method L: Suzuki reaction

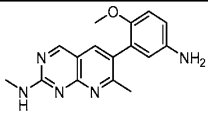
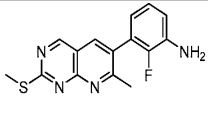
Example **D1**: 2,4-difluoro-5-(isoquinolin-7-yl)aniline

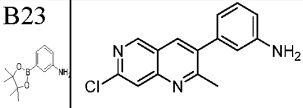
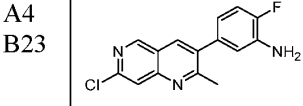
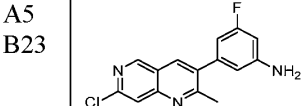
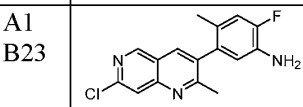
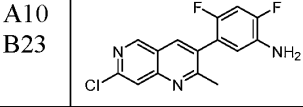
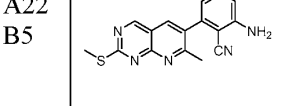
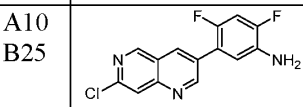
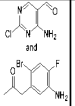
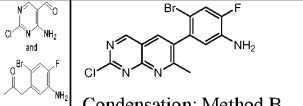
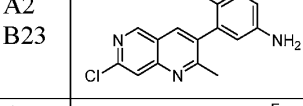
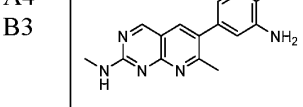
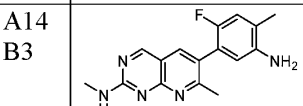


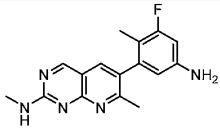
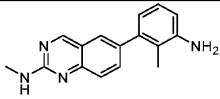
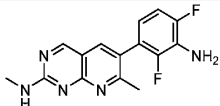
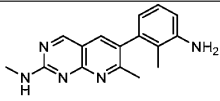
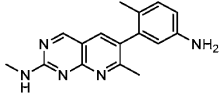
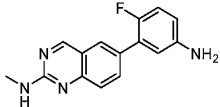
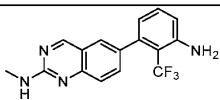
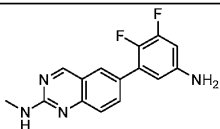
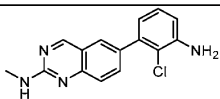
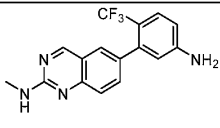
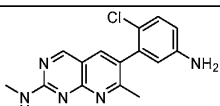
[0294] A solution of 7-chloro-2-methyl-1,6-naphthyridin-3-yl trifluoromethanesulfonate (**B27**, 3.0 g, 9.2 mmol), 2-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (**A6**, 2.2 g, 9.2 mmol) and K_2CO_3 (3.81 g, 28 mmol) in 1,4-dioxane (15 mL) and water (2.5 mL) was degassed with Ar for 10 5 min. $PdCl_2(dppf)$ (0.34 g, 0.46 mmol) was added and the reaction mixture was heated at 80 °C for 1 h. The reaction mixture was cooled to rt and then the solution was filtered through a pad of celite. The filtrate was concentrated under reduced pressure and the crude was purified by silica gel column chromatography (0 to 100% EtOAc/hexanes) to afford 3-(7-chloro-2-methyl-1,6-naphthyridin-3-yl)-2-fluoroaniline (2.0 g, 76% yield) as a brown solid. 1H NMR (500 MHz, DMSO- d_6): δ 9.27 (s, 1H), 8.45 (s, 1H), 8.02 (s, 1H), 7.03 (t, J = 7.7 Hz, 1H), 6.90 (t, J = 8.3 Hz, 1H), 6.56 (t, J = 6.9 Hz, 1H), 5.35 (s, 2H); MS (ESI) m/z: 288.0 ($M+H^+$). 15

[0295] Using the General Method L above, the following Intermediates of Table D were prepared.

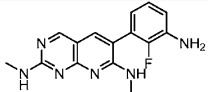
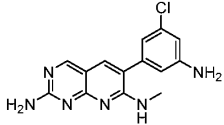
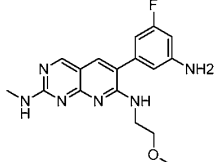
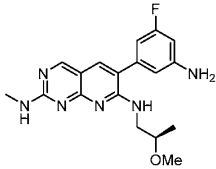
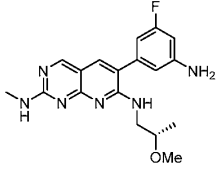
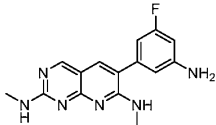
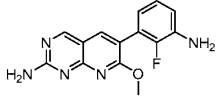
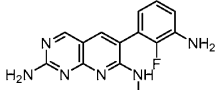
Table D.

Ex No	SM	Product	Yield (%)	1H NMR (400 or 500 MHz, DMSO- d_6): δ	MS (m/z: $M+H^+$)
D2	A16 B3		81	No Data	296.4
D3	A6 B5		81	9.43 (s, 1H, s), 8.35 (s, 1H, s), 7.02 (t, J = 7.7 Hz, 1H), 6.89 (t, J = 8.3 Hz, 1H), 6.54 (t, J = 6.9 Hz, 1H), 5.35 (s, 2H), 2.65 (s, 3H), 2.56 (s, 3H).	301.2

D4	B23		52	No Data	270.0
D5	A4 B23		85	9.23 (s, 1H), 8.34 (s, 1H), 7.98 (s, 1H), 7.10 (dd, J = 8.2 and 11.5 Hz, 1H), 6.83 (dd, J = 2.3 and 8.7 Hz, 1H), 6.61 (m, 1H), 5.32 (s, 2H), 2.61 (s, 3H).	288.1
D6	A5 B23		43	No Data	288.0
D7	A1 B23		41	No Data	302.0
D8	A10 B23		85	No Data	306.0
D9	A22 B5		77	9.45 (s, 1H), 8.39 (s, 1H), 7.43 (t, J = 7.9 Hz, 1H), 6.91 (d, J = 8.5 Hz, 1H), 6.66 (m, 1H), 6.30 (s, 2H), 2.66 (s, 3H), 2.55 (s, 3H).	308.2
D10	A10 B25		82	9.38 (s, 1H), 9.24 (t, J = 2.1 Hz, 1H), 8.72 (s, 1H), 8.12 (s, 1H), 7.29 (t, J = 10.9 Hz, 1H), 7.05 (m, 1H), 5.25 (s, 2H).	292.0
D11	 Condensation: Method B		Crude	No Data	366.0 368.0
D12	A2 B23		69	No Data	284.0
D13	A4 B3		57	9.09 (s, 1H), 7.95 (s, 1H), 7.6 (brs, 1H), 7.06 (m, 1H), 6.78 (dd, J = 2.0 and 8.8 Hz, 1H), 6.54 (m, 1H), 5.2 (brs, 2H), 2.90 (d, J = 4.4 Hz, 3H), 2.49 (s, 3H).	284.1
D14	A14 B3		62	9.09 (s, 1H), 7.98 (s, 1H), 7.7 (brs, 1H), 6.91 (d, J = 10.4 Hz, 1H), 6.54 (d, J = 7.2 Hz, 1H), 4.8 (brs, 2H), 2.91 (d, J = 4.4 Hz, 3H), 2.42 (s, 3H), 2.11 (s, 3H).	297.9

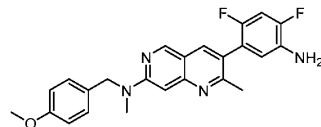
D15	A13 B36		65	9.07 (s, 1H), 7.89 (s, 1H), 7.7 (brs, 1H), 6.38 (dd, J = 12.4 Hz & 1.6 Hz, 1H), 6.23 (s, 1H), 5.3 (brs, 2H), 2.90 (d, J = 4.4 Hz, 3H), 2.32 (s, 3H), 1.75 (s, 3H).	298.0
D16	A17 B24		Crude	No Data	265.1
D17	A12 B36		61	9.09 (s, 1H), 8.00 (s, 1H), 7.7 (brs, 1H), 7.01 (m, 1H), 6.53 (m, 1H), 5.4 (brs, 2H), 2.91 (d, J = 4.8 Hz, 3H), 2.41 (s, 3H).	301.8
D18	A17 B36		54	No Data	280.1
D19	A2 B36		53	No Data	280.1
D20	A3 B24		66	9.15 (s, 1H), 7.90 (s, 1H), 7.7 (m, 1H), 7.53 (d, J = 8.8 Hz, 1H), 7.42 (brs, 1H), 6.97 (m, 1H), 6.73 (dd, J = 3.2 and 7.2 Hz, 1H), 6.56 (m, 1H), 5.0 (brs, 2H), 2.90 (d, J = 4.8 Hz, 3H).	268.8
D21	A19 B24		49	No Data	319.2
D22	A8 B24		33	9.15 (s, 1H), 7.93 (s, 1H), 7.78 (d, J = 8.4 Hz, 1H), 7.55 (m, 1H), 7.4 (brs, 1H), 6.52 (m, 2H), 5.4 (brs, 2H), 2.90 (d, J = 4.0 Hz, 3H).	286.8
D23	A21 B24		33	No Data	285.1
D24	A18 B24		41	9.11 (s, 1H), 7.67 (s, 1H), 7.57 (d, J = 8.8 Hz, 1H), 7.48 (d, J = 8.8 Hz, 1H), 7.41 (m, 2H), 6.64 (d, J = 8.8 Hz, 1H), 6.51 (s, 1H), 5.9 (brs, 2H), 2.91 (d, J = 4.4 Hz, 3H).	No Data
D25	A20 B36		42	9.08 (s, 1H), 7.93 (s, 1H), 7.7 (brs, 1H), 7.18 (d, J = 8.4 Hz, 1H), 6.62 (dd, J = 2.8 and 8.4 Hz, 1H), 6.52 (m, 1H), 5.3 (brs, 2H), 2.91 (d, J = 4.0 Hz, 3H), 2.36 (s, 3H).	No Data

D26	A21 B36		45	No Data	300.0
D27	A20 B24		85	9.13 (s, 1H), 7.78 (d, J = 1.6 Hz, 1H), 7.70 (dd, J = 2.0 and 8.8 Hz, 1H), 7.5 (m, 1H), 7.40 (brs, 1H), 7.16 (d, J = 8.4 Hz, 1H), 6.64 (d, J = 2.4 Hz, 1H), 6.57 (dd, J = 2.4 and 8.4 Hz, 1H), 5.3 (brs, 2H), 2.90 (d, J = 4.4 Hz, 3H).	285.1
D28	A6 B24		94	9.14 (s, 1H), 7.93 (s, 1H), 7.82 (d, J = 8.8 Hz, 1H), 7.53 (d, J = 8.8 Hz, 1H), 7.4 (brs, 1H), 6.96 (t, J = 7.6 Hz, 1H), 6.77 (t, J = 8.0 Hz, 1H), 6.68 (t, J = 7.2 Hz, 1H), 5.2 (brs, 2H), 2.91 (d, J = 4.8 Hz, 3H).	268.9
D29	A18 B36		50	No Data	334.4
D30	A16 B24		43	No Data	281.3
D31	A23 B15		85	8.61 (s, 1H), 7.53 (s, 1H), 7.13 (brs, 1H), 6.64 (s, 1H), 6.2 (brs, 1H), 6.5 (m, 2H), 5.41 (brs, 2H), 2.87 (m, 6H).	315.1
D32	A6 B23		54	9.28 (s, 1H), 8.45 (s, 1H), 8.04 (s, 1H), 7.03 (t, J = 7.7 Hz, 1H), 6.90 (t, J = 8.3 Hz, 1H), 6.56 (t, J = 7.0 Hz, 1H), 5.35 (s, 2H), 2.57 (s, 3H).	288.0
D33	 B36		59	No Data	266.3
D34	A8 B36		33	No Data	302.1
D35	 and Condensation: Method B		crude	No Data	366.1 368.1

D36	A6 B15		crude	No Data	299.2
D37	A23 B38		crude	No Data	301.1
D38	A5 B47		55	No Data	343.1
D39	A5 B48		80	8.64 (s, 1H), 7.59 (s, 1H), 7.17 (brs, 1H), 6.42 (s, 1H), 6.37 (d, J = 11.6 Hz, 1H), 6.31 (d, J = 9.6 Hz, 1H), 6.18 (brs, 1H), 5.61 (brs, 2H), 3.57 (m, 2H), 3.39 (m, 1H), 3.25 (s, 3H), 2.87 (d, J = 4.4 Hz, 3H), 1.09 (d, J = 5.6 Hz, 3H).	357.1
D40	A5 B49		41	8.63 (s, 1H), 7.59 (s, 1H), 7.19 (brs, 1H), 6.41 (s, 1H), 6.36 (d, J = 11.6 Hz, 1H), 6.31 (d, J = 8.8 Hz, 1H), 6.18 (brs, 1H), 5.61 (brs, 2H), 3.58 (m, 2H), 3.37 (m, 1H), 3.25 (s, 3H), 2.85 (d, J = 4.8 Hz, 3H), 1.09 (d, J = 5.6 Hz, 3H).	357.0
D41	A5 B15		58	8.61 (s, 1H), 7.50 (s, 1H), 7.14 (br s, 1H), 6.58 (brs, 1H), 6.46 (s, 1H), 6.28-6.40 (m, 2H), 5.57 (brs, 2H), 2.89 (d, J = 4.0 Hz, 3H), 2.87 (d, J = 4.8 Hz, 3H).	298.9
D42	A6 B39		36	8.97 (s, 1H), 8.00 (s, 1H), 7.08 (s, 2H), 6.91 (t, J = 7.6 Hz, 1H), 6.79 (t, J = 8.0 Hz, 1H), 6.51 (t, J = 6.4 Hz, 1H), 5.18 (s, 2H), 3.92 (s, 3H).	285.9
D43	A6 B38		54	No Data	285.1

General Method M: Substitution reaction

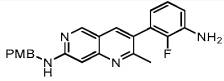
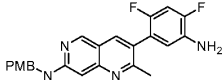
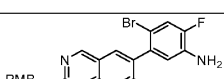
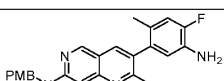
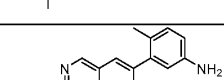
Example E1: 3-(5-amino-2,4-difluorophenyl)-N-(4-methoxybenzyl)-N,2-dimethyl-1,6-naphthyridin-7-amine



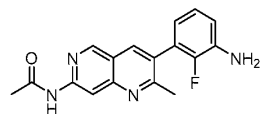
- 5 **[0296]** A solution of 5-(7-chloro-2-methyl-1,6-naphthyridin-3-yl)-2,4-difluoroaniline (**D8**, 0.60 g, 2.0 mmol) and 4-methoxy-N-methylbenzylamine (1.2 g, 8.0 mmol) in NMP (7 mL) was treated with DIEA (1.4 mL, 8.0 mmol). The pressure tube was capped tightly and the mixture heated to 185 °C for 3 days. The mixture was cooled to rt and diluted with sat'd NaHCO₃ (aq, 20 mL). The solution was extracted with EtOAc (4 x 20 mL) and the combined organics were washed with 5%
- 10 LiCl (aq), then brine. The organic layer was dried over anhydrous MgSO₄ and concentrated under reduced pressure. The crude was purified by silica gel column chromatography (5 to 50% EtOAc/hexanes) to obtain 3-(5-amino-2,4-difluorophenyl)-N-(4-methoxybenzyl)-N,2-dimethyl-1,6-naphthyridin-7-amine (0.77 g, 94% yield). MS (ESI) m/z: 421.2 (M+H⁺).
- 15 **[0297]** Using the General Method M above, the following Intermediates of Table E were prepared.

Table E.

Ex No	SM	Product	Yield (%)	¹ H NMR (400 or 500 MHz, DMSO-d ₆): δ	MS (m/z: M+H ⁺)
E2	D10		29	No Data	393.2
E3	D5		68	8.95 (s, 1H), 7.95 (s, 1H), 7.15 (d, J = 8.4 Hz, 1H), 7.05 (m, 1H), 6.85 (m, 2H), 6.78 (dd, 2.3 and 8.8 Hz, 1H), 6.71 (s, 1H), 6.54 (m, 1H), 5.24 (s, 2H), 4.85 (s, 2H), 3.69 (s, 3H), 3.08 (s, 3H), 2.47 (s, 3H).	403.2
E4	D6		70	No Data	403.2
E5	D32		84	No Data	403.2

E6	D32		94	No Data	389.2
E7	D8		88	No Data	393.0
E8	D35		crude	8.99 (s, 1H), 7.96 (s, 1H), 7.46 (d, J = 10.9 Hz, 1H), 7.20 (d, J = 8.3 Hz, 2H), 6.90 (d, J = 8.4 Hz, 2H), 6.78 (m, 2H), 5.52 (s, 2H), 4.85-4.94 (m, 2H), 3.74 (s, 3H), 3.13 (s, 3H), 2.36 (s, 3H).	481.2 483.2
E9	D7		crude	No Data	417.2
E10	D12		51	No Data	399.2

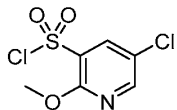
Preparation of Example **E11** by Pd-catalyzed reaction: N-(3-(3-amino-2-fluorophenyl)-2-methyl-1,6-naphthyridin-7-yl)acetamide



- 5 **[0298]** A mixture of 3-(7-chloro-2-methyl-1,6-naphthyridin-3-yl)-2-fluoroaniline (**D1**, 0.29 g, 1.0 mmol), acetamide (0.48 g, 8.1 mol) and K_3PO_4 (0.86 g, 4.0 mmol) in 1,4-dioxane (10 mL) was degassed with Ar for 5 min. $Pd_2(dba)_3$ (0.046 g, 0.05 mmol) and 5-(di-tert-butylphosphanyl)-1',3',5'-triphenyl-1'H-1,4'-bipyrazole (0.026 g, 0.05 mmol) were added and the reaction mixture was degassed with Ar for an additional 5 min. The reaction mixture was stirred at 80 °C for 2 h. The
- 10 reaction mixture was filtered through a pad of celite and concentrated under reduced pressure. The crude was purified by silica gel column chromatography (0 to 100% EtOAc/hexanes) to obtain N-(3-(3-amino-2-fluorophenyl)-2-methyl-1,6-naphthyridin-7-yl)acetamide (0.15 g, 48% yield) as a brown solid. 1H NMR (500 MHz, DMSO- d_6): δ 10.8 (s, 1H), 9.16 (s, 1H), 8.52 (s, 1H), 8.27 (s, 1H), 7.01 (m, 1H), 6.88 (m, 1H), 6.53 (m, 1H), 5.31 (s, 2H), 2.52 (s, 3H), 2.18 (s, 3H); MS (ESI) m/z: 311.0
- 15 ($M+H^+$).

General Method N: Preparation of sulfonyl chlorides

Example F1: 5-chloro-2-methoxypyridine-3-sulfonyl chloride



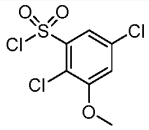
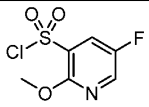
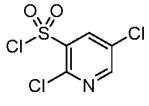
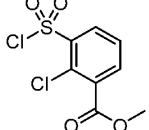
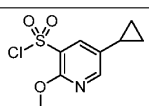
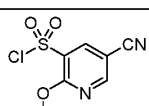
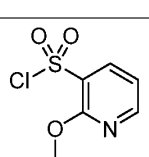
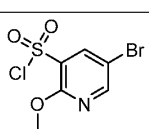
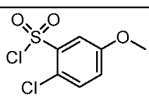
[0299] A mixture of 3-bromo-5-chloro-2-methoxypyridine (50 g, 225 mmol), benzylthiol (29 mL, 247 mmol), DIEA (79 mL, 450 mol), and XantPhos (13 g, 22 mmol) in toluene (500 mL) was purged with Ar for 5 min. Pd₂(dba)₃ (10 g, 11 mmol) was added and the reaction was sealed under Ar and heated to 90 °C for 3h. The reaction was cooled to rt and concentrated under reduced pressure. The residue was treated with in EtOAc (500 mL). The solution was filtered through a pad of silica gel and washed with EtOAc (500 mL). The filtrate was concentrated under reduced pressure to afford 3-(benzylthio)-5-chloro-2-methoxypyridine (60 g, 100% yield) as an orange solid. ¹H NMR (500 MHz, DMSO-d₆): δ 7.94 (d, J = 2.4 Hz, 1 H), 7.65 (d, J = 2.6 Hz, 1H), 7.41 (d, J = 7.9 Hz, 2H), 7.32 (t, J = 7.6 Hz, 2H), 7.26 (d, J = 8.3 Hz, 1H), 4.27 (s, 2H), 3.89 (s, 3H).

[0300] A solution of 3-(benzylthio)-5-chloro-2-methoxypyridine (19.3 g, 73 mol) in acetonitrile (200 mL) was cooled to 0 °C. Acetic acid (42 mL, 725 mmol) and distilled water (10 mL) were added followed by addition of 1,3-dichloro-5,5-dimethylimidazolidine-2,4-dione (available chlorine 68%) (41 g, 141 mol). The resulting solution was stirred for 1 h at rt. The reaction mixture was diluted with EtOAc (200 mL) and then the solution was washed with water (2 x 100 mL). The organic extracts were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The crude was purified by silica gel column chromatography (5% EtOAc/hexanes) to afford 5-chloro-2-methoxypyridine-3-sulfonyl chloride (10 g, 57% yield) as a white crystalline solid. ¹H NMR (500 MHz, DMSO- d₆): δ 8.18 (d, J = 2.7 Hz, 1H), 7.93 (d, J = 2.7 Hz, 1H), 3.87 (s, 3H).

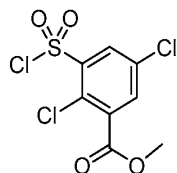
[0301] Using the General Method N above, the following Intermediates of Table F were prepared.

25 **Table F.**

Ex No	Product	Yield (%)	¹ H NMR (400 or 500 MHz, DMSO-d ₆): δ	MS (m/z: M+H ⁺)
F2		19	8.55 (d, J = 2.6 Hz, 1H), 8.13 (d, J = 2.6 Hz, 1H), 3.20 (s, 3H).	No Data

F3		69	7.45 (d, J = 2.0 Hz, 1H), 7.18 (d, J = 2.0 Hz, 1H), 3.86 (s, 3H).	No Data
F4		60	8.16 (d, J = 2.4 Hz, 1H), 7.91 (d, J = 2.4 Hz, 1H), 3.85 (s, 3H).	No Data
F5		50	8.45 (d, J = 2.4 Hz, 1H), 8.17 (d, J = 2.4 Hz, 1H).	No Data
F6		50	8.03 (dd, J = 1.8 and 7.8 Hz, 1H), 7.57 (dd, J = 1.8 and 7.6 Hz, 1H), 7.37 (t, J = 7.7 Hz, 1H), 3.83 (s, 3H).	No Data
F7		35	7.91 (d, J = 2.4 Hz, 1H), 7.60 (d, J = 2.4 Hz, 1H), 3.80 (s, 3H), 1.89 (m, 1H), 0.91 (m, 2H), 0.58 (m, 2H).	247.7
F8		56	8.79 (s, 1H), 8.23 (s, 1H), 3.95 (s, 3H).	No Data
F9		50	8.09 (dd, J = 2.0 and 5.2 Hz, 1H), 7.95 (dd, J = 1.6 and 7.2 Hz, 1H), 6.92 (dd, J = 2.4 and 7.2 Hz, 1H), 3.89 (s, 3H).	No Data
F10		65	8.24 (d, J = 2.4 Hz, 1H), 8.02 (d, J = 2.4 Hz, 1H), 3.85 (s, 3H).	No Data
F11		67	7.42 (d, J = 3.2 Hz, 1H), 7.25 (d, J = 8.8 Hz, 1H), 6.88 (dd, J = 8.8, 3.2 Hz, 1H), 3.74 (s, 3H).	No Data

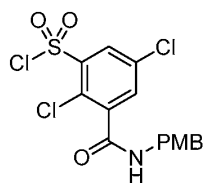
Preparation of Example **F12**: methyl 2,5-dichloro-3-(chlorosulfonyl)benzoate



[0302] A solution of thionyl chloride (12 mL, 164 mmol) in MeOH (45 mL) at 0 °C were stirring for 15 min. 3-Amino-2,5-dichlorobenzoic acid (7.5 g, 36 mmol) was added under the same conditions. The reaction mixture was warmed to rt and stirred for 1 h then heated to refluxed for 5 h. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in EtOAc. The solution was washed with 1 N Na₂CO₃ solution (aq, 200 mL) and the organic layer was washed with brine (50 mL). The organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated under reduce pressure to obtain the crude methyl 3-amino-2,5-dichlorobenzoate (7.0 g, 87% yield) which was proceeded to the next step without further purification. ¹H NMR (500 MHz, DMSO-d₆): δ 6.98 (d, J = 2.5 Hz, 1H), 6.88 (d, J = 2.5 Hz, 1H), 5.97 (s, 2H), 3.83 (s, 3H); MS (ESI) m/z: 220.0 (M+H⁺).

[0303] Solution A (prep: a solution of sodium nitrite (0.68 g, 9.8 mmol) in water (5.4 mL) was treated with a solution of methyl 3-amino-2,5-dichlorobenzoate (2.0 g, 9.1 mmol) in HCl (18 mL) at -15 °C. The solution was stirred under the same conditions for 30 min.) was added dropwise into solution B (prep: thionyl chloride (2.8 mL, 39 mmol) was added dropwise into water (17 mL) under an acetone and ice bath. The mixture was stirred for 16 h at rt. Copper(I) chloride (10 mg, 1 mmol) was added at rt and then the mixture was cooled to -15 °C and stirred for 30 min.) at -15 °C and the reaction mixture was stirred under the same conditions for 2 h. Once the reaction was completed the mixture was diluted with DCM (100 mL). The aqueous phase was extracted with DCM (3 x 50 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude was purified by silica gel column chromatography (0 to 50% EtOAc/hexanes) to obtain methyl 2,5-dichloro-3-(chlorosulfonyl)benzoate (**F12**, 2.1 g, 76% yield) as a yellow viscous liquid. ¹H NMR (500 MHz, DMSO-d₆): δ 8.00 (d, J = 2.7 Hz, 1H), 7.72 (d, J = 2.7 Hz, 1H), 3.86 (s, 3H).

25 Preparation of Example **F13**: 2,5-dichloro-3-((4-methoxybenzyl)carbamoyl)benzenesulfonyl chloride



[0304] A solution of 3-amino-2,5-dichlorobenzoic acid (3.00 g, 15 mmol) in DMF (10 mL) was added 4-methoxybenzylamine (2.09 mL, 16 mmol). DIEA (5.34 mL, 31 mmol) and HATU (5.81 g, 15 mmol) were added and then the reaction was stirred overnight at rt. The reaction mixture was poured into water and extracted with EtOAc (3x). The combined organic layers were washed with

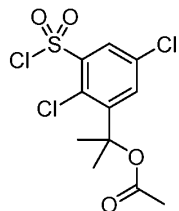
sat'd aqueous NaHCO₃ (2x), brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was rinsed with hexanes to afford 3-amino-2,5-dichloro-N-(4-methoxybenzyl)benzamide (2.40 g, 51% yield) as a beige solid. ¹H NMR (500 MHz, DMSO-d₆): δ 8.86 (t, J = 6.0 Hz, 1H), 7.26 (d, J = 8.4 Hz, 2H), 6.91 (d, J = 8.4 Hz, 2H), 6.85 (d, J = 2.5 Hz, 1H), 6.55 (d, J = 2.5 Hz, 1H), 5.83 (s, 2H), 4.34 (d, J = 6.0 Hz, 2H), 3.74 (s, 3H).

[0305] Pot A: water (13.7 mL, 760 mmol) was cooled to -15 °C. SOCl₂ (2.32 mL, 32 mmol) was then added dropwise and the mixture was stirred for 16 h at rt. Copper(I) chloride (0.008 g, 0.08 mmol) was added at rt and the mixture cooled to -15 °C and stirred for 30 min.

[0306] Pot B: sodium nitrite (0.55 g, 7.9 mmol) in H₂O (4.4 mL, 244 mmol) and 1,4-dioxane (4 mL) was added dropwise to a solution of 3-amino-2,5-dichloro-N-(4-methoxybenzyl)benzamide (2.40 g, 7.4 mmol) in HCl (14.8 mL, 487 mmol) at -15 °C and stirred for 30 min, maintaining temp.

[0307] Pot B was then added dropwise to **Pot A** at -15 °C, warmed to rt slowly and stirred rapidly for 1.5 h. (**Pot B** was rinsed with an additional 4 mL of H₂O and added to **Pot A**). The solids were filtration and the crude was purified by silica gel column chromatography (5-100% EtOAc/hexanes plus 0.5% acetic acid modifier) to obtain 2,5-dichloro-3-((4-methoxybenzyl)carbamoyl)benzenesulfonyl chloride (**F13**, 1.5 g, 50% yield) as a light orange solid.

Preparation of Example **F14**: 2-(2,5-dichloro-3-(chlorosulfonyl)phenyl)propan-2-yl acetate



[0308] A solution of 3-amino-2,5-dichlorobenzoic acid (14.0 g, 68.0 mmol) in EtOH (120 mL) was cooled to 0 °C and thionyl chloride (20.0 mL, 169 mmol) was added dropwise. The reaction mixture was further heated at 85 °C for 16 h. The reaction mixture was cooled to rt and concentrated under reduced pressure. The crude was triturated with *n*-pentane to afford ethyl 3-amino-2,5-dichlorobenzoate (14.0 g, 83% yield) as brown solid. ¹H NMR (500 MHz, DMSO-d₆): δ 6.96 (d, J = 2.4 Hz, 1H), 6.85 (d, J = 2.4 Hz, 1H), 5.96 (brs, 2H), 4.29 (q, J = 7.2 Hz, 2H), 1.29 (t, J = 6.8 Hz, 3H).

[0309] A solution of ethyl 3-amino-2,5-dichlorobenzoate (12.0 g, 51.0 mmol) in CH₃CN (250 mL) was treated with amyl nitrite (9.64 mL, 81.0 mmol). Dibenzyl disulphide (12.6 g, 51.0 mmol) was added at rt and the reaction mixture was heated at 70 °C for 3 h. The reaction mixture was quenched with ice water (100 mL) and extracted with EtOAc (3x). The combined organics were dried over

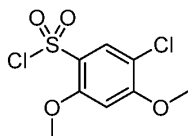
anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The crude was purified by silica gel column chromatography (10 to 20% EtOAc/hexanes) to afford ethyl 3-(benzylthio)-2,5-dichlorobenzoate (10.0 g, 58% yield) as an off white solid. ¹H NMR (500 MHz, DMSO-d₆): δ 7.63 (d, J = 2.8 Hz, 1H), 7.56 (d, J = 2.4 Hz, 1H), 7.44 (d, J = 7.2 Hz, 2H), 7.35 (t, J = 7.6 Hz, 2H), 7.28 (d, J = 7.2 Hz, 1H), 4.42 (s, 2H), 4.33 (q, J = 7.2 Hz, 2H), 1.29 (t, J = 6.8 Hz, 3H).

[0310] A solution of ethyl 3-(benzylthio)-2,5-dichlorobenzoate (10.0 g, 29.32 mmol) in diethyl ether (20 mL) was stirred at 0 °C under Ar. Methyl magnesium bromide (9.0 g, 76.24 mmol) was added under the same conditions and then the mixture was stirred at rt for 6 h. The reaction mixture was quenched with ice water (50 mL) and extracted with EtOAc (3x). The combined organics were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The crude was purified by silica gel column chromatography (5 to 10% EtOAc/hexanes) to afford 2-(3-(benzylthio)-2,5-dichlorophenyl)propan-2-ol (6.0 g, 62% yield) as an off white solid. ¹H NMR (500 MHz, DMSO-d₆): δ 7.59 (s, 1H), 7.43 (d, J = 7.2 Hz, 2H), 7.35 (m, 3H), 7.28 (m, 1H), 5.49 (s, 1H), 4.33 (s, 2H), 1.58 (s, 6H).

[0311] A solution of 2-(3-(benzylthio)-2,5-dichlorophenyl)propan-2-ol (3.0 g, 9.2 mmol), acetic anhydride (2.81 g, 27.6 mmol, 3.0 equiv.), triethyl amine (4.0 mL, 27.6 mmol, 3.0 eq) and dimethyl amino pyridine (2.24 g, 18.4 mmol, 2.0 equiv.) in THF (60 mL) were heated at 80 °C for 24 h. The reaction mixture was cooled to rt and quenched with water (100 mL). The mixture was extracted with EtOAc (3x) and the combined organics were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The crude was purified by silica gel column chromatography (1 to 2% MeOH/DCM) to afford the 2-(3-(benzylthio)-2,5-dichlorophenyl)propan-2-yl acetate (2.20 g, 65% yield) as a brown solid. ¹H NMR (500 MHz, DMSO-d₆): δ 7.42 (d, J = 7.6 Hz, 2H), 7.35 (m, 3H), 7.28 (d, J = 7.2 Hz, 1H), 7.25 (s, 1H), 4.33 (s, 2H), 1.98 (s, 3H), 1.72 (s, 6H).

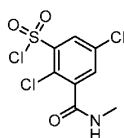
[0312] A solution of 2-(3-(benzylthio)-2,5-dichlorophenyl)propan-2-yl acetate (3.0 g, 9.2 mmol) and 1,3-dichloro-5,5-dimethylimidazolidine-2,4-dione (2.35 g, 11.9 mmol) in CH₃CN (60 mL) was treated with acetic acid (3.6 g, 59.7 mmol) and water (2.0 mL). The reaction mixture was stirred at rt for 16 h and quenched with sat'd NaHCO₃ solution (100 mL). The mixture was extracted with EtOAc (3x) and the combined organics were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to afford 2-(2,5-dichloro-3-(chlorosulfonyl)phenyl)propan-2-yl acetate (F14, 1.5 g, crude) as a white solid which was used for the next reaction without further purification.

Preparation of Example **F15**: 5-chloro-2,4-dimethoxybenzenesulfonyl chloride



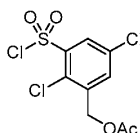
[0313] A solution of 1-chloro-2,4-dimethoxybenzene (1.0 g, 5.8 mmol) in CHCl_3 (15 mL) under Ar was cooled to 0 °C. Chlorosulfonic acid (1.5 mL, 12.9 mmol) was added dropwise at 0 °C and the mixture was further stirred at rt for 3 h. The mixture was quenched with ice water (50 mL) and extracted with EtOAc (2x). The combined organics were dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure. The crude was further triturated with *n*-pentane to afford desired 5-chloro-2,4-dimethoxybenzenesulfonyl chloride (**F15**, 0.9 g, 51% yield) as off white solid. ^1H NMR (500 MHz, DMSO-d_6): δ 7.60 (s, 1H), 6.70 (s, 1H), 3.88 (s, 3H), 3.80 (s, 3H).

Preparation of Example **F16**: 2,5-dichloro-3-(methylcarbamoyl)benzenesulfonyl chloride



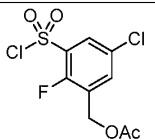
[0314] Using General Methods J and N, 2,5-dichloro-3-(methylcarbamoyl)benzenesulfonyl chloride was prepared from methyl 3-bromo-2,5-dichlorobenzoate. ^1H NMR (500 MHz, DMSO-d_6): δ 8.46 (brn, 1H), 7.86 (d, J = 2.8 Hz, 1H), 7.41 (d, J = 2.8 Hz, 1H), 2.73 (d, J = 4.4 Hz, 3H); MS (ESI) m/z : 302.1 ($\text{M}+\text{H}^+$).

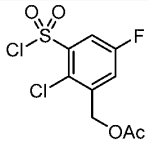
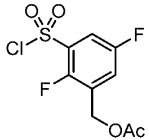
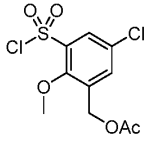
Preparation of Example **F17**: 2,5-dichloro-3-(chlorosulfonyl)benzyl acetate



[0315] A solution of ethyl 3-amino-2,5-dichlorobenzoate (14.0 g, 51.0 mmol) in acetonitrile (250 mL) was treated with amyl nitrite (9.64 mL, 81.0 mmol) and dibenzyl disulphide (12.6 g, 51.0 mmol.). The reaction was heated at 70 °C for 3 h and then quenched with ice-cold water (100 mL). The aqueous layer was extracted with EtOAc (3x). The combined organics were dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure. The crude was purified by silica gel column chromatography (1 to 10% EtOAc/hexanes) to afford ethyl 3-(benzylthio)-2,5-dichlorobenzoate (14.0 g, 58% yield) as an off white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 7.65 (d, J = 2.8 Hz, 1H), 7.56 (d, J = 2.4 Hz, 1H), 7.43-7.45 (m, 2H), 7.33-7.37 (m, 2H), 7.28 (m, 1H), 4.42 (s, 2H), 4.33 (q, J = 7.2 Hz, 2H), 1.31 (t, J = 6.8 Hz, 3H).

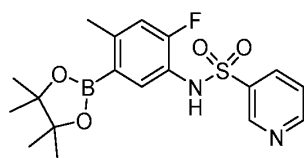
- [0316]** A solution of ethyl 3-(benzylthio)-2,5-dichlorobenzoate (14.0 g, 9.2 mmol) in THF/EtOH (1:1, 400 mL) was treated with CaCl₂ (0.45 g, 0.92 mmol). NaBH₄ (6.20 g, 36.8 mmol, 4.0 equiv) was added at 0 °C and the reaction mixture was further heated at 60 °C for 5 h. The reaction was cooled to rt and quenched with NH₄Cl solution (50 mL). The solution was extracted with EtOAc (3x) and the combined organics were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The crude was purified by silica gel column chromatography (1 to 10% EtOAc/hexanes) to afford the (3-(benzylthio)-2,5-dichlorophenyl)methanol (8.0 g, 66% yield) as a brown solid. ¹H NMR (400 MHz, DMSO-d₆) δ 7.42-7.45 (m, 2H), 7.33-7.36 (m, 3H), 7.25-7.32 (m, 2H), 5.57 (t, J = 5.6 Hz, 1H), 4.51 (d, J = 6.0 Hz, 2H), 4.36 (s, 2H).
- [0317]** A solution of (3-(benzylthio)-2,5-dichlorophenyl)methanol (8.0 g, 2.60 mmol) in THF (60 mL) was treated with acetic anhydride (8.32 g, 8.08 mmol), triethyl amine (13.6 g, 67.1 mmol) and dimethyl amino pyridine (0.90 g, 0.26 mmol). The reaction mixture was heated at 80 °C for 3 h and then cooled to rt. The reaction mixture was quenched with water (300 mL) and extracted with EtOAc (3x). The combined organics were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The crude was purified by silica gel column chromatography (10 to 20% EtOAc/hexanes) to afford the 3-(benzylthio)-2,5-dichlorobenzyl acetate (8.0 g, 88% yield) as an off-white solid. ¹H NMR (400 MHz, DMSO-d₆) δ 7.44-7.46 (m, 2H), 7.43 (s, 1H), 7.36 (s, 1H), 7.33-7.35 (m, 2H), 7.27 (m, 1H), 5.10 (s, 2H), 4.39 (s, 2H), 2.09 (s, 3H).
- [0318]** A solution of 3-(benzylthio)-2,5-dichlorobenzyl acetate (8.0 g, 2.3 mmol) in AcOH/THF/water (8:1:1, 400.0 mL) was treated with N-chlorosuccinimide (12.0 g, 4.8 mmol). The reaction mixture was stirred at rt for 2 h and then quenched with water (100 mL). The mixture was extracted with EtOAc (3x) and the combined organics were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The crude was purified by silica gel column chromatography (10 to 20% EtOAc/hexanes) to afford the 2,5-dichloro-3-(chlorosulfonyl)benzyl acetate (F17, 4.2 g, 88% yield) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ 7.84 (d, J = 2.8 Hz, 1H), 7.52 (d, J = 2.8 Hz, 1H), 5.13 (s, 2H), 2.11 (s, 3H).

F18		74	7.60 (m, 1H), 7.50 (m, 1H), 5.08 (s, 2H), 2.07 (s, 3H).	No Data
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F19		63	7.58-7.64 (m, 1H), 7.29-7.35 (m, 1H), 5.13 (s, 2H), 2.11 (s, 3H).	No Data
F20		75	7.33 (m, 1H), 7.30 (m, 1H), 5.07 (s, 2H), 2.07 (s, 3H).	No Data
F21		47	No Data	312.0

General Method O: Sulfonamide coupling

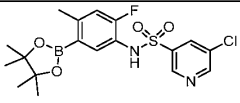
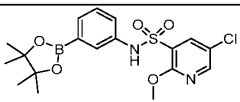
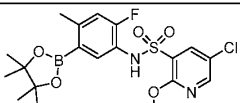
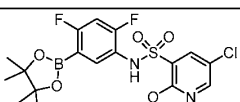
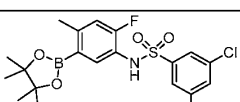
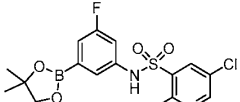
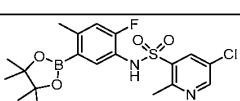
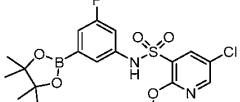
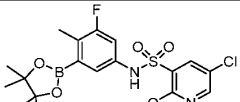
Example **G1**: N-(6-bromoquinazolin-2-yl)acetamide

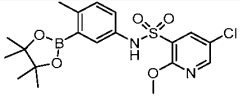
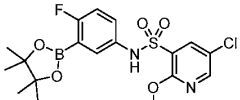
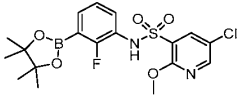
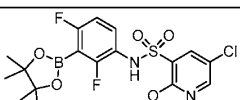
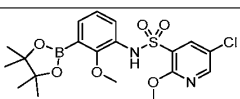
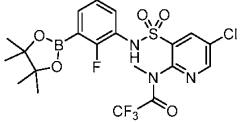
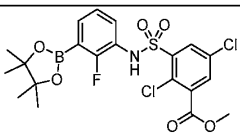
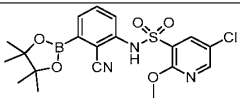
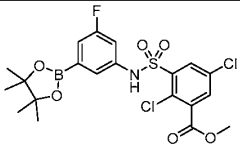


- 5 **[0319]** A solution of 2-fluoro-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (**A1**, 0.2 g, 0.80 mmol) in DCM (3 mL) was cooled to 0 °C. Pyridine-3-sulfonyl chloride (0.14 g, 0.80 mmol) was added portion-wise and the reaction mixture was slowly warmed to rt overnight.
- [0320]** The solvent was removed under reduced pressure and the crude was purified by silica gel column chromatography (0 to 10% DCM/MeOH) to obtain N-(2-fluoro-4-methyl-5-(4,4,5,5-
- 10 tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyridine-3-sulfonamide (0.30 g, 98% yield) as a white solid. ¹H NMR (500 MHz, DMSO-d₆): δ 10.2 (s, 1H), 8.80 (m, 2H), 8.03 (d, J = 8.2 Hz, 1H), 7.62 (m, 1H), 7.39 (d, J = 9.0 Hz, 1H), 7.03 (d, J = 11.6 Hz, 1H), 2.41 (s, 3H), 1.29 (s, 12H); MS (ESI) m/z: 393.2 (M+H⁺).
- 15 **[0321]** Using the General Method O above, the following Intermediates of Table G were prepared.

Table G.

Ex No	SM	Product	Yield (%)	¹ H NMR (400 or 500 MHz, DMSO-d ₆): δ	MS (m/z: M+H ⁺)
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G2	A1 		91	10.3 (s, 1H), 8.95 (d, J = 2.3 Hz, 1H), 8.73 (d, J = 2.0 Hz, 1H), 8.14 (t, J = 2.1 Hz, 1H), 7.34 (d, J = 8.9 Hz, 1H), 7.08 (d, J = 11.6 Hz, 1H), 2.42 (s, 3H), 1.28 (s, 12H).	427.0
G3	F1 		98	10.5 (s, 1H), 8.46 (d, J = 2.6 Hz, 1H), 8.14 (d, J = 2.6 Hz, 1H), 7.42 (d, J = 2.2 Hz, 1H), 7.33 (m, 1H), 7.25 (m, 2H), 3.95 (s, 3H), 1.27 (s, 12H).	425.0
G4	A1 F1		93	10.1 (s, 1H), 8.51 (d, J = 2.6 Hz, 1H), 7.99 (d, J = 2.6 Hz, 1H), 7.43 (d, J = 9.0 Hz, 1H), 7.03 (d, J = 11.6 Hz, 1H), 3.97 (s, 3H), 2.40 (s, 3H), 1.28 (s, 12H).	457.2
G5	A10 F1		44	10.3 (s, 1H), 8.53 (d, J = 2.6 Hz, 1H), 8.04 (d, J = 2.6 Hz, 1H), 7.50 (m, 1H), 7.25 (m, 1H), 3.96 (s, 3H), 1.30 (s, 12H).	461.0
G6	A1 		20	10.2 (s, 1H), 8.01 (t, J = 1.9 Hz, 1H), 7.65 (d, J = 1.9 Hz, 2H), 7.29 (d, J = 9.0 Hz, 1H), 7.09 (d, J = 11.6 Hz, 1H), 2.42 (s, 3H), 1.28 (s, 12H).	482.2 (M+23)
G7	A5 		78	10.9 (s, 1H), 7.87 (d, J = 2.3 Hz, 1H), 7.63 (dd, J = 2.3 and 8.2 Hz, 1H), 7.44 (d, J = 8.2 Hz, 1H), 7.23 (d, J = 2.0 Hz, 1H), 6.99 (m, 2H), 2.56 (s, 3H), 1.28 (s, 12H).	448.0 (M+23)
G8	A1 		53	10.2 (s, 1H), 7.61 (m, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.34 (d, J = 9.0 Hz, 1H), 7.01 (d, J = 11.6 Hz, 1H), 2.54 (s, 3H), 2.38 (s, 3H), 1.26 (s, 12H).	462.2 (M+23)
G9	A5 F1		27	10.8 (s, 1H), 8.48 (d, J = 2.6 Hz, 1H), 8.22 (d, J = 2.6 Hz, 1H), 7.25 (d, J = 2.0 Hz, 1H), 7.02 (m, 2 H), 3.93 (s, 3H), 1.28 (s, 12H).	443.0
G10	A13 F1		38	No Data	457.0

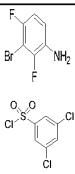
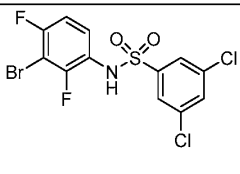
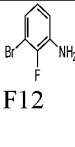
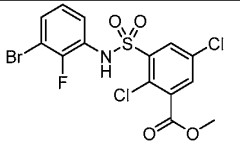
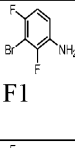
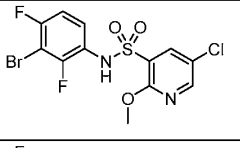
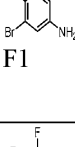
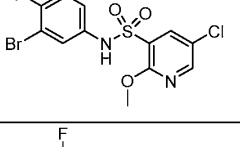
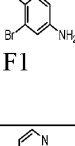
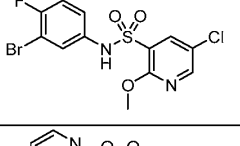
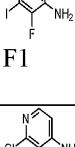
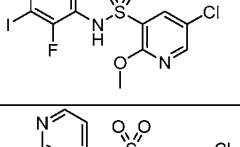
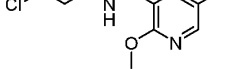
G11	A2 F1		62	10.2 (s, 1H), 8.45 (d, J = 2.6 Hz, 1H), 8.08 (d, J = 2.6 Hz, 1H), 7.36 (d, J = 2.4 Hz, 1H), 7.06 (m, 2H), 3.98 (s, 3H), 2.33 (s, 3H), 1.27 (s, 12H).	439.0
G12	A3 F1		56	10.4 (s, 1H, s), 8.47 (d, J = 2.6 Hz, 1H), 8.10 (d, J = 2.6 Hz, 1H), 7.36 (m, 1H), 7.24 (m, 1H), 7.07 (t, J = 8.8 Hz, 1H), 3.96 (s, 3H), 1.27 (s, 12H)	465.0 (M+23)
G13	A6 F1		94	10.3 (s, 1H), 8.50 (d, J = 2.5 Hz, 1H), 8.06 (d, J = 2.6 Hz, 1H), 7.45 (s, 1H), 7.39 (dd, J = 1.7 and 7.7 Hz, 1H), 7.15 (t, J = 7.7 Hz, 1H), 3.89 (s, 3H), 1.27 (s, 12H).	443.2
G14	A9 F1		21	10.2 (s, 1H), 8.52 (d, J = 2.6 Hz, 1H), 8.04 (d, J = 2.6 Hz, 1H), 7.37 (d, J = 8.1 Hz, 1H), 7.02 (t, J = 8.5 Hz, 1H), 3.89 (s, 3H), 1.28 (s, 12H).	441.2
G15	A15 F1		82	No Data	455.0
G16	A6 F2		63	11.0 (s, 1H), 8.97 (d, J = 2.4 Hz, 1H), 8.42 (d, J = 2.4 Hz, 1H), 7.50 (t, J = 6.0 Hz, 1H), 7.40 (m, 1H), 7.19 (t, J = 7.7 Hz, 1H), 3.18 (s, 3H), 1.28 (s, 12H).	560 (M+23)
G17	A6 F12		56	No Data	526.0
G18	A22 F1		crude	No Data	450.0
G19	A5 F12		70	No Data	504.0

G20	A6 F13		32	No Data	609.2
G21	A21 F1		64	10.2 (s, 1H), 8.51 (d, J = 2.6 Hz, 1H), 8.01 (d, J = 2.6 Hz, 1H), 7.47 (dd, J = 1.7 and 7.3 Hz, 1H), 7.42 (dd, J = 1.7 and 7.9 Hz, 1H), 7.32 (t, J = 7.6 Hz, 1H), 3.87 (s, 3H), 1.28 (s, 12H).	459.2
G22	A8 F1		94	10.7 (d, J = 2.3 Hz, 1H), 8.50 (m, 1H), 8.19 (d, J = 2.6 Hz, 1H), 7.25 (ddd, J = 11.8, 6.9, 2.7 Hz, 1H), 7.14 (t, J = 3.0 Hz, 1H), 3.94 (s, 3H), 1.28 (s, 12H).	461.2
G23	A6 		49	10.1 (s, 1H), 8.15 (d, J = 4.4 Hz, 1H), 7.76 (dd, J = 1.1 and 8.5 Hz, 1H), 7.65 (dd, J = 4.5 and 8.5 Hz, 1H), 7.30-7.42 (m, 2H), 7.06 (t, J = 7.7 Hz, 1H), 3.88 (s, 3H), 1.28 (s, 12H).	409.2
G24	A6 F17		68	10.6 (s, 1H), 7.85 (m, 2H), 7.41 (m, 1H), 7.35 (m, 1H), 7.12 (t, J = 7.6 Hz, 1H), 5.13 (s, 2H), 2.12 (s, 3H), 1.26 (s, 12H).	434.0 (boronic acid)
G25	A6 F18		60	7.88 (m, 1H), 7.66 (m, 1H), 7.45-7.51 (m, 1H), 7.38 (m, 1H), 7.15 (m, 1H), 5.14 (s, 2H), 2.07 (s, 3H), 1.26 (s, 12H). NH is missing	No Data
G26	A6 F19		86	10.61 (br s, 1H), 7.70 (m, 1H), 7.55 (t, J = 7.2 Hz, 1H), 7.43 (t, J = 5.6 Hz, 1H), 7.35 (t, J = 7.6 Hz, 1H), 7.13 (t, J = 7.6 Hz, 1H), 5.21 (s, 2H), 2.13 (s, 3H), 1.22 (s, 12H).	No Data
G27	A6 F20		86	10.58 (br m, 1H), 7.68 (m, 1H), 7.57 (m, 1H), 7.43 (m, 1H), 7.39 (m, 1H), 7.13 (t, J = 4.0 Hz, 1H), 5.08 (s, 2H), 2.08 (s, 3H), 1.23 (s, 12H).	No Data
G28	A6 F21		98	10.15 (br s, 1H), 7.74 (m, 1H), 7.64 (d, J = 2.8 Hz, 1H), 7.41 (t, J = 5.6 Hz, 1H), 7.33 (t, J = 7.6 Hz, 1H), 7.11 (t, J = 8.0 Hz,	512.2

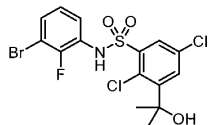
				1H), 5.14 (s, 2H), 3.84 (s, 3H), 2.10 (s, 3H), 1.27 (s, 12H).	
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[0322] Using the General Method O above, the following Intermediates of Table H were prepared.

Table H.

Ex No	SM	Product	Yield (%)	¹ H NMR (400 or 500 MHz, DMSO-d ₆): δ	MS (m/z: M+H ⁺)
H1			100	10.6 (s, 1H), 8.01 (d, J = 2.2 Hz, 1H), 7.66 (d, J = 1.9 Hz, 2H), 7.26 (m, 2H);	322.2
H2	 F12		59	No Data	No Data
H3	 F1		57	10.5 (s, 1H), 8.53 (d, J = 2.6 Hz, 1H), 8.07 (d, J = 2.6 Hz, 1H), 7.23-7.37 (m, 2H), 3.92 (s, 3H).	413.0 415.0
H4	 F1		81	No Data	395.0 397.0
H5	 F1		93	10.9 (s, 1H), 8.52 (d, J = 2.6 Hz, 1H), 8.29 (d, J = 2.6 Hz, 1H), 7.18 (m, 2H), 3.95 (s, 3H).	412.9 414.9
H6	 F1		54	11.6 (s, 1H), 8.48 (s, 1H), 8.22 (s, 1H), 7.60 (d, J = 3.6 Hz, 1H), 7.49 (brs, 1H), 3.87 (s, 3H).	443.7
H7	 F1		crude	No Data	334.0

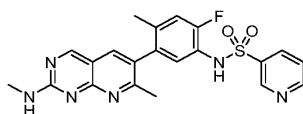
Preparation of Example **H8**: N-(3-bromo-2-fluorophenyl)-2,5-dichloro-3-(2-hydroxypropan-2-yl)benzenesulfonamide



[0323] A solution of methyl 3-(N-(3-bromo-2-fluorophenyl)sulfamoyl)-2,5-dichlorobenzoate (**H2**, 0.85 g, 1.9 mmol) in THF (10 mL) was stirred at -78 °C. Methylmagnesium bromide (3.2 M in THF, 3.8 mL, 12 mmol) was added dropwise at -78 °C. The reaction mixture was slowly warmed to rt overnight. The reaction was quenched with sat'd NH₄Cl (aq, 20 mL) and the solution was extracted with EtOAc (3 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 (1% EtOAc/DCM) to obtain N-(3-bromo-2-fluorophenyl)-2,5-dichloro-3-(2-hydroxypropan-2-yl)benzenesulfonamide (0.4 g, 47% yield).

General Method P: Suzuki reaction

Example 1: N-(2-fluoro-4-methyl-5-(7-methyl-2-(methylamino)pyrido[2,3-d]pyrimidin-6-yl)phenyl)pyridine-3-sulfonamide

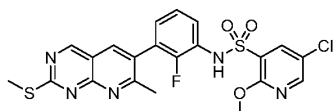


[0324] A mixture of N-(2-fluoro-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyridine-3-sulfonamide (**G1**, 0.20 g, 0.51 mmol), 6-bromo-N,7-dimethylpyrido[2,3-d]pyrimidin-2-amine (**B3**, 0.13 g, 0.51 mmol), and K₂CO₃ (0.21 g, 1.5 mmol) in 1,4-dioxane (2 mL) and water (0.5 mL) was purged with Ar for 10 min. Pd(PPh₃)₄ (0.059 g, 0.05 mmol) was added and the reaction was heated at 80 °C under microwave for 3 h. The reaction was cooled to rt and filtered through a pad of celite. The filtrate was concentrated under reduced pressure and then the residue was purified by silica gel column chromatography (0 to 10% MeOH/DCM) to obtain N-(2-fluoro-4-methyl-5-(7-methyl-2-(methylamino)pyrido[2,3-d]pyrimidin-6-yl)phenyl)pyridine-3-sulfonamide (0.11 g, 48% yield) as an orange solid. ¹H NMR (500 MHz, DMSO-d₆): δ 10.4 (s, 1H), 9.08 (s, 1H), 8.82 (m, 2H), 8.10 (m, 1H), 7.89 (s, 1H), 7.72 (s, 1H), 7.65 (dd, J = 4.9 and 8.1 Hz, 1H), 7.23 (d, J = 11.2 Hz, 1H), 6.99 (d, J = 8.0 Hz, 1H), 2.93 (d, J = 4.7 Hz, 3H), 2.20 (s, 3H), 1.99 (s, 3H); MS (ESI) m/z: 439.2 (M+H⁺).

30

General Method Q: Sulfonamide coupling

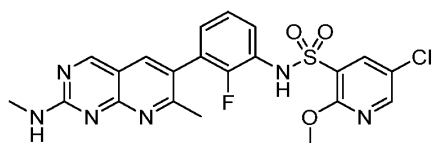
Example 2: 5-chloro-N-(2-fluoro-3-(7-methyl-2-(methylthio)pyrido[2,3-d]pyrimidin-6-yl)phenyl)-2-methoxypyridine-3-sulfonamide



- 5 **[0325]** A solution of 2-fluoro-3-(7-methyl-2-(methylthio)pyrido[2,3-d]pyrimidin-6-yl)aniline (**D3**, 0.50 g, 1.7 mmol) in pyridine (2 mL) was added a solution of 5-chloro-2-methoxypyridine-3-sulfonyl chloride (**F1**, 0.44 g, 1.8 mmol) in pyridine (2 mL) at 0 °C. The reaction mixture was warmed to rt and stirred for 12 h. The reaction mixture was concentrated under reduced pressure. The crude was purified by silica gel column chromatography (0 to 100% EtOAc/hexanes) to afford 5-chloro-N-(2-fluoro-3-(7-methyl-2-(methylthio)pyrido[2,3-d]pyrimidin-6-yl)phenyl)-2-methoxypyridine-3-sulfonamide (0.60 g, 71% yield) as a yellow solid. MS (ESI) m/z: 506.0 (M+H⁺).

General Method R: Oxidation and Substitution

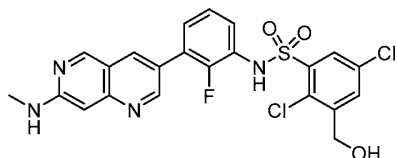
- 15 Example 3: 5-chloro-N-(2-fluoro-3-(7-methyl-2-(methylamino)pyrido[2,3-d]pyrimidin-6-yl)phenyl)-2-methoxypyridine-3-sulfonamide



- 20 **[0326]** A solution of 5-chloro-N-(2-fluoro-3-(7-methyl-2-(methylthio)pyrido[2,3-d]pyrimidin-6-yl)phenyl)-2-methoxypyridine-3-sulfonamide (**2**, 0.26 g, 0.52 mmol) in DCM (2 mL) at 0 °C was treated with mCPBA (0.12 g, 0.54 mmol). The reaction stirred for 60 min. The solid was filtered off and rinsed with cold DCM (25 mL). The filtrate was concentrated under reduced pressure. The residue was dissolved in THF (2 mL) and then DIEA (0.17 mL, 0.97 mmol) was added. Methylamine (33% in EtOH, 0.65 mL, 5.2 mmol) was added and the reaction mixture was slowly warmed to rt over 1 h. The reaction mixture was quenched with sat'd NaHCO₃ (aq, 30 mL) and then the solution was extracted with DCM (2 x 25 mL). The combined organics were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The crude was purified by reverse phase column chromatography (0 to 100% (0.4% FA)water/CH₃CN) to obtain 5-chloro-N-(2-fluoro-3-(7-methyl-2-(methylamino)pyrido[2,3-d]pyrimidin-6-yl)phenyl)-2-methoxypyridine-3-sulfonamide (0.13 g, 53% yield) as a yellow solid. ¹H NMR (500 MHz, DMSO-d₆): δ 10.4 (brs, 1H), 9.09 (s, 1H), 8.34 (s, 1H), 8.00 (m, 3H), 7.72 (s, 1H), 7.30 (s, 1H), 7.06 (m, 1H), 3.88 (s, 3H), 2.92 (d, J = 4.8 Hz, 3H), 2.27 (s, 3H); MS (ESI) m/z: 489.0 (M+H⁺).

General Method S: Reduction with LiAlH₄

Example 4: 2,5-dichloro-N-(2-fluoro-3-(7-(methylamino)-1,6-naphthyridin-3-yl)phenyl)-3-(hydroxymethyl)benzenesulfonamide



5

[0327] Methyl 2,5-dichloro-3-(N-(2-fluoro-3-(7-(methylamino)-1,6-naphthyridin-3-yl)phenyl)sulfamoyl)benzoate (0.21 g, 47% yield) was prepared from 3-bromo-N-methyl-1,6-naphthyridin-7-amine (**B26**, 0.20 g, 0.84 mmol), and methyl 2,5-dichloro-3-(N-(2-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)sulfamoyl)benzoate (**G17**, 0.42 g, 0.84 mmol) by

10 General Method Q. MS (ESI) *m/z*: 535.0 (M+H⁺).

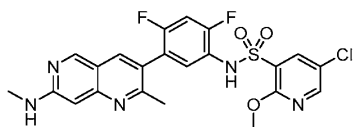
[0328] A solution of methyl 2,5-dichloro-3-(N-(2-fluoro-3-(7-(methylamino)-1,6-naphthyridin-3-yl)phenyl)sulfamoyl)benzoate (0.10 g, 0.19 mmol) in THF (2 mL) was treated with LiAlH₄ (0.021 g, 0.56 mmol) under Ar. The reaction mixture was stirred at 0 °C for 1 h. The reaction mixture was quenched with EtOAc (1 mL) and MeOH (1 mL) at 0 °C. The reaction mixture was warmed to rt and stirred for 2 h. The mixture was filtered through a pad of celite and the filtrate was concentrated under reduced pressure. The crude was purified reverse phase column chromatography (0 to 100% (0.4% FA)water/CH₃CN) to afford 2,5-dichloro-N-(2-fluoro-3-(7-(methylamino)-1,6-naphthyridin-3-yl)phenyl)-3-(hydroxymethyl)benzenesulfonamide (0.02 g, 21% yield) as a yellow solid. ¹H NMR (500 MHz, DMSO-*d*₆): δ 10.8 (s, 1H), 8.98 (s, 1H), 8.82 (s, 1H), 8.30 (s, 1H), 7.83 (m, 2H), 7.51 (t, J = 5.6 Hz, 1H), 7.28 (m, 2H), 6.99 (m, 1H), 6.60 (s, 1H), 5.75 (m, 1H), 4.63 (d, J = 5.4 Hz, 2H), 2.87 (d, J = 4.9 Hz, 3H); MS (ESI) *m/z*: 507.0 (M+H⁺).

20

General Method T: Deprotection with TFA

Example 5: 5-chloro-N-(2,4-difluoro-5-(2-methyl-7-(methylamino)-1,6-naphthyridin-3-yl)phenyl)-2-methoxypyridine-3-sulfonamide

25



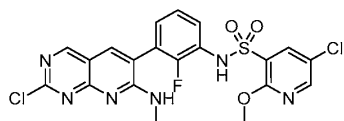
[0329] 5-chloro-N-(2,4-difluoro-5-(7-((4-methoxybenzyl)(methyl)amino)-2-methyl-1,6-naphthyridin-3-yl)phenyl)-2-methoxypyridine-3-sulfonamide (0.14 g, 93% yield) was prepared by

reacting 3-(5-amino-2,4-difluorophenyl)-N-(4-methoxybenzyl)-N,2-dimethyl-1,6-naphthyridin-7-amine (**E7**, 0.10 g, 0.24 mmol) and 5-chloro-2-methoxypyridine-3-sulfonyl chloride (**F1**, 0.07 g, 0.29 mmol) by method Q. MS (ESI) m/z: 626.2 (M+H⁺).

[0330] A solution of 5-chloro-N-(2,4-difluoro-5-(7-((4-methoxybenzyl)(methylamino)-2-methyl-1,6-naphthyridin-3-yl)phenyl)-2-methoxypyridine-3-sulfonamide (0.10 g, 0.16 mmol) in TFA (1.0 mL) was stirred at rt for 1 h. The reaction mixture was concentrated under reduced pressure and the crude was purified via flash column chromatography (0 to 100% EtOAc/hexanes) to obtain 5-chloro-N-(2,4-difluoro-5-(2-methyl-7-(methylamino)-1,6-naphthyridin-3-yl)phenyl)-2-methoxypyridine-3-sulfonamide (0.070g, 84% yield) as a yellow solid. ¹H NMR (500 MHz, DMSO-d₆): δ 10.5 (s, 1H), 8.88 (s, 1H), 8.53 (d, J = 2.6 Hz, 1H), 8.08 (d, J = 2.6 Hz, 1H), 7.99 (s, 1H), 7.47 (t, J = 9.8 Hz, 1H), 7.32 (t, J = 8.3 Hz, 1H), 6.89 (d, J = 5.7 Hz, 1H), 6.54 (s, 1H), 3.96 (s, 3H), 2.86 (d, J = 4.9 Hz, 3H), 2.32 (s, 3H); MS (ESI) m/z: 506.0 (M+H⁺).

General Method U: Conversion from SMe to Cl

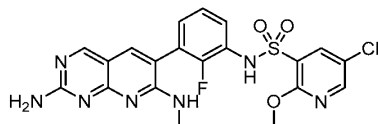
Example 109A: 5-chloro-N-(3-(2-chloro-7-(methylamino)pyrido[2,3-d]pyrimidin-6-yl)-2-fluorophenyl)-2-methoxypyridine-3-sulfonamide



[0331] A solution of 5-chloro-N-(2-fluoro-3-(7-(methylamino)-2-(methylthio)pyrido[2,3-d]pyrimidin-6-yl)phenyl)-2-methoxypyridine-3-sulfonamide (0.88 g, 1.7 mmol) in CH₃CN (8.5 mL) was cooled to 0 °C for 10 min. A solution of sulfonyl chloride (1.37 mL, 17 mmol) in DCM (8.5 mL) was then added dropwise and the reaction was allowed to warm to rt over 1h. The reaction mixture was quenched with sat'd NaHCO₃ (aq) and then poured into 10% AcOH (aq) (25 mL). The solution was extracted with DCM (3x). The combined organics were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to obtain 5-chloro-N-(3-(2-chloro-7-(methylamino)pyrido[2,3-d]pyrimidin-6-yl)-2-fluorophenyl)-2-methoxypyridine-3-sulfonamide (0.36 g, 41% yield) as an orange solid. MS (ESI) m/z: 509.0 (M+H⁺).

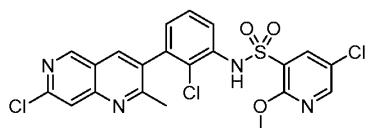
General Method V: Substitution

Example **109**: N-(3-(2-amino-7-(methylamino)pyrido[2,3-d]pyrimidin-6-yl)-2-fluorophenyl)-5-chloro-2-methoxypyridine-3-sulfonamide



- 5 **[0332]** A mixture of 5-chloro-N-(3-(2-chloro-7-(methylamino)pyrido[2,3-d]pyrimidin-6-yl)-2-fluorophenyl)-2-methoxypyridine-3-sulfonamide (**109A**, 0.25 g, 0.49 mmol) in NH_4OH (30%, 1.27 mL, 9.8 mmol) was sealed and heated to 100 °C for overnight. The reaction mixture was cooled to rt and dissolved into a small amount of DMSO and purified by reverse phase column chromatography (10 to 100% (0.4% FA)water/ CH_3CN). The residue was neutralized with sat'd NaHCO_3 (aq) and the
- 10 solution was extracted with DCM (3x). The combined organics were dried over anhydrous Na_2SO_4 , filtered and concentrated N-(3-(2-amino-7-(methylamino)pyrido[2,3-d]pyrimidin-6-yl)-2-fluorophenyl)-5-chloro-2-methoxypyridine-3-sulfonamide (0.14 g, 60% yield) as a pale yellow solid.
- ^1H NMR (500 MHz, DMSO-d_6): δ 10.3 (brs, 1H), 8.55 (s, 1H), 8.42 (d, $J = 2.6$ Hz, 1H), 8.02 (d, $J = 2.6$ Hz, 1H), 7.41 (s, 1H), 7.31 (td, $J = 1.8$ and 7.7 Hz, 1H), 7.16 (t, $J = 7.7$ Hz, 1H), 7.11 (m, 1H),
- 15 6.62 (s, 2H), 6.39 (q, $J = 4.5$ Hz, 1H), 3.84 (s, 3H), 2.71 (d $J = 4.5$ Hz, 3H); MS (ESI) m/z : 490.0 ($\text{M}+\text{H}^+$).

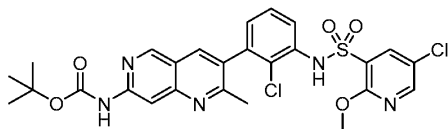
Preparation of Example **121A**: 5-chloro-N-(2-chloro-3-(7-chloro-2-methyl-1,6-naphthyridin-3-yl)phenyl)-2-methoxypyridine-3-sulfonamide



- 20 **[0333]** Using the General Method P, 5-chloro-N-(2-chloro-3-(7-chloro-2-methyl-1,6-naphthyridin-3-yl)phenyl)-2-methoxypyridine-3-sulfonamide (1.5 g, 96% yield) was prepared from 7-chloro-2-methyl-1,6-naphthyridin-3-yl trifluoromethanesulfonate (**B23**) and 5-chloro-N-(2-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-2-methoxypyridine-3-sulfonamide (**G21**). ^1H NMR
- 25 (500 MHz, DMSO-d_6): δ 9.24 (s, 1H), 8.31 (s, 1H), 8.20 (s, 1H), 8.01 (d, $J = 6.6$ Hz, 2H), 7.33 (d, $J = 8.3$ Hz, 1H), 7.05 (t, $J = 7.8$ Hz, 1H), 6.57 (d, $J = 7.3$ Hz, 1H), 3.82 (s, 3H), 2.46 (s, 3H).

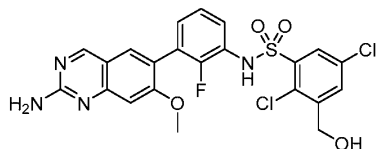
General Method W: Buchwald Reaction

Example **121B**: tert-butyl (3-(2-chloro-3-((5-chloro-2-methoxypyridine)-3-sulfonamido)phenyl)-2-methyl-1,6-naphthyridin-7-yl)carbamate



- 5 **[0334]** A mixture of 5-chloro-N-(2-chloro-3-(7-chloro-2-methyl-1,6-naphthyridin-3-yl)phenyl)-2-methoxypyridine-3-sulfonamide (**121A**, 0.50 g, 0.98 mmol), Cs₂CO₃ (0.96 g, 2.9 mmol) and tert-butyl carbamate (0.17 g, 1.5 mmol) in 1,4-dioxane (5mL) was degassed with Ar for 3 min. tBuBrettPhos Pd G3 (0.042 g, 0.05 mmol) was added and the mixture was degassed with Ar again for 2 min. The reaction mixture was stirred at 100 °C for 12 h. The reaction mixture was cooled to rt and diluted with EtOAc (20 mL). The mixture was filtered through a pad of celite and washed with EtOAc (10 mL). The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (0 to 50% MeOH/DCM) to obtain tert-butyl (3-(2-chloro-3-((5-chloro-2-methoxypyridine)-3-sulfonamido)phenyl)-2-methyl-1,6-naphthyridin-7-yl)carbamate (0.54 g, 93% yield) as a brown solid. MS (ESI) m/z: 590.2 (M+H⁺).

15

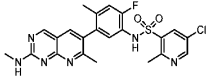
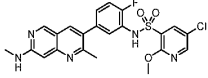
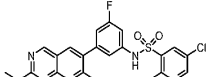
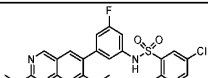
General Method X: Deprotection with K₂CO₃

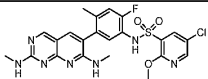
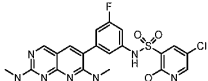
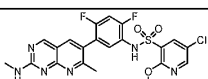
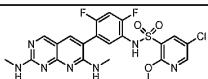
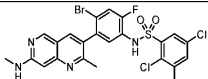
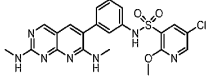
- 20 **[0335]** 3-(N-(3-(2-amino-7-methoxyquinazolin-6-yl)-2-fluorophenyl)sulfamoyl)-2,5-dichlorobenzyl acetate (0.16 g, 29% yield) was prepared by reacting 2,5-dichloro-3-(N-(2-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)sulfamoyl)benzyl acetate (**G24**, 0.65 g, 0.012mmol) and 6-bromo-7-methoxyquinazolin-2-amine (**B41**, 0.25 g, 0.098 mmol) by method P. ¹H NMR (400 MHz, DMSO-d₆) δ 10.68 (s, 1H), 8.92 (s, 1H), 7.88 (m, 2H), 7.56 (s, 1H), 7.17-7.28 (m, 3H), 6.86 (s, 1H), 6.80 (s, 2H), 5.20 (s, 2H), 3.75 (s, 3H), 2.06 (s, 3H); MS (ESI) m/z: 565.0 (M+H⁺).
- 25 **[0336]** A solution of 3-(N-(3-(2-amino-7-methoxyquinazolin-6-yl)-2-fluorophenyl)sulfamoyl)-2,5-dichlorobenzyl acetate (0.16 g, 0.028 mmol) in MeOH (5.0 mL) was treated with K₂CO₃ (0.16 g, 0.11 mmol). The reaction mixture was stirred at rt for 4 h and then concentrated under reduced pressure. the crude was acidified with citric acid (pH: 4~5) to get solid precipitate. Solids were filtered and then triturated in CH₃CN to afford a N-(3-(2-amino-7-methoxyquinazolin-6-yl)-2-fluorophenyl)-2,5-dichloro-3-(hydroxymethyl)benzenesulfonamide (0.075g, 57% yield) as an off-

white solid. ^1H NMR (400 MHz, DMSO- d_6) δ 10.6 (s, 1H), 8.92 (s, 1H), 7.8 (brs, 1H), 7.80 (d, J = 2.4 Hz, 1H), 7.78 (brs, 1H), 7.56 (s, 1H), 7.25-7.23 (m, 1H), 7.18 (brs, 1H), 6.85 (s, 1H), 6.79 (s, 2H), 5.73 (t, J = 5.6 Hz, 1H), 4.60 (d, J = 5.6 Hz, 2H), 3.75 (s, 3H); LCMS (ES) m/z 523.23 ($\text{M}^+ \text{H}^+$).

- 5 [0337] Using the General Methods P-X above, the following compounds (Examples) of Table I were prepared.

Table I.

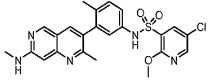
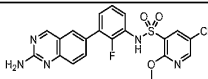
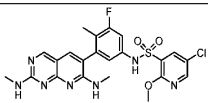
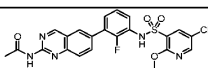
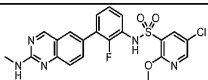
Ex. No	SM	Product	Method	Yield (%)	^1H NMR (400 or 500 MHz, DMSO- d_6): δ	MS (m/z : $\text{M}^+ \text{H}^+$)
6	B3 G8		P	33	9.00 (s, 1H), 7.77 (s, 1H), 7.64 (s, 1H), 7.58 (s, 1H), 7.52 (dd, J = 2.4 and 8.2 Hz, 1H), 7.37 (d, J = 8.2 Hz, 1H), 7.13 (d, J = 11.3 Hz, 1H), 6.88 (d, J = 8.0 Hz, 1H), 2.85 (d, J = 4.7 Hz, 3H), 2.50 (s, 3H), 2.11 (s, 3H), 1.89 (s, 3H).	486.2
7	E3 F1		Q & T	72	10.6 (s, 1H), 9.06 (s, 1H), 8.53 (d, J = 2.6 Hz, 1H), 8.34 (m, 1H), 8.11 (d, J = 2.6 Hz, 1H), 7.42 (d, J = 7.3 Hz, 1H), 7.37 (d, J = 7.6 Hz, 2H), 6.57 (s, 1H), 3.94 (s, 3H), 2.87 (s, 3H), 2.44 (s, 3H). NH missing	488.0
8	B3 G7		P	48	9.00 (s, 1H), 7.85 (s, 1H), 7.83 (d, J = 2.3 Hz, 1H), 7.68 (d, J = 5.8 Hz, 1H), 7.57 (m, J = 2.3 and 8.2 Hz, 1H), 7.39 (d, J = 8.2 Hz, 1H), 6.92 (d, J = 9.2 Hz, 1H), 6.82 (m, 2H), 2.85 (t, J = 4.8 Hz, 3H), 2.51 (s, 3H), 2.29 (s, 3H).	472.0
9	B15 G7		P	51	8.53 (s, 1H), 8.07 (s, 1H), 7.88 (d, J = 2.3 Hz, 1H), 7.60 (dd, J = 2.3 and 8.2 Hz, 1H), 7.40 (d, J = 8.2 Hz, 1H), 7.35 (s, 1H), 7.15 (s, 1H), 6.85 (m, 1H), 6.82-6.82 (m, 1H), 6.57 (s, 1H), 2.80 (d, J = 4.8 Hz,	487.2

					3H), 2.77 (d, J = 4.5 Hz, 3H), 2.51 (s, 3H).	
10	B15 G4		P	23	10.3 (s, 1H), 8.61 (s, 1H), 8.51 (d, J = 2.6 Hz, 1H), 8.06 (d, J = 2.6 Hz, 1H), 7.36 (s, 1H), 7.19 (d, J = 11.4 Hz, 1H), 6.96 (d, J = 8.1 Hz, 1H), 6.22 (s, 1H), 3.97 (m, 3H), 2.88 (m, 4H), 2.84 (d, J = 4.6 Hz, 3H), 2.02 (m, 3H).	518.2
11	B15 G9		P	52	10.9 (s, 1H), 8.61 (s, 1H), 8.53 (d, J = 2.6 Hz, 1H), 8.32 (d, J = 2.6 Hz, 1H), 7.45 (s, 1H), 7.22 (s, 1H), 6.96 (m, 3H), 6.60 (s, 1H), 3.98 (s, 3H), 2.88 (d, J = 4.8 Hz, 3H), 2.84 (d, J = 4.6 Hz, 3H).	504.2
12	B3 G5		P	25	10.5 (s, 1H), 9.11 (s, 1H), 8.51 (d, J = 2.5 Hz, 1H), 8.07 (d, J = 2.6 Hz, 1H), 8.02 (s, 1H), 7.79 (d, J = 5.6 Hz, 1H), 7.45 (t, J = 9.8 Hz, 1H), 7.32 (t, J = 8.3 Hz, 1H), 3.94 (s, 3H), 2.93 (d, J = 4.7 Hz, 3H), 2.34 (s, 3H).	507.0
13	B15 G5		P	40	8.60 (s, 1H), 8.23 (d, J = 2.5 Hz, 1H), 7.99 (d, J = 2.6 Hz, 1H), 7.40 (s, 1H), 7.11 (m, 1H), 7.02 (t, J = 10.3 Hz, 1H), 6.42 (s, 1H), 3.80 (m, 3H), 2.88 (d, J = 4.8 Hz, 3H), 2.84 (d, J = 4.6 Hz, 3H). NH missing	522.2
14	E8 F12		Q, S & T	90	11.0 (brs, 1H), 9.02 (s, 1H), 8.25 (s, 1H), 7.90 (m, 3H), 7.39 (d, J = 8.0 Hz, 1H), 6.58 (s, 1H), 4.61 (s, 2H), 2.90 (s, 3H), 2.29 (s, 3H). NH and OH missing	601.0
15	B15 G3		P	71	10.6 (brs, 1H), 8.62 (s, 1H), 8.47 (t, J = 2.6 Hz, 1H), 8.22 (d, J = 2.6 Hz, 1H), 7.41 (s, 1H), 7.33 (t,	486.2

					J = 7.8 Hz, 1H), 7.14 (m, 3H), 7.00 (m, 1H), 6.42 (m, 1H), 3.97 (m, 3H), 2.88 (d, J = 4.8 Hz, 3H), 2.86 (d, J = 4.6 Hz, 3H).	
16	B15 G13		P	39	10.4 (s, 1H), 8.61 (s, 1H), 8.47 (d, J = 2.6 Hz, 1H), 8.10 (d, J = 2.6 Hz, 1H), 7.48 (s, 1H), 7.36 (t, J = 7.7 Hz, 1H), 7.14-7.24 (m, 3H), 6.44 (s, 1H), 3.91 (s, 3H), 2.88 (d, J = 4.8 Hz, 3H), 2.82 (d, J = 4.5 Hz, 3H).	504.2
17	B3 G4		P	87	10.4 (s, 1H), 9.08 (s, 1H), 8.51 (d, J = 2.6 Hz, 1H), 8.04 (d, J = 2.6 Hz, 1H), 7.88 (s, 1H), 7.71 (s, 1H), 7.22 (d, J = 11.3 Hz, 1H), 7.04 (d, J = 8.0 Hz, 1H), 3.96 (m, 3H), 2.92 (d, J = 4.7 Hz, 3H), 2.51 (t, J = 2.2 Hz, 3H), 2.18 (s, 3H), 1.98 (s, 3H).	503.2
18	E8 F1		Q & T	63	10.6 (brs, 1H), 8.84 (s, 1H), 8.33 (m, 1H), 7.98 (s, 1H), 7.81 (s, 1H), 7.51 (brs, 1H), 7.22 (d, J = 8.6 Hz, 1H), 6.80 (d, J = 5.7 Hz, 1H), 6.52 (s, 1H), 3.84 (s, 3H), 2.83 (d, J = 4.9 Hz, 3H), 2.20 (s, 3H).	568.0
19	E3 F12		Q, S & T	69	10.8 (s, 1H), 8.86 (s, 1H), 7.90 (s, 1H), 7.82 (m, 2H), 7.32 (m, 2H), 7.24 (m, 1H), 6.82 (m, 1H), 6.53 (s, 1H), 5.75 (t, J = 6.1 Hz, 1H), 4.62 (d, J = 5.6 Hz, 2H), 2.85 (d, J = 4.9 Hz, 3H), 2.35 (s, 3H).	521.0
20	D13 F1		Q	22	10.5 (s, 1H), 9.09 (s, 1H), 8.51 (d, J = 1.8 Hz, 1H), 8.09 (d, J = 2.0 Hz, 1H), 7.96 (s, 1H), 7.71 (s, 1H), 7.32 (m, 3H), 3.93 (s, 3H), 2.92 (d, J = 3.4 Hz, 3H), 2.40 (s, 3H).	489.3

21	D14 F1		Q	20	10.0 (s, 1H), 9.08 (s, 1H), 8.52 (d, J = 2.4 Hz, 1H), 8.02 (d, J = 2.3 Hz, 1H), 7.91 (s, 1H), 7.77 (brs, 1H), 7.24 (d, J = 10.4 Hz, 1H), 6.97 (d, J = 7.3 Hz, 1H), 3.94 (s, 3H), 2.92 (d, J = 4.6 Hz, 3H), 2.28 (s, 3H), 2.19 (s, 3H).	503.2
22	E1 F1		Q, S & T	74	10.7 (s, 1H), 8.87 (s, 1H), 7.95 (s, 1H), 7.81 (t, J = 3.4 Hz, 2H), 7.48 (t, J = 9.8 Hz, 1H), 7.25 (t, J = 8.2 Hz, 1H), 6.89 (d, J = 5.6 Hz, 1H), 6.54 (s, 1H), 5.76 (t, J = 5.7 Hz, 1H), 4.62 (d, J = 5.5 Hz, 2H), 2.85 (d, J = 4.9 Hz, 3H), 2.29 (s, 3H).	539.0
23	E4 F1		Q & T	41	11.0 (s, 1H), 9.01 (s, 1H), 8.53 (d, J = 2.5 Hz, 1H), 8.34 (d, J = 2.6 Hz, 1H), 8.28 (brs, 1H), 7.05 (m, 3H), 6.56 (s, 1H), 3.98 (s, 3H), 2.89 (s, 3H), 2.44 (s, 3H). NH missing	488.0
24	B15 G11		P	44	10.5 (s, 1H), 8.59 (s, 1H), 8.49 (d, J = 2.6 Hz, 1H), 8.18 (d, J = 2.6 Hz, 1H), 7.30 (s, 1H), 7.20 (d, J = 8.4 Hz, 1H), 7.15 (brs, 1H), 7.09 (dd, J = 2.4 and 8.3 Hz, 1H), 6.88 (d, J = 2.3 Hz, 1H), 6.07 (d, J = 5.5 Hz, 1H), 3.97 (s, 3H), 2.88 (d, J = 4.8 Hz, 3H), 2.83 (d, J = 4.6 Hz, 3H), 1.96 (s, 3H).	500.0
25	E4 F12		Q, S & T	43	11.3 (s, 1H), 9.00 (m, 1H), 8.32 (m, 1H), 8.06 (d, J = 2.6 Hz, 1H), 7.83 (d, J = 2.5 Hz, 1H), 7.07 (m, 2H), 6.98 (d, J = 10.4 Hz, 1H), 6.55 (s, 1H), 4.60 (s, 2H), 2.90 (s, 3H), 2.43 (s, 3H). NH and OH missing	521.0

26	D15 F1		Q	20	9.10 (s, 1H), 8.51 (d, J = 2.4 Hz, 1H), 8.24 (d, J = 2.4 Hz, 1H), 7.85 (s, 1H), 7.7 (brs, 1H), 6.96 (d, J = 12.6 Hz, 1H), 6.76 (s, 1H), 3.96 (s, 3H), 2.91 (d, J = 4.4 Hz, 3H), 2.10 (s, 3H), 1.82 (s, 3H).	503.2
27	C3 H3		P	14	10.4 (brs, 1H), 9.02 (s, 1H), 8.42 (d, J = 2.6 Hz, 1H), 8.01 (s, 1H), 7.95 (d, J = 2.6 Hz, 1H), 7.78 (d, J = 5.7 Hz, 1H), 7.35 (m, 1H), 7.17 (t, J = 8.8 Hz, 1H), 3.86 (s, 3H), 2.85 (d, J = 4.7 Hz, 3H), 2.09 (s, 3H).	507.0
28	G11 		P	51	10.4 (s, 1H), 8.84 (s, 1H), 8.50 (d, J = 2.6 Hz, 1H), 8.19 (d, J = 2.6 Hz, 1H), 7.57 (m, 2H), 7.31 (dd, J = 1.8 and 8.6 Hz, 1H), 7.18 (d, J = 8.2 Hz, 1H), 7.00 (m, 2H), 6.65 (s, 1H), 6.00 (m, 2H), 3.98 (s, 3H), 2.15 (s, 3H).	451.0
29	G13 		P	40	10.4 (s, 1H), 8.86 (s, 1H), 8.50 (d, J = 2.6 Hz, 1H), 8.09 (d, J = 2.6 Hz, 1H), 7.86 (s, 1H), 7.59 (d, J = 8.7 Hz, 1H), 7.48 (d, J = 8.8 Hz, 1H), 7.41 (s, 1H), 7.26 (m, 2H), 6.63 (s, 1H), 6.08 (s, 2H), 3.92 (s, 3H).	459.0
30	B13 G11		P	23	10.5 (s, 1H), 9.19 (s, 1H), 8.71 (d, J = 2.6 Hz, 1H), 8.50 (d, J = 2.6 Hz, 1H), 8.21 (d, J = 2.6 Hz, 1H), 8.12 (d, J = 2.6 Hz, 1H), 7.85 (d, J = 5.6 Hz, 1H), 7.23 (d, J = 8.2 Hz, 1H), 7.06 (m, 2H), 3.97 (s, 3H), 2.94 (d, J = 4.7 Hz, 3H), 2.17 (s, 3H).	471.0
31	E5 F1		Q & T	61	10.5 (s, 1H), 8.99 (s, 1H), 8.52 (d, J = 2.6 Hz, 1H), 8.30 (d, J = 17.3 Hz, 1H),	488.0

					8.05 (d, J = 2.6 Hz, 1H), 7.42 (m, 1H), 7.32 (m, 2H), 6.54 (s, 1H), 3.95 (s, 3H), 2.88 (s, 3H), 2.23 (s, 3H). NH missing	
32	E10 F1		Q & T	74	10.6 (s, 1H), 9.02 (s, 1H), 8.49 (d, J = 2.6 Hz, 1H), 8.30 (m, 1H), 8.18 (d, J = 2.6 Hz, 1H), 7.26 (d, J = 8.3 Hz, 1H), 7.09 (m, 1H), 6.99 (d, J = 2.3 Hz, 1H), 6.56 (s, 1H), 3.98 (s, 3H), 2.90 (s, 3H), 2.20 (s, 3H), 1.96 (s, 3H). NH missing	484.0
33	G13 		P	45	10.4 (s, 1H), 9.17 (s, 1H), 8.50 (d, J = 2.6 Hz, 1H), 8.09 (d, J = 2.6 Hz, 1H), 7.87 (s, 1H), 7.70-7.73 (m, 1H), 7.49 (d, J = 8.8 Hz, 1H), 7.41 (t, J = 7.1 Hz, 1H), 7.23-7.32 (m, 2H), 7.00 (s, 2H), 3.91 (s, 3H).	460.0
34	B15 G10		P	64	10.7 (s, 1H), 8.53 (s, 1H), 8.45 (d, J = 2.6 Hz, 1H), 8.20 (d, J = 2.6 Hz, 1H), 7.28 (s, 1H), 7.14 (s, 1H), 6.89 (dd, J = 2.2 and 11.2 Hz, 1H), 6.67 (s, 1H), 6.21 (s, 1H), 3.90 (m, 3H), 2.80 (d, J = 4.7 Hz, 3H), 2.75 (d, J = 4.5 Hz, 3H), 1.78 (s, 3H).	518.2
35	B9 G13		P	24	10.8 (s, 1H), 10.5 (s, 1H), 9.55 (s, 1H), 8.51 (d, J = 2.6 Hz, 1H), 8.16 (s, 1H), 8.11 (d, J = 2.6 Hz, 1H), 7.98 (d, J = 8.9 Hz, 1H), 7.88 (d, J = 8.8 Hz, 1H), 7.48 (s, 1H), 7.27-7.36 (m, 2H), 3.91 (s, 3H), 2.29 (s, 3H).	502.0
36	B24 G13		P	31	10.4 (s, 1H), 9.12 (s, 1H), 8.51 (d, J = 2.6 Hz, 1H), 8.10 (d, J = 2.6 Hz, 1H), 7.86 (s, 1H), 7.73 (dd, J = 1.9 and 9.0 Hz, 1H), 7.53 (m, 2H), 7.42 (t, J = 7.3	474.0

					Hz, 1H), 7.23-7.31 (m, 2H), 3.89 (s, 3H), 2.91 (d, J = 4.7 Hz, 3H).	
37	B24 G9		P	75	10.9 (s, 1H), 9.14 (s, 1H), 8.50 (d, J = 2.6 Hz, 1H), 8.39 (d, J = 2.6 Hz, 1H), 7.99 (d, J = 2.2 Hz, 1H), 7.87 (dd, J = 2.2 and 8.8 Hz, 1H), 7.54 (m, 2H), 7.29 (m, 2H), 6.90 (m, 1H), 3.95 (s, 3H), 2.91 (d, J = 4.7 Hz, 3H).	474.0
38	B3 G12		P	44	10.6 (brs, 1H), 9.20 (s, 1H), 8.49 (d, J = 2.8 Hz, 1H), 8.19 (d, J = 2.8 Hz, 1H), 7.95 (s, 1H), 7.80 (brs, 1H), 7.27 (t, J = 8.8 Hz, 1H), 7.18 (m, 1H), 7.08 (m, 1H), 3.92 (s, 3H), 2.81 (s, 3H), 2.19 (s, 3H).	489.1
39	B15 G12		P	44	10.5 (s, 1H), 8.55 (s, 1H), 8.44 (d, J = 2.6 Hz, 1H), 8.13 (d, J = 2.6 Hz, 1H), 7.38 (s, 1H), 7.09-7.17 (m, 3H), 6.97 (dd, J = 2.6 and 6.4 Hz, 1H), 6.47 (d, J = 5.5 Hz, 1H), 3.91 (s, 3H), 2.80 (d, J = 4.7 Hz, 3H), 2.76 (d, J = 4.5 Hz, 3H).	504.0
42	B3 G2		P	5	10.5 (s, 1H), 9.00 (s, 1H), 8.86 (d, J = 2.3 Hz, 1H), 8.69 (d, J = 1.9 Hz, 1H), 8.09 (t, J = 2.1 Hz, 1H), 7.82 (s, 1H), 7.64 (d, J = 5.8 Hz, 1H), 7.17 (d, J = 11.2 Hz, 1H), 6.94 (d, J = 8.0 Hz, 1H), 2.85 (d, J = 4.7 Hz, 3H), 2.14 (s, 3H), 1.92 (s, 3H).	473.0
43	B24 G3		P	45	10.6 (brs, 1H), 9.10 (brs, 1H), 8.47 (d, J = 2.4 Hz, 1H), 8.28 (d, J = 2.4 Hz, 1H), 7.94 (s, 1H), 7.85 (dd, J = 2.0 and 8.8 Hz, 1H), 7.55 (d, J = 8.8 Hz,	456.2

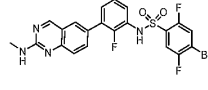
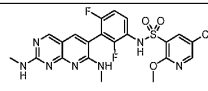
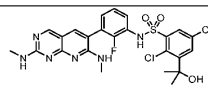
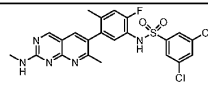
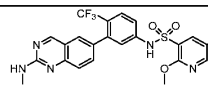
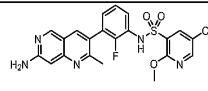
					1H), 7.43 (m, 3H), 7.35 (t, J = 7.6 Hz, 1H), 7.08 (d, J = 8.0 Hz, 1H), 3.97 (s, 3H), 2.91 (d, J = 4.4 Hz, 3H).	
44	C2 H4		P & T	37	10.6 (s, 1H), 8.87 (s, 1H), 8.51 (d, J = 2.6 Hz, 1H), 8.21 (d, J = 2.6 Hz, 1H), 7.93 (s, 1H), 7.27 (t, J = 9.1 Hz, 1H), 7.18 (m, 1H), 7.09 (m, 1H), 6.89 (m, 1H), 6.53 (s, 1H), 3.98 (s, 3H), 2.84 (m, 3H), 2.24 (s, 3H).	488.0
45	E5 F12		Q, S & T	54 42	10.7 (s, 1H), 8.85 (s, 1H), 7.96 (s, 1H), 7.79 (s, 1H), 7.70 (s, 1H), 7.28 (s, 1H), 7.12 (brs, 1H), 6.84 (d, J = 5.8 Hz, 1H), 6.52 (s, 1H), 5.71 (s, 1H), 4.58 (d, J = 5.6 Hz, 2H), 2.84 (d, J = 4.9 Hz, 3H), 2.22 (s, 3H). NH and OH missing	521.0
46	D17 F1		Q	6	10.4 (brs, 1H), 9.08 (s, 1H), 8.49 (s, 1H), 8.03 (d, J = 2.4 Hz, 1H), 8.01 (s, 1H), 7.80 (brs, 1H), 7.38 (s, 1H), 7.26 (s, 1H), 3.94 (s, 3H), 2.90 (s, 3H), 2.22 (s, 3H).	507.2
47	D33 F1		Q	8	10.6 (brs, 1H), 9.09 (s, 1H), 8.49 (s, 1H), 8.23 (s, 1H), 7.90 (s, 1H), 7.70 (brs, 1H), 7.36 (s, 1H), 7.13 (m, 3H), 3.97 (s, 3H), 2.91 (s, 3H), 2.33 (s, 3H).	471.1
48	D34 F1		Q	50	10.9 (brs, 1H), 9.09 (s, 1H), 8.52 (d, J = 2.8 Hz, 1H), 8.29 (d, J = 2.4 Hz, 1H), 8.00 (s, 1H), 7.8 (brs, 1H), 7.19 (m, 1H), 6.91 (m, 1H), 3.96 (s, 3H), 2.91 (s, 3H), 2.28 (s, 3H).	507.2
49	C5 H5		P	28	10.8 (s, 1H), 8.54 (s, 1H), 8.46 (d, J = 2.6 Hz, 1H), 8.21 (d, J = 2.6 Hz, 1H), 7.44 (s, 1H), 7.21 (s, 1H),	522.0

					7.10 (m, 1H), 6.76 (m, 1H), 6.58 (d, J = 5.4 Hz, 1H), 3.91 (s, 3H), 2.80 (d, J = 4.7 Hz, 3H), 2.75 (d, J = 4.5 Hz, 3H).	
50	B24 G16		P	47	10.5 (s, 1H), 9.13 (s, 1H), 8.33 (s, 1H), 7.87 (s, 1H), 7.77 (d, J = 2.6 Hz, 1H), 7.73 (d, J = 8.9 Hz, 1H), 7.53 (m, 3H), 7.23-7.35 (m, 3H), 3.18 (s, 3H), 3.17 (s, 3H).	473.0
51	D18 F1		Q	12	10.0 (brs, 1H), 9.07 (s, 1H), 8.51 (d, J = 2.4 Hz, 1H), 7.96 (d, J = 2.4 Hz, 1H), 7.86 (s, 1H), 7.7 (brs, 1H), 7.23 (t, J = 8.0 Hz, 1H), 7.08 (m, 2H), 3.97 (s, 3H), 2.91 (brs, 3H), 2.18 (s, 3H), 1.86 (s, 3H).	485.1
52	D16 F1		Q	42	9.90 (brs, 1H), 9.11 (s, 1H), 8.52 (d, J = 4.8 Hz, 1H), 8.03 (d, J = 2.0 Hz, 1H), 7.68 (s, 1H), 7.53 (m, 2H), 7.40 (brm, 1H), 7.19 (m, 2H), 7.99 (d, J = 7.6 Hz, 1H), 3.96 (s, 3H), 2.90 (s, 3H), 2.08 (s, 3H).	470.1
53	D19 F1		Q	23	10.4 (brs, 1H), 9.06 (s, 1H), 8.47 (d, J = 2.8 Hz, 1H), 8.14 (d, J = 2.4 Hz, 1H), 7.82 (s, 1H), 7.7 (brs, 1H), 7.21 (d, J = 8.4 Hz, 1H), 7.06 (d, J = 8.0 Hz, 1H), 6.87 (s, 1H), 3.96 (s, 3H), 2.91 (s, 3H), 2.8 (s, 3H), 1.90 (s, 3H).	485.2
54	D20 F1		Q	41	10.6 (brs, 1H), 9.16 (s, 1H), 8.49 (d, J = 2.8 Hz, 1H), 8.22 (d, J = 2.4 Hz, 1H), 7.84 (s, 1H), 7.21 (d, J = 8.8 Hz, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.50 (brs, 1H), 7.26 (m, 2H), 7.10 (m, 1H), 3.97 (s, 3H), 2.91 (s, 3H).	474.2

55	D22 F1		Q	41	10.8 (brs, 1H), 9.2 (brs, 1H), 8.51 (d, J = 2.40 Hz, 1H), 8.32 (d, J = 2.40 Hz, 1H), 7.87 (s, 1H), 7.72 (d, J = 8.8 Hz, 1H), 7.57 (m, 2H), 7.12 (m, 2H), 3.96 (s, 3H), 2.90 (s, 3H).	492.1
56	B26 G13		P	58	10.5 (s, 1H), 8.98 (s, 1H), 8.80 (t, J = 2.1 Hz, 1H), 8.51 (m, 1H), 8.30 (s, 1H), 8.10 (d, J = 2.6 Hz, 1H), 7.51 (m, 1H), 7.3 (m, 2H), 7.01 (m, 1H), 6.60 (s, 1H), 3.92 (s, 3H), 2.86 (d, J = 4.9 Hz, 3H).	474.0
57	B15 G19		P & S	4	8.53 (s, 1H), 7.96 (d, J = 2.6 Hz, 1H), 7.72 (s, 1H), 7.35 (s, 1H), 7.15 (s, 1H), 6.81 (s, 3H), 6.53 (d, J = 5.6 Hz, 1H), 5.66 (m, 1H), 4.52 (d, J = 5.6 Hz, 2H), 2.80 (d, J = 4.8 Hz, 3H), 2.76 (d, J = 4.5 Hz, 3H). Nh missing	537.2
58	B26 G9		P	19	11.0 (s, 1H), 8.99 (m, 2H), 8.50 (d, J = 2.6 Hz, 1H), 8.41 (d, J = 2.6 Hz, 1H), 8.38 (d, J = 2.4 Hz, 1H), 7.39 (m, 1H), 7.02 (m, 1H), 6.94 (m, 1H), 6.60 (s, 1H), 3.98 (s, 3H), 2.87 (d, J = 4.9 Hz, 3H). NH missing	474.0
59	B21 G3		P	10	10.1 (s, 1H), 9.28 (s, 1H), 9.04 (s, 1H), 8.37 (d, J = 2.5 Hz, 2H), 8.19 (m, 2H), 7.58 (s, 1H), 7.29-7.39 (m, 4H), 7.04 (d, J = 8.0 Hz, 1H), 3.89 (m, 3H), 3.81 (s, 3H).	523.1
60	B26 G12		P	20	10.6 (s, 1H), 9.01 (s, 1H), 8.81 (t, J = 2.1 Hz, 1H), 8.50 (d, J = 2.6 Hz, 1H), 8.28 (s, 1H), 8.25 (d, J = 2.6 Hz, 1H), 7.28-7.36 (m, 2H), 7.14 (m, 1H), 7.03 (m, 1H), 6.61 (s, 1H), 3.98	474.0

					(s, 3H), 2.87 (d, J = 4.9 Hz, 3H).	
61	B16 G13		P	24	10.3 (s, 1H), 8.56 (s, 1H), 8.42 (d, J = 2.6 Hz, 1H), 8.03 (d, J = 2.6 Hz, 1H), 7.49 (s, 1H), 7.27 (m, 1H), 7.13 (m, 3H), 6.41 (brs, 2H), 3.84 (s, 3H), 2.78 (d, J = 4.7 Hz, 3H).	490.0
62	D23 F1		Q	41	10.3 (brs, 1H), 9.10 (brs, 1H), 8.49 (d, J = 2.4 Hz, 1H), 8.06 (d, J = 2.4 Hz, 1H), 7.76 (d, J = 1.6 Hz, 1H), 7.62 (dd, J = 2.0 and 8.8 Hz, 1H), 7.51 (m, 1H), 7.36 (m, 4H), 3.85 (s, 3H), 2.90 (d, J = 4.4 Hz, 3H).	490.1
63	B16 G9		P	29	10.8 (s, 1H), 8.56 (s, 1H), 8.43 (d, J = 2.6 Hz, 1H), 8.24 (d, J = 2.6 Hz, 1H), 7.47 (s, 1H), 7.18 (s, 1H), 6.93 (s, 1H), 6.86 (m, 2H), 6.53 (brs, 2H), 3.89 (s, 3H), 2.78 (d, J = 4.7 Hz, 3H).	490.0
64	B16 G3		P	31	10.6 (brs, 1H), 8.57 (s, 1H), 8.40 (d, J = 2.6 Hz, 1H), 8.16 (d, J = 2.6 Hz, 1H), 7.43 (s, 1H), 7.27 (t, J = 7.9 Hz, 1H), 7.11 (m, 2H), 7.05 (t, J = 7.1 Hz, 2H), 6.41 (brs, 2H), 3.88 (s, 3H), 2.78 (d, J = 4.7 Hz, 3H).	472.0
65	B3 G9		P	21	10.9 (brs, 1H), 9.10 (m, 1H), 8.51 (d, J = 2.4 Hz, 1H), 8.32 (d, J = 2.4 Hz, 1H), 7.94 (s, 1H), 7.7 (brs, 1H), 7.02 (d, J = 9.2 Hz, 1H), 6.95 (m, 2H), 3.96 (s, 3H), 2.90 (d, J = 4.4 Hz, 3H), 2.35 (s, 3H).	490.0
66	B32 G13		P	46	10.4 (s, 1H), 8.95 (s, 1H), 8.52 (d, J = 2.6 Hz, 1H), 8.08 (d, J = 2.6 Hz, 1H), 8.00 (s, 1H), 7.69 (s, 1H), 7.35 (t, J = 7.5 Hz, 1H),	505.0

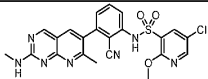
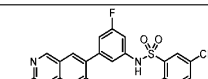
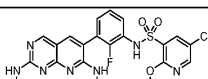
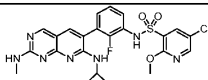
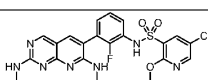
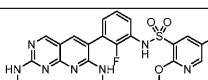
					7.24 (m, 2H), 3.91 (s, 3H), 3.87 (s, 3H), 2.91 (d, J = 4.7 Hz, 3 H).	
67	D26 F1		Q	25	10.4 (brs, 1H), 9.08 (s, 1H), 8.49 (d, J = 2.0 Hz, 1H), 7.97 (d, J = 2.4 Hz, 1H), 7.92 (s, 1H), 7.70 (brs, 1H), 7.44 (m, 2H), 7.29 (s, 1H), 3.90 (s, 3H), 2.91 (d, J = 4.0 Hz, 3H), 2.15 (s, 3H).	505.1
68	D25 F1		Q	5	10.8 (brs, 1H), 9.08 (s, 1H), 8.51 (d, J = 2.4 Hz, 1H), 8.22 (d, J = 2.4 Hz, 1H), 7.89 (s, 1H), 7.6 (brs, 1H), 7.50 (d, J = 8.8 Hz, 1H), 7.19 (dd, J = 2.4 and 8.8 Hz, 1H), 7.09 (d, J = 2.4 Hz, 1H), 3.95 (s, 3H), 2.92 (d, J = 3.6 Hz, 3H), 2.16 (s, 3H).	505.2
69	D27 F1		Q	47	10.8 (brs, 1H), 9.13 (s, 1H), 8.51 (d, J = 2.4 Hz, 1H), 8.26 (d, J = 2.4 Hz, 1H), 7.70 (d, J = 1.2 Hz, 1H), 7.62 (dd, J = 2.0 and 10.8 Hz, 1H), 7.5 (brs, 1H), 7.46 (d, J = 8.4 Hz, 2H), 7.18 (d, J = 2.4 Hz, 1H), 7.13 (dd, J = 2.8 and 8.8 Hz, 1H), 3.95 (s, 3H), 2.91 (d, J = 4.4 Hz, 3H).	490.1
70	D28 		Q	45	10.2 (brs, 1H), 9.11 (s, 1H), 7.84 (s, 1H), 7.75 (d, J = 2.0 Hz, 1H), 7.69 (m, 2H), 7.53 (d, J = 8.0 Hz, 1H), 7.5 (brs, 1H), 7.40 (m, 1H), 7.32 (d, J = 8.4 Hz, 1H), 7.25 (m, 2H), 3.90 (s, 3H), 2.91 (d, J = 4.8 Hz, 3H).	473.1
71	D28 		Q	25	10.6 (brs, 1H), 9.10 (s, 1H), 8.15 (d, J = 8.4 Hz, 1H), 8.03 (s, 1H), 7.90 (d, J = 8.4 Hz, 1H), 7.79 (s, 1H), 7.65 (d, J = 8.8 Hz, 1H), 7.47 (m, 3H), 7.26	555.1 557.1

					(m, 2H), 2.91 (d, J = 4.4 Hz, 3H).	
72	D28 		Q	26	10.8 (brs, 1H), 9.13 (s, 1H), 8.10 (m, 1H), 7.85 (s, 1H), 7.70 (m, 2H), 7.50 (brm, 1H), 7.45 (m, 2H), 7.25 (m, 2H), 2.91 (d, J = 4.4 Hz, 3H).	523.1 525.1
73	C5 H3		P	6	10.3 (s, 1H), 8.53 (s, 1H), 8.31 (s, 1H), 7.97 (d, J = 2.6 Hz, 1H), 7.47 (s, 1H), 7.27 (s, 1H), 7.17 (brs, 1H), 6.99 (brs, 1H), 6.52 (brs, 1H), 3.81 (m, 3H), 2.80 (s, 3H), 2.75 (s, 3H).	522.2
74	C5 H8		P	17	10.6 (s, 1H), 8.51 (s, 1H), 8.01 (d, J = 2.7 Hz, 1H), 7.81 (d, J = 2.7 Hz, 1H), 7.36 (s, 1H), 7.25 (t, J = 7.6 Hz, 1H), 7.12 (m, 3H), 6.39 (m, 1H), 5.60 (s, 1H), 2.80 (d, J = 4.8 Hz, 3H), 2.75 (d, J = 4.5 Hz, 3H), 1.52 (s, 6H).	565.2
75	B3 G6		P	36	9.00 (s, 1H), 7.93 (s, 1H), 7.81 (s, 1H), 7.64 (s, 1H), 7.59 (s, 2H), 7.19 (d, J = 11.3 Hz, 1H), 6.89 (d, J = 7.9 Hz, 1H), 2.85 (d, J = 4.7 Hz, 3H), 2.14 (s, 3H), 1.92 (s, 3H). NH missing	506.0
76	D24 F1		Q	17	11.2 (brs, 1H), 9.11 (s, 1H), 8.52 (d, J = 2.4 Hz, 1H), 8.31 (d, J = 2.4 Hz, 1H), 7.72 (d, J = 8.8 Hz, 1H), 7.62 (s, 1H), 7.50 (m, 3H), 7.30 (d, J = 8.8 Hz, 1H), 7.10 (s, 1H), 3.92 (s, 3H), 2.91 (d, J = 4.4 Hz, 3H).	524.2
77	B28 G13		P & T	18	10.4 (brs, 1H), 8.74 (s, 1H), 8.43 (d, J = 2.6 Hz, 1H), 7.95 (d, J = 2.6 Hz, 1H), 7.87 (s, 1H), 7.31 (m, 1H), 7.19 (m, 2H), 6.57 (s, 1H), 6.27 (s, 2H), 3.87 (s, 3H), 2.03 (s, 3H).	474.0

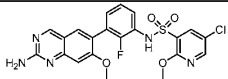
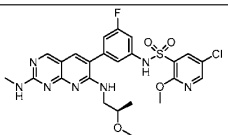
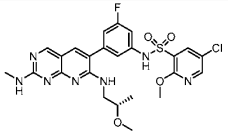
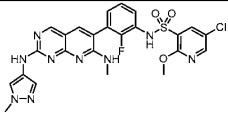
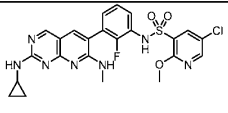
78	B29 G16		P	22	10.5 (s, 1H), 8.85 (s, 1H), 8.33 (d, J = 2.5 Hz, 1H), 7.96 (s, 1H), 7.68 (d, J = 2.6 Hz, 1H), 7.41 (td, J = 2.1 and 7.6 Hz, 1H), 7.28 (m, 2H), 6.87 (d, J = 5.6 Hz, 1H), 6.72 (q, J = 4.7 Hz, 1H), 6.53 (s, 1H), 2.90 (d, J = 4.6 Hz, 3H), 2.85 (d, J = 4.9 Hz, 3H), 2.14 (s, 3H).	487.0
79	D21 F1		Q	3	10.3 (brs, 1H), 9.12 (s, 1H), 8.49 (s, 1H), 8.06 (d, J = 2.4 Hz, 1H), 7.66 (s, 1H), 7.6 (brs, 1H), 7.50 (m, 2H), 7.40 (s, 1H), 7.26 (d, J = 8.0 Hz, 2H), 3.87 (s, 3H), 2.91 (d, J = 4.8 Hz, 3H).	524.2
80	D29 F1		Q	12	11.2 (brs, 1H), 9.08 (s, 1H), 8.50 (d, J = 2.8 Hz, 1H), 8.28 (d, J = 2.4 Hz, 1H), 7.91 (s, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.6 (brs, 1H), 7.33 (d, J = 8.4 Hz, 1H), 7.07 (s, 1H), 3.93 (s, 3H), 2.92 (d, J = 3.6 Hz, 3H), 2.07 (s, 3H).	539.2
81	D30 F1		Q	24	10.2 (brs, 1H), 9.11 (s, 1H), 8.48 (d, J = 2.8 Hz, 1H), 8.13 (d, J = 2.4 Hz, 1H), 7.71 (d, J = 2.0 Hz, 1H), 7.67 (dd, J = 2.0 and 8.4 Hz, 1H), 7.48 (d, J = 8.8 Hz, 1H), 7.4 (brs, 1H), 7.08 (d, J = 2.0 Hz, 1H), 7.03 (m, 2H), 4.00 (s, 3H), 3.71 (s, 3H), 2.91 (d, J = 4.4 Hz, 3H).	486.2
82	D2 F1		Q	9	10.3 (brs, 1H), 9.07 (s, 1H), 8.49 (d, J = 2.4 Hz, 1H), 8.09 (d, J = 2.4 Hz, 1H), 7.74 (s, 1H), 7.7 (brs, 1H), 7.12 (dd, J = 2.4 and 8.8 Hz, 1H), 7.02 (d, J = 9.2 Hz, 1H), 6.89 (d, J = 2.4 Hz, 1H), 3.98 (s, 3H).	501.2

					3.65 (s, 3H), 2.91 (d, J = 4.0 Hz, 3H), 2.17 (s, 3H).	
83	D28 F3		Q	10	11.9 (brs, 1H), 10.67 (s, 1H), 7.88 (s, 1H), 7.72 (d, J = 8.8 Hz, 1H), 7.55 (m, 2H), 7.47 (d, J = 2.4 Hz, 2H), 7.4 (brs, 1H), 7.23 (m, 2H), 3.94 (s, 3H), 2.90 (d, J = 4.8 Hz, 3H).	507.2
84	E11 F1		Q	92	10.8 (s, 1H), 10.5 (s, 1H), 9.15 (s, 1H), 8.52 (m, 2H), 8.25 (s, 1H), 8.04 (d, J = 2.6 Hz, 1H), 7.44 (m, 1H), 7.31 (m, 2H), 3.95 (s, 3H), 2.23 (s, 3H), 2.18 (s, 3H).	516.0
85	B33 G13		P & T	10	10.4 (brs, 1H), 8.87 (s, 1H), 8.71 (s, 1H), 8.42 (t, J = 2.3 Hz, 1H), 8.21 (s, 1H), 8.02 (d, J = 2.6 Hz, 1H), 7.38 (s, 1H), 7.24 (m, 1H), 7.19 (s, 1H), 6.66 (s, 1H), 6.39 (s, 2H), 3.84 (s, 3H).	460.0
86	B34 G9		P	33	11.0 (brs, 1H), 9.26 (s, 1H), 9.08 (d, J = 2.7 Hz, 1H), 8.49 (d, J = 2.6 Hz, 1H), 8.39 (d, J = 2.6 Hz, 2H), 7.41 (s, 2H), 7.36 (d, J = 10.0 Hz, 1H), 7.30 (s, 1H), 6.95 (d, J = 10.3 Hz, 1H), 3.97 (s, 3H).	461.0
87	B6 G9		P	57	10.9 (brs, 1H), 10.0 (s, 1H), 9.14 (s, 1H), 8.44 (d, J = 2.6 Hz, 1H), 8.26 (d, J = 2.6 Hz, 1H), 8.15 (s, 1H), 7.95 (s, 1H), 7.55 (s, 1H), 6.89-6.97 (m, 3H), 3.89 (m, 3H), 3.81 (s, 3H), 2.34 (s, 3H).	555.2
88	B6 G13		P	61	10.4 (s, 1H), 10.0 (s, 1H), 9.14 (s, 1H), 8.44 (d, J = 2.6 Hz, 1H), 8.15 (s, 1H), 8.01 (s, 1H), 7.96 (d, J = 2.6 Hz, 1H), 7.55 (s, 1H), 7.33 (m, 1H), 7.22 (m, 2H), 3.88 (m, 3H), 3.81 (s, 3H), 2.13 (s, 3H).	555.2

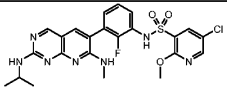
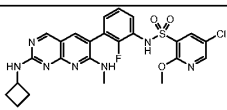
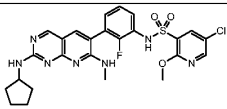
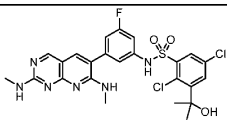
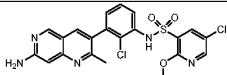
89	B5 G15		P & R	26	9.90 (s, 1H), 9.07 (s, 1H), 8.51 (d, J = 2.6 Hz, 1H), 7.98 (m, 2H), 7.71 (s, 1H), 7.38 (dd, J = 1.7 and 8.0 Hz, 1H), 7.20 (t, J = 7.8 Hz, 1H), 7.13 (d, J = 7.6 Hz, 1H), 4.00 (s, 3H), 3.09 (s, 3H), 2.91 (d, J = 4.7 Hz, 3H), 2.07 (s, 3H).	501.0
90	B36 G16		P	61	10.5 (s, 1H), 9.08 (s, 1H), 8.33 (d, J = 2.5 Hz, 1H), 7.98 (s, 1H), 7.77 (m, 1H), 7.69 (d, J = 2.5 Hz, 1H), 7.42 (m, 1H), 7.30 (t, J = 7.8 Hz, 1H), 7.25 (t, J = 6.9 Hz, 1H), 6.73 (d, J = 5.4 Hz, 1H), 2.92 (d, J = 4.5 Hz, 3H), 2.90 (d, J = 4.6 Hz, 3H), 2.16 (s, 3H).	488.2
91	D28 	Q	78	10.1 (brs, 1H), 9.11 (s, 1H), 7.84 (s, 1H), 7.69 (d, J = 8.8 Hz, 1H), 7.59 (dd, J = 2.4 and 8.4 Hz, 1H), 7.53 (m, 2H), 7.5 (brs, 1H), 7.35 (m, 1H), 7.23 (m, 2H), 7.08 (d, J = 8.8 Hz, 1H), 3.84 (s, 3H), 2.90 (d, J = 4.8 Hz, 3H), 2.15 (s, 3H).	453.1	
92	B37 G9		P	7	10.9 (brs, 1H), 8.63 (s, 1H), 8.46 (brs, 1H), 8.27 (brs, 1H), 7.52 (s, 1H), 6.94 (brs, 1H), 6.89 (m, 2H), 6.7 (s, 2H), 6.5 (brs, 2H), 3.94 (s, 3H).	476.1
93	B39 G9		P	6	10.8 (s, 1H), 8.97 (s, 1H), 8.50 (s, 1H), 8.30 (s, 1H), 8.04 (s, 1H), 7.15 (m, 3H), 7.08 (d, J = 8.8 Hz, 1H), 6.91 (d, J = 10.0 Hz, 1H), 3.97 (s, 3H), 3.94 (s, 3H).	491.0
94	D31 F1		Q	7	10.9 (brs, 1H), 8.60 (brs, 1H), 8.49 (d, J = 2.0 Hz, 1H), 8.26 (d, J = 2.0 Hz, 1H), 7.45 (s, 1H), 7.2 (brs, 1H), 7.15 (s, 1H), 7.05 (m, 2H), 6.57 (d, J = 4.0 Hz, 1H), 3.96 (s, 3H), 2.87 (d,	520.1

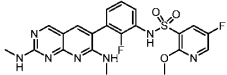
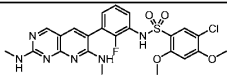
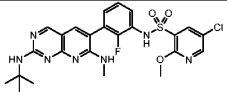
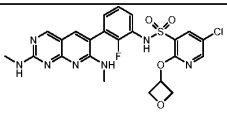
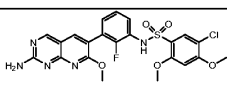
					J = 4.4 Hz, 3H), 2.82 (d, J = 4.8 Hz, 3H)	
95	D9 F1		Q & R	27	9.11 (s, 1H), 8.28 (s, 1H), 8.05 (d, J = 2.6 Hz, 1H), 8.01 (s, 1H), 7.74 (s, 1H), 7.33 (s, 2H), 6.67 (brs, 1H), 3.83 (s, 3H), 2.93 (d, J = 4.7 Hz, 3H), 2.39 (s, 3H).	496.1
96	B38 G9		P	12	10.9 (brs, 1H), 8.61 (s, 1H), 8.51 (d, J = 2.8 Hz, 1H), 8.30 (d, J = 2.4 Hz, 1H), 7.44 (s, 1H), 6.93 (m, 3H), 6.70 (brs, 2H), 6.60 (brs, 1H), 3.97 (s, 3H), 2.82 (d, J = 4.0 Hz, 3H).	490.0
97	B17 G13		P	46	10.3 (s, 1H), 8.55 (s, 1H), 8.42 (d, J = 2.6 Hz, 1H), 8.04 (d, J = 2.6 Hz, 1H), 7.44 (s, 1H), 7.30 (t, J = 7.7 Hz, 1H), 7.13-7.19 (m, 3H), 6.22 (s, 1H), 4.74 (s, 1H), 3.84-3.84 (m, 3H), 3.37-3.40 (m, 4H), 2.80 (d, J = 4.7 Hz, 3H).	534.2
98	B18 G13		P	23	10.01 (brs, 1H), 8.49 (brs, 1H), 8.37 (d, J = 2.5 Hz, 1H), 8.00 (d, J = 2.5 Hz, 1H), 7.59 (brs, 1H), 7.26 (t, J = 7.2 Hz, 2H), 7.13 (t, J = 7.9 Hz, 1H), 4.74 (brm, 1H), 4.25 (s, 2H), 3.85 (m, 3H), 3.50 (d, J = 10.1 Hz, 1H), 3.42 (s, 1H), 2.86 (d, J = 4.8 Hz, 3H)- two NHs missing: high temp NMR (at 70 °C).	546.2
99	B19 G13		P	26	Complicated NMR due to atropisomers	560.2
100	B35 G13		P	27	10.3 (s, 1H), 8.56 (d, J = 7.6 Hz, 1H), 8.42 (d, J = 2.6 Hz, 1H), 8.03 (d, J = 2.6 Hz, 1H), 7.45 (s, 1H), 7.30 (t, J = 7.7 Hz, 1H), 7.18 (t, J = 7.8 Hz, 2H),	548.2

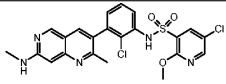
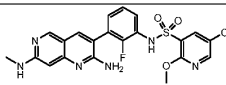
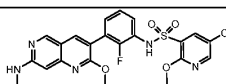
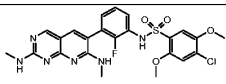
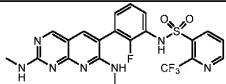
					7.12 (t, J = 7.1 Hz, 1H), 6.21 (brs, 1H), 3.84 (s, 3H), 3.46 (s, 2H), 3.35 (t, J = 6.2 Hz, 2H), 3.16 (s, 3H), 2.80 (d, J = 4.7 Hz, 3H).	
101	B20 G13		P	36	8.64 (brs, 1H), 8.25 (d, J = 2.6 Hz, 1H), 8.05 (d, J = 2.6 Hz, 1H), 7.58 (s, 1H), 7.27 (brs, 1H), 7.19 (t, J = 8.2 Hz, 1H), 6.92 (t, J = 8.2 Hz, 1H), 6.64 (brm, 1H), 6.59 (brs, 1H), 3.85 (s, 3H), 3.69 (brm, 2H), 3.06 (brm, 2H), 2.86 (d, J = 4.7 Hz, 3H), 2.57 (s, 3H). two NHs missing	547.2
102	D36 F12		Q	18	10.8 (brs, 1H), 8.53 (s, 1H), 8.03 (t, J = 6.0 Hz, 2H), 7.41 (s, 1H), 7.27 (t, J = 7.6 Hz, 1H), 7.15 (m, 3H), 6.44 (s, 1H), 3.81 (s, 3H), 2.80 (d, J = 4.7 Hz, 3H), 2.75 (d, J = 4.5 Hz, 3H).	565.0
103	B32 G9		P	20	10.8 (brs, 1H), 9.05 (s, 1H), 8.51 (d, J = 2.8 Hz, 1H), 8.31 (d, J = 2.4 Hz, 1H), 8.05 (s, 1H), 7.7 (brs, 1H), 7.19 (s, 1H), 7.10 (d, J = 9.2 Hz, 1H), 6.92 (m, 1H), 3.97 (s, 3H), 3.96 (s, 3H), 2.91 (d, J = 4.4 Hz, 3H).	504.9
104	D37 F1		Q	31	10.9 (s, 1H), 8.61 (s, 1H), 8.52 (s, 1H), 8.29 (s, 1H), 7.45 (s, 1H), 7.16 (s, 1H), 7.12 (s, 1H), 7.06 (s, 1H), 6.7 (s, 2H), 6.6 (m, 1H), 3.97 (s, 3H), 2.81 (d, J = 3.6 Hz, 3H).	505.8
105	D38 F1		Q	32	10.9 (brs, 1H), 8.62 (s, 1H), 8.52 (d, J = 2.4 Hz, 1H), 8.32 (d, J = 2.4 Hz, 1H), 7.48 (s, 1H), 7.3 (brs, 1H), 6.95 (m, 3H), 6.5 (brs, 1H), 3.96 (s, 3H), 3.54 (m, 2H), 3.45 (m,	548.0

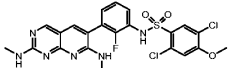
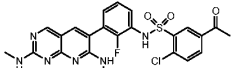
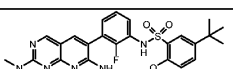
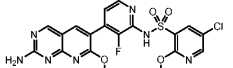
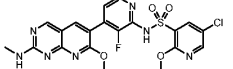
					2H), 3.24 (s, 3H), 2.85 (brs, 3H).	
106	B41 G13		P	16	10.3 (brs, 1H), 8.92 (s, 1H), 8.50 (d, J = 2.4 Hz, 1H), 8.06 (d, J = 2.8 Hz, 1H), 7.56 (s, 1H), 7.32 (m, 1H), 7.19 (m, 2H), 6.85 (s, 1H), 6.79 (brs, 2H), 3.90 (s, 3H), 3.74 (s, 3H).	489.9
107	D39 F1		Q	28	11.0 (brs, 1H), 8.62 (s, 1H), 8.51 (d, J = 2.0 Hz, 1H), 8.33 (d, J = 2.4 Hz, 1H), 7.49 (s, 1H), 7.24 (brs, 1H), 6.94-6.02 (m, 3H), 6.27 (brs, 1H), 3.96 (s, 3H), 3.55 (m, 1H), 3.46 (m, 1H), 3.36 (m, 1H), 3.22 (s, 3H), 2.86 (d, J = 4.0 Hz, 3H), 1.07 (d, J = 6.0 Hz, 3H).	561.9
108	D40 F1		Q	46	11.0 (brs, 1H), 8.63 (s, 1H), 8.51 (d, J = 2.4 Hz, 1H), 8.32 (d, J = 2.4 Hz, 1H), 7.49 (s, 1H), 7.24 (br s, 1H), 6.97 (m, 3H), 6.26 (brs, 1H), 3.96 (s, 3H), 3.56 (m, 1H), 3.47 (m, 1H), 3.38 (m, 1H), 3.22 (s, 3H), 2.87 (d, J = 4.0 Hz, 3H), 1.07 (d, J = 6.0 Hz, 3H).	562.1
110	109A 		V	53	10.3 (s, 1H), 9.45 (s, 1H), 8.66 (s, 1H), 8.42 (d, J = 2.6 Hz, 1H), 8.03 (d, J = 2.6 Hz, 1H), 7.97 (br s, 1H), 7.49 (brs, 1H), 7.48 (s, 1H), 7.32 (td, J = 1.9 and 7.7 Hz, 1H), 7.19 (t, J = 7.7 Hz, 1H), 7.14 (m, 1H), 6.51 (brm, 1H), 3.84 (s, 3H), 3.77 (s, 3H), 2.79 (d, J = 4.5 Hz, 3H)	570.2
111	109A 		V	24	10.4 (s, 1H), 8.62 (s, 1H), 8.44 (s, 1H), 8.08 (s, 1H), 7.49 (m, 2H), 7.41 (s, 1H), 7.34 (s, 1H), 7.24 (s, 1H), 6.43 (s, 1H), 3.89 (s, 3H),	530.2

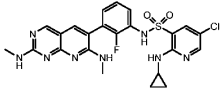
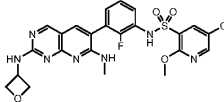
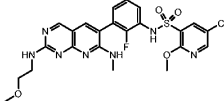
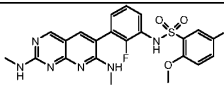
					2.83 (m, 4H), 0.71 (m, 2H), 0.50 (m, 2H).	
112	B15 G20		P & T	36	10.8 (s, 1H), 8.62 (s, 1H), 8.11 (s, 1H), 8.00 (d, J = 2.6 Hz, 1H), 7.85 (brm, 2H), 7.53 (s, 1H), 7.30 (brm, 1H), 7.21 (brm, 3H), 6.49 (brm, 1H), 2.88 (d, J = 4.8 Hz, 3H), 2.85 (d, J = 4.5 Hz, 3H).	550.0
113	B51 G21		P & T	47	10.2 (brs, 1H), 8.49 (d, J = 2.6 Hz, 1H), 8.41 (s, 1H), 8.07 (d, J = 2.6 Hz, 1H), 7.43 (m, 3H), 7.23 (dd, J = 1.9 and 7.2 Hz, 1H), 6.42 (m, 1H), 6.22 (s, 1H), 5.98 (brm, 1H), 3.89 (s, 3H), 2.80 (d, J = 4.7 Hz, 6H).	519.0
114	B51 G13		P & T	60	10.4 (s, 1H), 8.48 (d, J = 2.5 Hz, 1H), 8.40 (s, 1H), 8.09 (d, J = 2.6 Hz, 1H), 7.47 (s, 1H), 7.36 (dt, J = 1.9 and 7.6 Hz, 1H), 7.24 (t, J = 7.8 Hz, 1H), 7.19 (m, 1H), 6.42 (m, 1H), 6.20 (s, 1H), 6.12 (m, 1H), 3.91 (s, 3H), 2.79 (d, J = 4.8 Hz, 6H).	503.2
115	109A EtNH2		V	38	10.3 (s, 1H), 8.55 (s, 1H), 8.42 (d, J = 2.6 Hz, 1H), 8.03 (d, J = 2.6 Hz, 1H), 7.42 (s, 1H), 7.31 (dt, J = 1.9 and 7.7 Hz, 1H), 7.28 (s, 1H), 7.18 (t, J = 7.9 Hz, 1H), 7.12 (m, 1H), 6.46 (brs, 1H), 3.84 (s, 3H), 3.31 (m, 2H), 2.75 (d, J = 4.6 Hz, 3H), 1.09 (t, J = 7.1 Hz, 3H).	518.2
116	109A 		V	16	10.3 (s, 1H), 8.64 (s, 1H), 8.42 (d, J = 2.6 Hz, 1H), 8.03 (d, J = 2.6 Hz, 1H), 7.75 (s, 1H), 7.48 (s, 1H), 7.32 (td, J = 1.7 and 7.6 Hz, 1H), 7.18 (t, J = 7.9 Hz, 1H), 7.12 (t, J = 6.9 Hz, 1H), 6.55 (s, 1H), 4.13-4.20 (m, 2H), 3.84 (s,	572.2

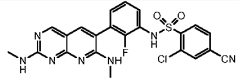
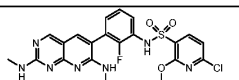
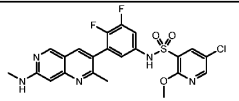
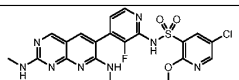
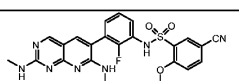
					3H), 2.75 (d, J = 4.5 Hz, 3H).	
117	109A 		V	25	10.3 (s, 1H), 8.53 (s, 1H), 8.42 (d, J = 2.6 Hz, 1H), 8.02 (d, J = 2.6 Hz, 1H), 7.38 (s, 1H), 7.30 (dt, J = 1.8 and 7.6 Hz, 1H), 7.17 (t, J = 7.9 Hz, 1H), 7.11 (t, J = 6.9 Hz, 1H), 7.02 (brs, 1H), 6.36 (brs, 1H), 4.11 (m, 1H), 3.84 (s, 3H), 2.73 (d, J = 4.5 Hz, 3H), 1.11 (d, J = 6.5 Hz, 6H).	532.2
118	109A 		V	23	10.3 (s, 1H), 8.53 (s, 1H), 8.42 (d, J = 2.6 Hz, 1H), 8.02 (d, J = 2.6 Hz, 1H), 7.48 (brs, 1H), 7.39 (s, 1H), 7.30 (dt, J = 1.7 and 7.6 Hz, 1H), 7.17 (t, J = 7.9 Hz, 1H), 7.10 (m, 1H), 6.39 (s, 1H), 4.45 (m, 1H), 3.84 (s, 3H), 2.74 (d, J = 4.5 Hz, 3H), 2.20 (m, 2H), 1.93 (m, 2H), 1.58 (m, 2H).	544.2
119	109A 		V	32	10.3 (s, 1H), 8.53 (s, 1H), 8.42 (d, J = 2.6 Hz, 1H), 8.02 (d, J = 2.6 Hz, 1H), 7.38 (s, 1H), 7.30 (dt, J = 1.8 and 7.6 Hz, 1H), 7.18 (m, 2H), 7.11 (t, J = 7.0 Hz, 1H), 6.36 (s, 1H), 4.24 (m, 1H), 3.84 (s, 3H), 2.73 (d, J = 4.5 Hz, 3H), 1.85 (m, 2H), 1.63 (m, 2H), 1.41-1.50 (m, 4H)	558.2
120	D41 F14		Q	10	11.14 (brs, 1H), 8.59 (brs, 1H), 8.09 (d, J = 2.4 Hz, 1H), 8.05 (d, J = 2.8 Hz, 1H), 7.39 (s, 1H), 7.22 (brs, 1H), 6.94 (m, 3H), 6.62 (brm, 1H), 5.69 (s, 1H), 2.86 (d, J = 4.4 Hz, 3H), 2.83 (d, J = 4.4 Hz, 3H), 1.58 (s, 6H).	565.1
121	121B		T	20	10.3 (brs, 1H), 8.79 (s, 1H), 8.50 (d, J = 2.6 Hz, 1H), 7.97 (d, J = 2.6 Hz,	490.0

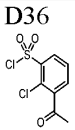
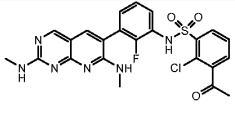
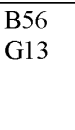
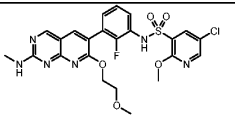
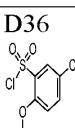
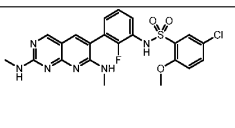
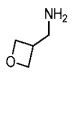
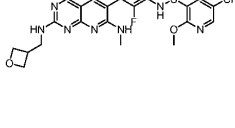
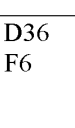
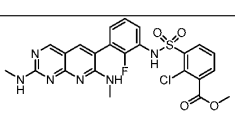
					1H), 7.87 (s, 1H), 7.45 (m, 2H), 7.30 (t, J = 4.7 Hz, 1H), 6.64 (s, 1H), 6.30 (s, 2H), 3.91 (s, 3H), 2.10 (s, 3H).	
122	D36 F4		Q	57	10.4 (brs, 1H), 8.60 (brs, 1H), 8.45 (d, J = 2.8 Hz, 1H), 8.03 (dd, J = 2.8 and 7.2 Hz, 1H), 7.47 (s, 1H), 7.36 (td, J = 1.6 and 7.6 Hz, 1H), 7.16-7.25 (m, 3H), 6.43 (brs, 1H), 3.89 (s, 3H), 2.87 (d, J = 4.4 Hz, 3H), 2.81 (d, J = 4.4 Hz, 3H).	488.2
123	D36 F15		Q	16	9.92 (brs, 1H), 8.60 (s, 1H), 7.65 (s, 1H), 7.46 (s, 1H), 7.35 (t, J = 6.4 Hz, 1H), 7.19 (t, J = 7.6 Hz, 1H), 7.10 (brm, 1H), 6.87 (s, 1H), 6.69 (brm, 2H), 6.44 (m, 1H), 3.95 (s, 3H), 3.85 (s, 3H), 2.80 (d, J = 4.0 Hz, 3H).	519.1
124	109A 		V	28	10.4 (brs, 1H), 8.54 (s, 1H), 8.39 (d, J = 2.6 Hz, 1H), 8.02 (d, J = 2.6 Hz, 1H), 7.39 (s, 1H), 7.29 (t, J = 7.8 Hz, 1H), 7.14 (t, J = 7.9 Hz, 1H), 7.05 (m, 1H), 6.73 (s, 1H), 6.33 (d, J = 5.5 Hz, 1H), 3.83 (s, 3H), 2.74 (d, J = 4.5 Hz, 3H), 1.37 (s, 9H).	546.2
125	D36 F5 		Q & V	6	10.5 (brs, 1H), 8.59 (brs, 1H), 8.42 (brs, 1H), 8.17 (d, J = 2.4 Hz, 1H), 7.49 (s, 1H), 7.44 (t, J = 7.6 Hz, 1H), 7.16-7.24 (brm, 3H), 6.47 (brm, 1H), 5.55 (m, 1H), 4.78 (m, 2H), 4.47 (m, 2H), 2.86 (d, J = 4.4 Hz, 3H), 2.80 (d, J = 4.0 Hz, 3H).	546.1
126	D42 F15		Q	22	9.89 (br s, 1H), 8.96 (s, 1H), 7.99 (s, 1H), 7.60 (s, 1H), 7.32 (br m, 1H), 7.16 (m, 3H), 6.90 (s, 1H), 3.96	519.9

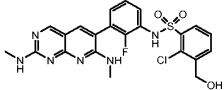
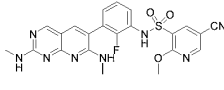
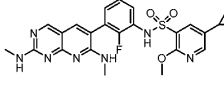
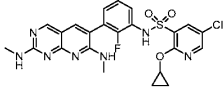
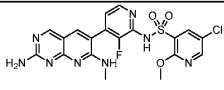
					(s, 3H), 3.86 (s, 3H), 3.84 (s, 3H). Note: one NH proton was not observed.	
127	121A 	V	28	10.4 (s, 1H), 8.85 (s, 1H), 8.51 (d, J = 2.6 Hz, 1H), 7.98 (d, J = 2.6 Hz, 1H), 7.90 (s, 1H), 7.45-7.46 (m, 2H), 7.32 (t, J = 4.7 Hz, 1H), 6.86 (s, 1H), 6.52 (s, 1H), 3.92 (s, 3H), 2.84 (d, J = 4.9 Hz, 3H), 2.12 (s, 3H).	504.0	
128	B52 G13 	P & T	11	10.5 (s, 1H), 8.50 (d, J = 2.5 Hz, 1H), 8.45 (s, 1H), 8.10 (d, J = 2.5 Hz, 1H), 7.57 (s, 1H), 7.33 (td, J = 2.6 and 7.3 Hz, 1H), 7.22 (m, 2H), 6.51 (q, J = 5.3 Hz, 1H), 6.21 (brs, 2H), 6.13 (s, 1H), 3.92 (s, 3H), 2.79 (d, J = 4.8 Hz, 3H).	489.2	
129	B54 G13 	P	63	10.4 (s, 1H), 8.72 (s, 1H), 8.53 (d, J = 2.5 Hz, 1H), 8.08 (d, J = 2.6 Hz, 1H), 7.98 (s, 1H), 7.34 (td, J = 1.9 and 7.6 Hz, 1H), 7.28 (m, 1H), 7.22 (t, J = 7.8 Hz, 1H), 6.87 (q, J = 5.3 Hz, 1H), 6.42 (s, 1H), 3.91 (s, 3H), 3.84 (s, 3H), 2.84 (d, J = 4.8 Hz, 3H).	504.0	
130	D36 F15 	Q	20	9.99 (s, 1H), 8.53 (s, 1H), 7.40 (s, 1H), 7.32 (d, J = 3.5 Hz, 1H), 7.29 (m, 2H), 7.17 (s, 1H), 7.12 (t, J = 7.9 Hz, 1H), 7.05 (t, J = 7.0 Hz, 1H), 6.37 (s, 1H), 3.76 (s, 3H), 3.70 (s, 3H), 2.80 (d, J = 4.8 Hz, 3H), 2.75 (d, J = 4.5 Hz, 3H).	533.0	
131	D36 	Q	10	10.8 (s, 1H), 8.93 (d, J = 4.7 Hz, 1H), 8.59 (s, 1H), 8.44 (d, J = 8.1 Hz, 1H), 7.92 (m, 2H), 7.45 (s, 2H), 7.32 (m, 2H), 7.27-7.17 (m, 4H), 6.47 (s, 1H), 2.86	508.2	

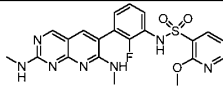
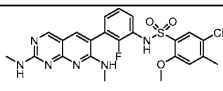
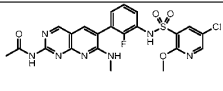
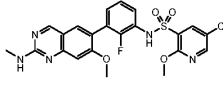
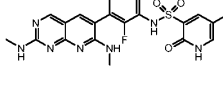
					(d, J = 4.7 Hz, 3H), 2.82 (d, J = 4.5 Hz, 3H).	
132	D36 		Q	18	10.6 (s, 1H), 8.58 (s, 1H), 7.91 (s, 1H), 7.46 (s, 1H), 7.42 (s, 1H), 7.29 (t, J = 7.2 Hz, 1H), 7.23 (m, 1H), 7.15 (m, 1H), 7.07 (s, 1H), 6.46 (s, 1H), 3.94 (s, 3H), 2.86 (d, J = 4.8 Hz, 3H), 2.82 (d, J = 4.5 Hz, 3H).	537.2
133	D36 		Q	32	10.7 (s, 1H), 8.59 (s, 1H), 8.42 (d, J = 2.1 Hz, 1H), 8.19 (dd, J = 2.2 and 8.3 Hz, 1H), 7.84 (d, J = 8.2 Hz, 1H), 7.46 (s, 1H), 7.34 (td, J = 1.8 and 7.7 Hz, 1H), 7.25 (s, 1H), 7.21 (t, J = 7.8 Hz, 1H), 7.16 (t, J = 7.0 Hz, 1H), 6.46 (s, 1H), 2.86 (d, J = 4.8 Hz, 3H), 2.79 (d, J = 4.5 Hz, 3H), 2.60 (s, 3H).	515.2
134	D36 		Q	32	9.92 (s, 1H), 8.59 (s, 1H), 7.70 (d, J = 2.5 Hz, 1H), 7.62 (dd, J = 2.6 and 8.7 Hz, 1H), 7.42 (s, 1H), 7.37 (td, J = 1.7 and 7.8 Hz, 1H), 7.24 (s, 1H), 7.16 (t, J = 7.9 Hz, 1H), 7.11 (d, J = 8.8 Hz, 1H), 7.07 (m, 1H), 6.44 (s, 1H), 3.74 (s, 3H), 2.86 (d, J = 4.8 Hz, 3H), 2.83 (d, J = 4.6 Hz, 3H), 1.22 (s, 9H).	525.2
135	C6 H6		P	11	8.99 (s, 1H), 8.43 (d, J = 2.0 Hz, 1H), 8.22 (d, J = 2.4 Hz, 1H), 8.17 (s, 1H), 7.97 (brd, J = 4.8 Hz, 1H), 7.14 (brs, 1H), 6.99 (s, 2H), 3.98 (s, 3H), 3.92 (s, 3H). at high Temp. Note: one NH proton was not observed.	492.0
136	C7 H6		P	5	8.98 (s, 1H), 8.41 (brs, 1H), 8.22 (d, J = 2.0 Hz, 1H), 8.15 (s, 1H), 7.94 (brm, 1H), 7.46 (brm, 1H), 7.07 (brs, 1H), 3.99	506.0

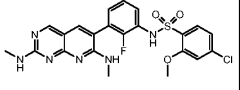
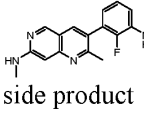
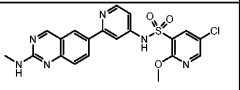
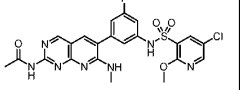
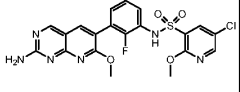
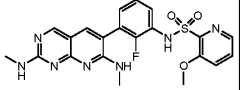
					(s, 3H), 3.92 (s, 3H), 2.97 (d, J = 4.4 Hz, 3H). at high Temp. Note: one NH proton was not observed.	
137	D36 F5 		Q & V	32	10.3 (brs, 1H), 8.60 (s, 1H), 8.32 (d, J = 2.4 Hz, 1H), 7.79 (d, J = 2.4 Hz, 1H), 7.43 (s, 1H), 7.35 (brt, J = 7.2 Hz, 1H), 7.23 (t, J = 7.6 Hz, 1H), 7.15 (brt, J = 6.8 Hz, 1H), 6.90 (brm, 1H), 6.68 (brm, 1H), 6.16 (brm, 1H), 2.92 (d, J = 4.4 Hz, 3H), 2.89 (d, J = 4.4 Hz, 3H), 2.81 (m, 1H), 0.72 (m, 2H), 0.44 (m, 2H). at high Temp.	529.1
138	109A 		V	33	8.58 (s, 1H), 8.27 (brs, 1H), 7.98 (m, 2H), 7.44 (m, 2H), 7.19 (brs, 1H), 6.97 (brs, 1H), 6.39 (brs, 1H), 5.00 (m, 1H), 4.75 (t, J = 6.6 Hz, 2H), 4.48 (m, 2H), 3.78 (m, 4H), 2.76 (d, J = 4.5 Hz, 3H).	546.2
139	109A 		V	73	10.4 (brs, 1H), 8.54 (s, 1H), 8.41 (d, J = 2.6 Hz, 1H), 8.02 (d, J = 2.6 Hz, 1H), 7.41 (s, 1H), 7.30 (t, J = 7.7 Hz, 1H), 7.16 (t, J = 8.6 Hz, 2H), 7.09 (s, 1H), 6.43 (s, 1H), 3.83 (s, 3H), 3.44 (brm, 4H), 3.21 (m, 3H), 2.73 (d, J = 4.5 Hz, 3H).	548.2
140	D36 		Q	39	9.94 (s, 1H), 8.60 (s, 1H), 7.47 (s, 1H), 7.34 (td, J = 1.7 and 7.8 Hz, 1H), 7.25 (m, 2H), 7.21-7.12 (m, 3H), 7.09 (m, 1H), 6.44 (s, 1H), 3.74 (s, 3H), 3.72 (s, 3H), 2.86 (d, J = 4.8 Hz, 3H), 2.82 (d, J = 4.6 Hz, 3H).	499.2

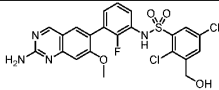
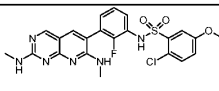
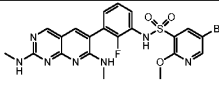
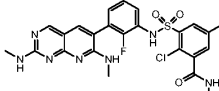
141	D36 		Q	17	10.9 (s, 1H), 8.60 (s, 1H), 8.33 (d, J = 1.7 Hz, 1H), 8.07 (d, J = 8.1 Hz, 1H), 8.00 (dd, J = 1.6 and 8.3 Hz, 1H), 7.45 (s, 1H), 7.34-7.15 (m, 4H), 6.47 (s, 1H), 2.86 (d, J = 4.7 Hz, 3H), 2.82 (d, J = 4.5 Hz, 3H).	498.0
142	D36 		Q	29	10.4 (s, 1H), 8.60 (s, 1H), 8.09 (d, J = 7.9 Hz, 1H), 7.45 (s, 1H), 7.35 (td, J = 1.8 and 7.7 Hz, 1H), 7.28-7.20 (m, 3H), 7.16 (m, 1H), 6.44 (s, 1H), 3.91 (s, 3H), 2.86 (d, J = 4.8 Hz, 3H), 2.82 (d, J = 4.5 Hz, 3H).	504.2
143	B23 G22 		P & V	9	10.9 (s, 1H), 8.87 (s, 1H), 8.53 (d, J = 2.6 Hz, 1H), 8.31 (d, J = 2.5 Hz, 1H), 7.99 (s, 1H), 7.20 (m, 1H), 6.95 (m, 2H), 6.53 (s, 1H), 3.97 (s, 3H), 2.85 (d, J = 4.9 Hz, 3H), 2.26 (s, 3H).	506.2
144	C5 H6		P	9	11.6 (brs, 1H), 8.63 (s, 1H), 8.40 (d, J = 2.0 Hz, 1H), 8.24 (d, J = 2.4 Hz, 1H), 7.92 (d, J = 5.6 Hz, 1H), 7.66 (s, 1H), 6.96 (brm, 2H), 6.58 (brm, 1H), 3.93 (s, 3H), 2.92 (d, J = 4.8 Hz, 3H), 2.91 (d, J = 5.6 Hz, 3H). at high Temp.	505.2
145	D36 		Q	29	10.2 (s, 1H), 8.52 (s, 1H), 8.04 (dd, J = 2.2 and 8.7 Hz, 1H), 8.01 (d, J = 2.1 Hz, 1H), 7.40 (s, 1H), 7.32 (d, J = 8.7 Hz, 1H), 7.28 (m, 1H), 7.15 (m, 2H), 7.07 (m, 1H), 6.38 (s, 1H), 3.83 (s, 3H), 2.79 (d, J = 4.8 Hz, 3H), 2.73 (d, J = 4.5 Hz, 3H).	494.2

146	D36 		Q	10	10.7 (s, 1H), 8.59 (s, 1H), 8.07 (d, J = 7.9 Hz, 1H), 7.82 (d, J = 7.6 Hz, 1H), 7.59 (t, J = 7.8 Hz, 1H), 7.45 (s, 1H), 7.35-7.20 (m, 2H), 7.17 (m, 1H), 7.11 (brs, 1H), 6.46 (brs, 1H), 2.86 (d, J = 4.8 Hz, 3H), 2.82 (d, J = 4.6 Hz, 3H), 2.56 (s, 3H).	515.0
147	B56 G13 		P	12	10.1 (brs, 1H), 8.94 (s, 1H), 8.45 (d, J = 2.4 Hz, 1H), 8.07 (d, J = 2.4 Hz, 1H), 7.96 (s, 1H), 7.27-7.36 (m, 3H), 7.20 (m, 1H), 4.52 (t, J = 4.8 Hz, 2H), 3.93 (s, 3H), 3.60 (t, J = 5.2 Hz, 2H), 3.20 (s, 3H), 2.95 (d, J = 4.4 Hz, 3H). at high Temp.	549.2
148	D36 		Q	10	10.1 (s, 1H), 8.60 (s, 1H), 7.67 (m, 2H), 7.47 (s, 1H), 7.34 (m, 1H), 7.17-7.28 (m, 3H), 7.14 (brm, 1H), 6.44 (brs, 1H), 3.80 (s, 3H), 2.86 (d, J = 4.4 Hz, 3H), 2.82 (d, J = 4.0 Hz, 3H).	503.2
149	109A 		V	6	8.87 (s, 1H), 8.26 (d, J = 2.6 Hz, 1H), 8.20 (s, 1H), 8.04 (d, J = 2.6 Hz, 1H), 7.82 (s, 1H), 7.73 (m, 1H), 7.24 (t, J = 8.1 Hz, 1H), 6.97 (t, J = 7.9 Hz, 1H), 6.61 (m, 1H), .79 (d, J = 13.5 Hz, 1H), 4.01 (m, 1H), 3.83 (s, 3H), 3.62-3.51 (m, 3H), 3.31 (m, 1H), 2.97 (d, J = 4.6 Hz, 3H), 2.32 (s, 1H).	560.2
150	D36 F6 		Q	64	10.7 (s, 1H), 8.59 (s, 1H), 8.13 (dd, J = 1.6 and 8.0 Hz, 1H), 7.95 (d, J = 7.7 Hz, 1H), 7.61 (t, J = 7.8 Hz, 1H), 7.45 (s, 1H), 7.32-7.22 (m, 2H), 7.18 (m, 1H), 7.14 (brs, 1H), 6.46 (brs, 1H), 3.87 (s,	531.0

					3H), 2.86 (d, J = 4.7 Hz, 3H), 2.82 (d, J = 4.6 Hz, 3H).	
151	150		S	7	10.5 (s, 1H), 8.52 (s, 1H), 7.83 (d, J = 7.9 Hz, 1H), 7.75 (d, J = 7.8 Hz, 1H), 7.47 (t, J = 7.8 Hz, 1H), 7.40 (s, 1H), 7.25-7.16 (m, 2H), 7.11 (t, J = 7.9 Hz, 1H), 7.06 (m, 1H), 6.42 (s, 1H), 5.54 (m, 1H), 4.54 (d, J = 5.5 Hz, 2H), 2.80 (d, J = 4.7 Hz, 3H), 2.76 (d, J = 4.5 Hz, 3H).	503.2
152	D36 F8		Q	15	10.4 (s, 1H), 8.91 (d, J = 1.6 Hz, 1H), 8.59 (brs, 1H), 8.45 (d, J = 1.6 Hz, 1H), 7.47 (s, 1H), 7.38 (brt, J = 7.6 Hz, 1H), 7.19-7.26 (m, 3H), 6.42 (brm, 1H), 4.00 (s, 3H), 2.86 (d, J = 4.4 Hz, 3H), 2.79 (d, J = 4.0 Hz, 3H).	495.3
153	D36 F7		Q	7	10.2 (s, 1H), 8.60 (s, 1H), 8.18 (d, J = 2.0 Hz, 1H), 7.72 (d, J = 2.4 Hz, 1H), 7.44 (s, 1H), 7.35 (brt, J = 7.6 Hz, 1H), 7.20 (m, 2H), 7.14 (brm, 1H), 6.41 (brm, 1H), 3.84 (s, 3H), 2.86 (d, J = 4.4 Hz, 3H), 2.81 (d, J = 4.4 Hz, 3H), 1.97 (m, 1H), 0.93 (m, 2H), 0.64 (m, 2H).	510.3
154	D36 F5 		Q & V	4	10.3 (s, 1H), 8.61 (brs, 1H), 8.52 (s, 1H), 8.12 (d, J = 2.8 Hz, 1H), 7.46 (s, 1H), 7.38 (t, J = 7.6 Hz, 1H), 7.16-7.22 (m, 3H), 6.45 (brm, 1H), 4.33 (m, 1H), 2.86 (d, J = 4.4 Hz, 3H), 2.80 (d, J = 4.0 Hz, 3H), 0.62 (m, 2H), 0.65 (m, 2H).	530.3
155	C8 H6		P	3	8.63 (s, 1H), 8.26 (d, J = 2.4 Hz, 1H), 8.22 (d, J = 2.4 Hz, 1H), 7.76 (d, J = 5.2 Hz, 1H), 7.60 (s, 1H),	491.2

					6.62 (br m, 1H), 6.42 (brs, 2H), 3.90 (s, 3H), 2.90 (d, J = 4.4 Hz, 3H), two NH protons not observed. at high Temp.	
156	D36 F9		Q	10	10.2 (s, 1H), 8.60 (s, 1H), 8.38 (brd, J = 4.0 Hz, 1H), 8.09 (dd, J = 7.6, 2.0 Hz, 1H), 7.44 (s, 1H), 7.33 (brt, J = 7.2 Hz, 1H), 7.27 (m, 2H), 7.11-7.18 (m, 2H), 6.37 (brm, 1H), 3.90 (s, 3H), 2.85 (d, J = 4.8 Hz, 3H), 2.81 (d, J = 4.4 Hz, 3H).	470.3
157	D36 		Q	13	10.0 (s, 1H), 8.59 (s, 1H), 7.63 (s, 1H), 7.47 (s, 1H), 7.34 (br t, J = 7.6 Hz, 1H), 7.25 (s, 1H), 7.19 (m, 2H), 7.12 (m, 1H), 6.43 (brm, 1H), 3.79 (s, 3H), 2.86 (d, J = 4.4 Hz, 3H), 2.81 (d, J = 4.0 Hz, 3H), 2.36 (s, 3H).	517.2
158	B40 G13		P	39	10.5 (s, 1H), 10.4 (brs, 1H), 8.92 (s, 1H), 8.48 (d, J = 2.0 Hz, 1H), 8.10 (d, J = 2.4 Hz, 1H), 7.72 (s, 1H), 7.41 (t, J = 7.2 Hz, 1H), 7.26 (m, 2H), 6.89 (br m, 1H), 3.90 (s, 3H), 2.83 (d, J = 4.8 Hz, 3H), 2.25 (s, 3H).	532.3
159	B58 G13		P	57	10.32 (s, 1H), 8.91 (br s, 1H), 8.50 (d, J = 2.4 Hz, 1H), 8.06 (d, J = 2.8 Hz, 1H), 7.55 (s, 1H), 7.31 (m, 2H), 7.19 (br m, 2H), 6.94 (br s, 1H), 3.90 (s, 3H), 3.76 (s, 3H), 2.88 (d, J = 4.8 Hz, 3H).	504.3
160	16		De-Me with BBr ₃	36	12.80 (br s, 1H), 9.92 (br s, 1H), 8.60 (br s, 1H), 8.02 (d, J = 2.8 Hz, 1H), 7.96 (d, J = 3.2 Hz, 1H), 7.51 (s, 1H), 7.37 (td, J = 8.0, 1.6 Hz, 1H), 7.15-7.24 (m, 3H), 6.41 (br m,	490.2

					1H), 2.86 (d, J = 4.8 Hz, 3H), 2.84 (d, J = 4.4 Hz, 3H).	
161	D36 		Q	8	10.01 (s, 1H), 8.60 (br s, 1H), 7.70 (d, J = 8.4 Hz, 1H), 7.44 (s, 1H), 7.32 (m, 2H), 7.18 (m, 2H), 7.11 (m, 2H), 6.38 (br m, 1H), 3.83 (s, 3H), 2.86 (d, J = 4.8 Hz, 3H), 2.82 (d, J = 4.4 Hz, 3H).	503.2
162	B23 G13 NH ₂	 side product	P & V	12	9.96 (brs, 1H), 8.77 (s, 1H), 7.88 (s, 1H), 7.57 (d, J = 2.9 Hz, 1H), 7.24-7.30 (m, 2H), 7.12-7.17 (m, 2H), 6.77 (d, J = 5.6 Hz, 1H), 6.45 (s, 1H), 5.66 (d, J = 6.0 Hz, 1H), 3.74 (s, 3H), 2.77 (d, J = 5.0 Hz, 3H), 2.56 (d, J = 4.7 Hz, 3H), 2.07 (s, 3H).	483.2
163	C4 H7		P	20	9.20 (s, 1H), 8.45 (brs, 1H), 8.29 (s, 1H), 8.03-8.23 (m, 2H), 7.37-7.73 (m, 4H), 7.07 (d, J = 5.2 Hz, 1H), 3.90 (s, 3H), 2.91 (d, J = 4.7 Hz, 3H). sulfonamide NH not observed.	457.0
164	B40 G9		P	4	11.0 (brs, 1H), 10.5 (s, 1H), 8.92 (s, 1H), 8.50 (s, 1H), 8.30 (s, 1H), 7.67 (s, 1H), 6.90-7.00 (m, 4H), 3.96 (s, 3H), 2.86 (d, J = 4.4 Hz, 3H), 2.24 (s, 3H).	532.3
165	B39 G13		P	10	10.4 (s, 1H), 8.96 (s, 1H), 8.51 (d, J = 2.4 Hz, 1H), 8.06 (d, J = 2.8 Hz, 1H), 7.99 (s, 1H), 7.34 (td, J = 2.0 and 8.0 Hz, 1H), 7.19-7.25 (m, 2H), 7.15 (brs, 2H), 3.90 (s, 3H), 3.83 (s, 3H).	491.2
166	B15 G23		P	34	10.3 (s, 1H), 8.61 (s, 1H), 8.18 (dd, J = 1.2 and 4.6 Hz, 1H), 7.77 (d, J = 8.6 Hz, 1H), 7.67 (dd, J = 4.5	470.2

					and 8.5 Hz, 1H), 7.52 (s, 1H), 7.33 (td, J = 1.8 and 7.8 Hz, 1H), 7.24 (s, 1H), 7.14 (t, J = 7.9 Hz, 1H), 7.07 (m, 1H), 6.51 (s, 1H), 3.90 (s, 3H), 2.87 (d, J = 4.8 Hz, 3H), 2.84 (d, J = 4.6 Hz, 3H).	
167	B41 G24		P & X	30	10.3 (brs, 1H), 8.91 (s, 1H), 7.84 (d, J = 2.4 Hz, 1H), 7.79 (d, J = 2.4 Hz, 1H), 7.54 (s, 1H), 7.23-7.28 (m, 1H), 7.10-7.21 (m, 2H), 6.89 (s, 1H), 6.50 (brs, 2H), 5.49 (t, J = 5.6 Hz, 1H), 4.62 (d, J = 4.0 Hz, 2H), 3.79 (s, 3H). at high Temp.	523.2
168	D36 F11		Q	9	10.6 (brs, 1H), 8.60 (brs, 1H), 7.57 (d, J = 8.8 Hz, 1H), 7.47 (s, 1H), 7.45 (d, J = 2.8 Hz, 1H), 7.31 (brt, J = 6.8 Hz, 1H), 7.10-7.28 (m, 4H), 6.45 (brm, 1H), 3.78 (s, 3H), 2.87 (d, J = 4.4 Hz, 3H), 2.82 (d, J = 4.4 Hz, 3H).	503.3
169	D36 F10		Q	22	10.4 (s, 1H), 8.60 (brs, 1H), 8.55 (d, J = 2.0 Hz, 1H), 8.16 (d, J = 2.4 Hz, 1H), 7.46 (s, 1H), 7.37 (t, J = 7.6 Hz, 1H), 7.18-7.25 (m, 3H), 6.45 (brs, 1H), 3.89 (s, 3H), 2.86 (d, J = 4.4 Hz, 3H), 2.80 (d, J = 4.4 Hz, 3H).	548.3 550.3
170	D36 F16		Q	2	8.62 (s, 1H), 8.32 (br m, 1H), 8.01 (d, J = 2.4 Hz, 1H), 7.68 (brs, 1H), 7.49 (s, 1H), 7.31 (t, J = 7.6 Hz, 1H), 7.16 (t, J = 7.6 Hz, 1H), 7.07 (brm, 1H), 6.86 (brm, 1H), 6.14 (brm, 1H), 2.92 (d, J = 4.8 Hz, 3H), 2.90 (d, J = 4.8 Hz, 3H), 2.78 (d, J = 4.4 Hz, 3H). NH proton was not observed. at high Temp.	564.3

171	B31 G17		P, T & S	15	10.8 (s, 1H), 8.45 (d, J = 0.7 Hz, 1H), 7.85 (d, J = 2.7 Hz, 1H), 7.79 (d, J = 2.6 Hz, 1H), 7.59 (s, 1H), 7.30 (m, 1H), 7.20 (m, 2H), 6.53 (q, J = 4.9 Hz, 1H), 6.27 (s, 2H), 6.14 (s, 1H), 5.74 (t, J = 5.7 Hz, 1H), 4.61 (d, J = 5.4 Hz, 2H), 2.79 (d, J = 4.9 Hz, 3H).	523.0
172	B59 G13		P	1	10.8 (s, 1H), 10.4 (s, 1H), 8.93 (s, 1H), 8.48 (m, J = 2.3 Hz, 1H), 8.11 (d, J = 2.6 Hz, 1H), 7.73 (s, 1H), 7.41 (td, J = 1.9 and 7.7 Hz, 1H), 7.19-7.30 (m, 2H), 6.90 (d, J = 4.7 Hz, 1H), 3.90 (s, 3H), 2.84 (d, J = 4.5 Hz, 3H), 2.18-2.27 (m, 1H), 0.79-0.87 (m, 4H).	558.0
173	E11 F17		Q & X	60	10.5 (s, 1H), 10.4 (brs, 1H), 9.11 (s, 1H), 8.47 (s, 1H), 8.20 (s, 1H), 7.81 (d, J = 2.4 Hz, 1H), 7.79 (d, J = 2.4 Hz, 1H), 7.40 (m, 1H), 7.29 (m, 2H), 5.50 (br t, J = 4.4 Hz, 1H), 4.62 (d, J = 4.8 Hz, 2H), 2.31 (s, 3H), 2.18 (s, 3H). at high Temp.	549.3
174	173		X (at 60 °C)	82	10.4 (brs, 1H), 8.79 (s, 1H), 7.90 (s, 1H), 7.82 (d, J = 2.4 Hz, 1H), 7.74 (d, J = 2.0 Hz, 1H), 7.33 (t, J = 7.2 Hz, 1H), 7.17 (t, J = 8.0 Hz, 1H), 7.10 (brm, 1H), 6.69 (s, 1H), 6.04 (brs, 2H), 5.46 (brt, J = 4.4 Hz, 1H), 4.61 (d, J = 4.8 Hz, 2H), 2.23 (s, 3H). at high Temp.	505.1
175	B15 G24		P & X	31	10.7 (s, 1H), 8.60 (s, 1H), 7.87 (d, J = 2.6 Hz, 1H), 7.79 (d, J = 2.6 Hz, 1H), 7.49 (s, 1H), 7.32 (td, J = 1.8 and 7.7 Hz, 1H), 7.10-	537.0

					7.27 (m, 3H), 6.49 (s, 1H), 5.74 (t, J = 5.7 Hz, 1H), 4.60 (d, J = 5.7 Hz, 2H), 2.88 (d, J = 4.8 Hz, 3H), 2.83 (d, J = 4.6 Hz, 3H).	
176	B15 G25		P & X	19	10.8 (brs, 1H), 8.59 (brs, 1H), 7.74 (brm, 1H), 7.65 (brm, 1H), 7.46 (s, 1H), 7.33 (m, 1H), 7.22 (brm, 3H), 6.49 (brs, 1H), 5.60 (t, J = 6.0 Hz, 1H), 4.55 (d, J = 5.6 Hz, 2H), 2.86 (d, J = 4.4 Hz, 3H), 2.82 (d, J = 4.4 Hz, 3H).	521.4
177	B15 G26		P & X	60	10.7 (brs, 1H), 8.60 (brs, 1H), 7.68 (dd, J = 3.2 and 8.0 Hz, 1H), 7.58 (brd, J = 9.6 Hz, 1H), 7.48 (s, 1H), 7.29 (brt, J = 7.6 Hz, 1H), 7.18 (brm, 3H), 6.44 (brs, 1H), 5.72 (t, J = 5.2 Hz, 1H), 4.59 (d, J = 5.6 Hz, 2H), 2.86 (d, J = 4.8 Hz, 3H), 2.83 (d, J = 4.4 Hz, 3H).	521.4
178	B15 G27		P & X	78	10.7 (brs, 1H), 8.60 (brs, 1H), 7.56 (brm, 1H), 7.47 (m, 1H), 7.46 (s, 1H), 7.34 (brt, J = 6.0 Hz, 1H), 7.24 (m, 3H), 6.46 (brs, 1H), 5.59 (t, J = 5.6 Hz, 1H), 4.56 (d, J = 5.6 Hz, 2H), 2.87 (d, J = 4.4 Hz, 3H), 2.82 (d, J = 4.0 Hz, 3H).	505.4
179	B15 G28		P & X	22	10.3 (s, 1H), 8.59 (brs, 1H), 7.72 (d, J = 2.8 Hz, 1H), 7.64 (d, J = 2.8 Hz, 1H), 7.48 (s, 1H), 7.31 (td, J = 1.6 and 8.0 Hz, 1H), 7.20 (m, 2H), 7.14 (brt, J = 6.4 Hz, 1H), 6.46 (brm, 1H), 5.52 (t, J = 5.6 Hz, 1H), 4.57 (d, J = 5.6 Hz, 2H), 3.79 (s, 3H), 2.86 (d, J = 4.8 Hz, 3H), 2.84 (d, J = 4.4 Hz, 3H).	533.1

Example 180. Biochemical assay for GCN2

- [0338] Activity of GCN2 kinase was determined using a TR-FRET kinase activity assay (e.g. Riddle *et al.* Analytical Biochemistry (2006) 356(1) 108-116). Assays were conducted in 384-well plates (13 μ L assay volume) using 2 nM GCN2 (Carna Biosciences), 130 nM GFP-Elf2 α (Invitrogen), 0.2 mg/mL *E. coli* tRNA (sigma) and 1 mM ATP in kinase buffer (Invitrogen). Inhibition of GCN2 was measured by adding serial diluted test compound (final assay concentration of 0.5% DMSO) followed by a 3-hour incubation. Tb-peIF2 α (pSer52) antibody (Invitrogen) (2 nM final assay concentration) in kinase buffer containing EDTA (final assay concentration of 20 mM) was added. After a 60 min incubation at room temperature, TR-FRET was monitored using an excitation wavelength of 340 nm and emission wavelengths of 490 nm and 520 nm. The emission ratio (520/490) at each compound concentration of 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).
- [0339] SEQ ID NO: 1 - GCN2 protein sequence (residues 1-1649; G556E with a N-terminal GST tag)

MAPILGYWKIKGLVQPTRLLEYLEEKYEEHLYERDEGDKWRNKKFELGLEFPNLPYYIDG
 DVKLTQSMAIIRYIADKHNMLGGCPKERAIEISMLEGAVLDIRYGVSRIAYSKDFETLKVDL
 20 SKLPEMLKMFEDRLCHKTYLNGDHVTHPDFMLYDALDVVLYMDPMCLDAFPKLVCFKKRI
 EAIPQIDKYLKSSKYIAWPLQGWQATFGGGDHPPKSDLEVLFGQPLGAMGSGIQRPTSTSS
 VMAGGRGAPGRGRDEPPESYPQRQDHELQALEAIYGADFQDLRPDACPVPKEPPEINLVLY
 PQGLTGEEVYVKVDLRVKCPPTYPDVVPEIELKNAKGLSNESVNLLKSRLEELAKKHCGEV
 MIFELAYHVQSFLSEHNKPPPKSFHEEMLERRAQEEQQRLLAKRKEEQEQRILHEIQRRKE
 25 EIKKEKKRKEMAKQERLEIASLSNQDHTSKKDPGGHRTAAILHGGSPDFVGNKGHRANSSG
 RSRRERQYSVCNSEDSPGSCEILYFNMGSPDQLMVHKGKCIGDEQLGKLVYNALETATGGF
 VLLYEWVLQWQKKMGPFLTSQEKEKIDCKKQIQGTETEFNSLVKLSHPNVVRYLAMNLK
 EQDDSIIVDILVEHISGVSLAAHLSHSGPIPVHQLRRYTAQLLSGLDYLSNSVVKVLSASN
 VLVDAEGTVKITDYSISKRLADICKEDVFEQTRVRFSDNALPYKTGKKGDVWRLGLLLLSLS
 30 QGQECGEYPVTIPSDLPADFQDLKCKVCLDDKERWSPQQLKHSFINPQPKMPLVEQSPED
 SGGQDYVETVIPSRLPSAAFFSETQRQFSRYFIEFEELQLLGKGAFGAVIKVQNKLDGCCYA
 VKRIPINPASRQFRRIKGEVTLLSRLHHENIVRYYNWIERHERPAGPGTPPPDSGPLAKDDR
 AARGQPASDTDGLDSVEAAAPPILSSSVIEWSTSGERSASARFPATGPGSSDDEDDDEDEHG
 GVFSQSFLPASDSSEDIIFDNEDENSKSQNQDEDCNEKNGCHESEPSVTTEAVHYLYIQMEYC
 35 EKSTLRDTIDQGLYRDTVRLWRLFREILDGLAYIHEKGMIHRDLKPVNIFLSDDHVKIGDF
 GLATDHLAFSADSKQDDQTGDLIKSDPSGHLTGMVGTALYVSPEVQGSTKSAYNQKVDLFS
 LGIIFFEMSYHPMVTASERIFVLNQLRDPTSPKFPEDFDDGEHAKQKSVISWLLNHDPAKRPT
 ATELLKSELLPPPQMEESLHEVLHHTLTNVDGKAYRTMMAQIFSQRISPAIDYTYDSILKG
 NFSIRTAKMQQHVCETIIRIFKRHGAVQLCTPLLPNRNQIYEHNEAALFMDHSGMLVMLPF
 40 DLRIPFARYVARNNILNLKRYCIERVFRPRKLDLRFHPKELLECAFDIVTSTTNSFLPTAEIITY
 YEIIQEFPALQERNYSIYLNHTMLLKAILLHCGIPEDKLSQVYIILYDAVTEKLTRREVEAKFC
 NLSLSSNSLCRLYKFIEQKGDQLQDLMPTINSLIKQKTGIAQLVKYGLKDLEEVVGLLKKLGIK

LQVLINLGLVYKVQQHNGIIFQFVAFIKRRQRAVPEILAAGGRYDLLIPQFRGPQALGPVPTA
 IGVSIAIDKISAAVLNMEESVTISSCDLLVSVSGQMSMSRAINLTQKLWTAGITAEIMYDWSQ
 SQEELQEYCRHHEITYVALVSDKEGSHVKVKSFEKERQTEKRVLETETLDHVLQKLRTKVT
 5 DERNGREASDNLAVQNLKGSFSNASGLFEIHGATVVPIVSVLAPEKLSASTRRRYETQVQTR
 LQTS LANLHQKSSEIEILAVDLPKETILQFLSLEWDADEQAFNTTVKQLLSRLPKQRYLKLVC
 DEIYNIKVEKKVSVLFLYSYRDDYYRILF

Example 181. Biochemical assay for PERK

[0340] Activity of PERK kinase was determined spectroscopically using a coupled pyruvate
 10 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 10 nM PERK (from Beryllium), 0.25 mg/mL Myelin
 Basic Protein substrate, 1.5 units pyruvate kinase, 2.1 units lactate dehydrogenase, 1 mM
 phosphoenol pyruvate, 0.28 mM NADH and 1 mM ATP in assay buffer (100 mM Tris, pH 7.5, 15
 15 mM $MgCl_2$, 0.5 mM DTT, 0.004% (w/v) BSA, and 0.004% Triton X-100). Inhibition of PERK 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 hours at 30 °C on a multi-mode
 microplate reader (BioTek). The reaction rate was calculated using the 2-3 h time frame. The
 reaction rate at each concentration of compound was converted to percent inhibition using controls
 20 (*i.e.* reaction with no test compound and reaction with a known inhibitor) and IC_{50} values were
 calculated using software routines in Prism (GraphPad software).

[0341] SEQ ID NO: 2 - PERK protein sequence (residues 563-1115; Sequence ID: NM 004836)

MSPILGYWKIKGLVQPTRLLLEYLEEKYEEHLYERDEGDKWRNKKFELGLEFPNLPYYIDG
 25 DVKLTQSMARIYIADKHNMLGGCPKERAISMLEGAVLDIRYGVSR IAYS KDFETLKVDFL
 SKLPEMLKMFEDRLCHKTYLNGDHVTHPDFMLYDALDVVLYMDPMCLDAFPKLVCFKKRI
 EAIPQIDKYLKSSKYIAWPLQGWQATFGGGDHPPKSDLVPRGSKYDSVSGEANDSSWNDIK
 NSGYISRYLTDFEPIQCLGRGGFGVVFEAKNKVDDCN YAIKRIRLPNRELAREKVMREVKAL
 AKLEHPGIVRYFNAWLEAPPEKWQEKMD EIW LKDESTDWPLSSPSPMDAPSVKIRMDPFS
 30 TKEHIEIAPSPQRSRSFSGISCDQTSSSESQFSPLEFSGMDHEDISESVDAAYNLQDSCLTDC
 DVEDGTMDGNDEGHSELCPS EASPYVRSRERTSSSIVFEDSGCDNASSKEEPKTNRLHIGN
 HCANKLTAFKPTSSKSSSEATLSISPPRPTTSLDLTKNTTEKLQPSSPKVYLYIQMLCRKEN
 LKDW MNGRCTIEERERSVCLHIFLQIAEAVEFLHSKGLMHRDLKPSNIFFTMDDVVKV GDF
 GLVTAMDQDEEEQTVLTPMPAYARHTGQVGTKLYMSPEQIHGNSYSHKVDIFSLGLILFELL
 35 YPFSTQMERTVRLTLDVRNLKFPPLFTQKYPCEYVMVQDMLSPSPMERPEAINIENAVFEDL
 DFPGKTVLRQRSRLSSSGTKHSRQSNNSHSP LPSN

Table 1. Inhibition of biochemical activity of GCN2 and PERK kinases by exemplary compounds.

Example No	GCN2 IC ₅₀ (nM)	PERK IC ₅₀ (nM)
1	++++	++++
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	+	++
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	+++	5
150	+++	
151	+	++
152	++	
153	+	++
154	++	++
155	++	++
156	++	+++
157	+	
158	+	++
159	+	+
160	+++	++++
161	++	++
162	+	++
163	++++	++++
164	+	++
165	+	+
166	++++	++++
167	+	+
168	+	+
169	+	++
170	++++	++++
171	+	+
172	++	15
173	+	
174	+	+
175	+	+
176	+	+
177	+	++
178	+	++
179	+	+

[0342] For Table 1, “+” 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.

Example 182. CCRF-CEM ASNase Cell Proliferation Assay, a phenotypic assay for cellular inhibition of GCN2.

[0343] CCRF-CEM leukemia cells (catalog #CCL-116) were obtained from the American Type Culture Collect (ATTC, Manassas, VA). Cells were grown in RPMI-1640 medium supplemented with 10% heat-inactivated fetal bovine serum (Invitrogen, Carlsbad, CA) and 1% Penicillin/Streptomycin/L-Glutamine at 37 °C, 5% CO₂, and 95% humidity. Cells were expanded until reaching one million cells per mL at which time they are subcultured or harvested for assay use. Ten thousand cells per well in 200 µL RPMI-1640 supplemented with 10% heat-inactivated fetal bovine serum and 1% Penicillin/Streptomycin were dispensed into a 96-well black clear bottom plate. A serial dilution of test compound and 1 mU/mL ASNase was added in triplicate and plates were incubated for 72 h at 37 °C, 5% CO₂, and 95% humidity. At the end of the incubation, 40 µL of a 440 mM solution of resazurin (Sigma, St. Louis, MO) in PBS was added to each well of the plate and plates were incubated for an additional 6 h at 37 °C, 5% CO₂, and 95% humidity. Plates were read on a Synergy2 or equivalent reader (Biotek, Winooski VT) using an excitation of 540 nm and an emission of 600 nm. Data was analyzed using GraphPad Prism software (GraphPad, San Diego, CA) to calculate IC₅₀ values.

Example 183. HCT116 Amino Acid Starved (-AA) Phospho-GCN2 and ATF4 Assay

[0344] HCT116 colorectal cancer cells (catalog #CCL-247) were obtained from the American Type Culture Collect (ATTC, Manassas, VA). Briefly, cells were grown in RPMI 1640 supplemented with 10% heat inactivated fetal bovine serum (Invitrogen, Carlsbad, CA) and 1% Penicillin/Streptomycin/L-Glutamine at 37 °C, 5% CO₂, and 95% humidity. Cells were expanded until reaching 70-95% confluency at which point they were subcultured or harvested for assay use. Cells were seeded in 12-well culture plate at five hundred thousand cells per well in 1 mL complete growth medium and incubated overnight at 37 °C, 5% CO₂, and 95% humidity. The next day each well was replaced with 1mL Earle's Balanced Salt Solution (EBSS, Invitrogen, Carlsbad, CA) supplemented with 10% Dialyzed Fetal Bovine Serum, 5.5 mM Glucose, 1% Penicillin/Streptomycin and 1% Vitamin solution (thermo #11120052). A serial dilution of test compound was dispensed into well. Plates were incubated for 4 h at 37 °C, 5% CO₂, and 95% humidity. At the end of the incubation, cells were washed with PBS supplemented with 1X Halt protease inhibitor, 1X Halt phosphatase inhibitor, 1X Sigma phosphatase inhibitor cocktail 2 and 1X EDTA and then lysed with M-PER Mammalian Protein Extraction Reagent supplemented with 3X of the inhibitor mix as described above. Cell lysates were sonicated with water bath sonicator (Qsonica, Newtown, CT) and supernatants were boiled with SDS buffer and reducing agent. Western blot was performed on each

lysate to quantify phospho-GCN2 (Thr899), total GCN2, ATF4 and beta-Actin. Membranes were imaged with LI-COR Odyssey CLx Imaging System (LI-COR, Lincoln, NE). Data were analyzed using GraphPad Prism software (GraphPad, San Diego, CA) to calculate IC₅₀ values.

5 Example 184. CCRF-CEM TG ATF4 ELISA, a phenotypic assay for cellular inhibition of PERK preactivated by thapsigargin (TG)

[0345] CCRF-CEM leukemia cells (catalog #CCL-116) were obtained from the American Type Culture Collection (ATTC, Manassas, VA). Briefly, cells were grown in RPMI-1640 medium supplemented with 10 % heat-inactivated fetal bovine serum (Invitrogen, Carlsbad, CA) and 1% Penicillin/Streptomycin/L-Glutamine at 37 °C, 5% CO₂, and 95% humidity. Cells were expanded until reaching one million cells per mL at which time they were subcultured or harvested for assay use. One million five hundred thousand cells per well in 1 mL complete growth medium were dispensed into 12-well plates and incubated overnight. A serial dilution of test compound was added and cells were incubated at 37 °C, 5% CO₂, and 95% for three hours, then 1 μM thapsigargin was added and cells were incubated for an additional hour at 37 °C, 5% CO₂, and 95%. Cells were lysed then ATF4 levels were measured using an ELISA assay (Proteintech, Rosemont, IL). Absorbance was measured at 450 nM and 544 nM using a Synergy2 or equivalent reader (Biotek, Winooski VT). Data was analyzed using PRISM software (Graphpad, San Diego, CA) to calculate IC₅₀ values.

20 Table 2. Inhibition of proliferation of ASNase treated CCRF-CEM cells, Phospho-GCN2 and ATF4 in amino acid starved HCT116 , and ATF4 in Thapsigargin stimulated CCRF-CEM cells by exemplary compounds..

Example No	CCRF-CEM ASNase Cell Proliferation	HCT116 -AA pGCN2 Western Blot	HCT116 -AA ATF4 Western Blot	CCRF-CEM Thapsigargin ATF4 ELISA
3	+	+	+	
4	++++			+
8	++	+	++	++++
9	+++	+	++	++++
11	++	+	+	++++
14	++++	++	+++	++++
15	++	+	++	
16	+	+	+	++++
17	++++	++	++++	++++
19	++	+	+	++++
22	+	+	+	++++
23	++	+	+	++++
25	+	+	+	++++

26	+	+	+	++++
27	+	+	+	++++
30	+	+	+	++++
31	+	+	+	++++
33	++	+	+	++++
35	+	+	+	++++
36	+	+	+	++++
38	++	+	++	++++
39	++	+	++	++++
44	+	+	+	++++
45	+	+	+	++
48	++	+	+	++++
49	+	+	++	++++
50	+	+	+	++++
51	+	+	+	++++
53	+	+	+	++++
56	+	+	+	+++
57	+	+	+	++++
59	+	+	+	++++
61	+	+	+	++
62	+	+	++	++++
63	+	+	+	++++
64	+	+	+	++++
65	++	+	++	++++
66	+	+	+	++++
67	+	+	+	++++
68	+	+	+	++++
74	+	+	+	++++
77	+	+	+	++
78	+	+	+	+++
84	+	+	+	++
85	+	+	+	++++
87	+	+	+	++++
88	+	+	+	++
89	++	+	++	++++
90	+	+	+	++++
92	+	+	+	++++
93	++	+	++	++++
95	++	+	++	++++
96	++	+	++	++++
97	+	+	++	++++
100	+	+	+	++++
102	+	+	+	++++
106	+	+	+	++

109	+	+	+	+++
110	+	+	+	++
111	++	++	+	++++
113	+	+	++	+++
114	+	+	++	++++
115	+	+	+	++++
117	++	++	++	++++
121	+	+	+	++
127	+	+	+	+++
128	+	+	+	+
129	+	+	+	++++
132	+	+	+	+++
135	+++	++	++++	++++
136	++	+	++	++++
137	+	+	+	++++
143	+	+	+	++++
148	+	+	+	++++
151	+	+	+	++
158	+	+	+	++++
159	+			+++
162	+			
164	++			++++
165	+			++++
167	+			+
168	++			++++
171	+			+
173	+			++
174	+			+
175	+			++
176	+			++++
177	+			++
178	+			++++
179	+			++

[0346] For Table 2, “+” 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.

Example 185. H929 ATF4 ELISA ASSAY

[0347] H929 multiple myeloma cells (catalog #CRL-9068) were obtained from the American Type Culture Collection (ATTC, Manassas, VA). Briefly, cells were grown in RPMI-1640 medium

supplemented with 20% heat-inactivated fetal bovine serum (catalog #A3840002, ThermoFisher Scientific, Waltham, MA), 1% Penicillin / Streptomycin / L-Glutamine (catalog #10378016, ThermoFisher Scientific, Waltham, MA), and 0.05 mM 2-mercaptoethanol (catalog #21985-023, ThermoFisher Scientific, Waltham, MA) at 37 °C, 5% CO₂, and 95% humidity. Cells were expanded until reaching one million five hundred thousand cells per mL at which time they were subcultured or harvested for assay use. One million five hundred thousand cells per well in 1 mL complete growth medium were dispensed into 12-well plates and incubated overnight. A serial dilution of test compound was added, and cells were incubated at 37 °C, 5% CO₂, and 95% for four hours. Cells were lysed then ATF4 levels were measured using an ELISA assay (Proteintech, Rosemont, IL). Absorbance is measured at 450 nM and 544 nM using a Synergy2 or equivalent reader (Biotek, Winooski VT). Data were analyzed using PRISM software (Graphpad, San Diego, CA) to calculate fold stimulation of cellular ATF4 relative to vehicle treated control.

Table 3. Stimulation of ATF4 in H929 Multiple Myeloma cells by exemplary compounds.

Example No	H929 NS ATF4 ELISA
16	+++
25	++
31	++
49	+
79	+++
86	+++
109	+++
110	++
128	+++
151	++
174	+++
175	+++
179	+++

[0348] For Table 3, “+” refers to an ATF4 stim less than or equal to 5-fold; “++” refers to an ATF4 stim greater than 5 fold and less than or equal to 10 fold; “+++” refers to an ATF4 stim greater than 10 fold and less than or equal to 20 fold.

[0349] Compound 16 unexpectedly exhibited stimulation of ATF4 in H929 multiple myeloma cells (in the absence of thapsigargin) across a concentration range of 123 nM to 10 mM. A graph of the stimulation of cellular ATF4 in H929 multiple myeloma cells induced by Compound 16 is shown in Figure 1.

Example 186. Detection of PERK Oligomerization Using NanoBRET

- [0350] Constructs for BRET were built using the NanoBRET™ Flexi® PPI Starter System (Promega, Madison, WI). The full-length PERK ORF was obtained from Genscript (Piscataway, NJ). HEK-293 cells (catalog # CRL-1573) were obtained from the American Type Culture Collection (ATTC, Manassas, VA). Cells were grown in MEM medium supplemented with 10% heat-inactivated fetal bovine serum (Invitrogen, Carlsbad, CA) and 1% Penicillin/Streptomycin/L-Glutamine at 37 °C, 5% CO₂, and 95% humidity. For BRET assays, cells were seeded at a density of 40,000 cells/mL in culture medium in 6-well plates and allowed to attach and recover. Cells were transfected with C-terminally tagged PERK-NLuc and C-terminally tagged PERK-Halo using Lipofectamine LTX (Thermo, Waltham, MA) and allowed to express proteins overnight at 37 °C, 5% CO₂, and 95% humidity. Cells were then detached from culture dishes using 0.05% trypsin-EDTA, collected, and diluted in assay medium consisting of Opti-MEM® I Reduced Serum Medium supplemented with 4% FBS (Thermo) to 22,000 cells/mL. Cells were dispensed into 96-well cell culture plates and HaloTag® NanoBRET™ 618 Ligand (Promega) was added to a final concentration of 100 nM. Compound or DMSO was added to the cells, and plates were incubated 4 to 24 h at 37 °C, 5% CO₂, and 95% humidity. NanoBRET™ Nano-Glo® Substrate was added to the cells, and cells were shaken for 30 sec. Donor (460 nM) and acceptor (618) emissions were measured on a Synergy Neo2 Multi-Mode Reader (BioTek, Winooski, VT) within 10 min of substrate addition. Data was reported as BRET ratio (Acceptor/Donor).
- [0351] Compound 16 unexpectedly exhibited stimulation of the formation of PERK oligomers, with an EC₅₀ of 270 nM. A graph of the stimulation PERK oligomers induced by Compound 16 is shown in Figure 2.

Example 187. Stimulation of Multiple Myeloma UPR/ISR Signaling Pathway Proteins ATF4 and CHOP

- [0352] H929 multiple myeloma cells (catalog # CRL-9068) were obtained from the American Type Culture Collection (ATTC, Manassas, VA), grown in RPMI 1640 supplemented with 20% heat inactivated fetal bovine serum (Invitrogen, Carlsbad, CA), 1% Penicillin/Streptomycin/L-Glutamine and 0.05 mM 2-mercaptoethanol at 37 °C, 5% CO₂, and 95% humidity and maintained at 1-2 million cells per mL. Cells were seeded in 6 well plates at 4 million cells per well in 2 mL complete growth medium and treated with a serial dilution of test compounds for 4 h at 37 °C, 5% CO₂, and 95% humidity. At the end of the incubation, cells are washed with PBS supplemented with 1X Halt protease inhibitor, 1X Halt phosphatase inhibitor, 1X Sigma phosphatase inhibitor cocktail 2 and 1X EDTA and then lysed with M-PER Mammalian Protein Extraction Reagent supplemented with 3X of

the inhibitor mix as described above. Cell lysates were sonicated with water bath sonicator (Qsonica, Newtown, CT) and supernatants were boiled with SDS buffer and reducing agent. Western blot was performed to quantify ATF4, CHOP and beta-Actin (Cell Signaling Technology, Danvers, MA). Membranes were imaged with LI-COR Odyssey CLx Imaging System (LI-COR, Lincoln, NE).

- 5 **[0353]** Compound 16 unexpectedly exhibited stimulation of the PERK pathway in H929 multiple myeloma cells. A figure of the stimulation PERK downstream signaling proteins ATF4 and CHOP (Actin as a loading control) is shown in Figure 3. ATF4 is stimulated across a concentration range of 123 nM to 10 μ M. CHOP is stimulated across a concentration range of 1.1 to 10 μ M.

10 **Example 188. Stimulation of Multiple Myeloma UPR/ISR Target Genes Using quantitative RT-PCR**

- [0354]** H929 multiple myeloma cells (catalog #CRL-9068) multiple myeloma cells were obtained from the American Type Culture Collection (ATTC, Manassas, VA). Cells were grown in RPMI-1640 medium supplemented with 20% heat-inactivated fetal bovine serum (catalog #A3840002, ThermoFisher Scientific, Waltham, MA), 1% Penicillin/ Streptomycin /L-Glutamine (catalog #10378016, ThermoFisher Scientific, Waltham, MA), and 0.05 mM 2-mercaptoethanol (catalog #21985-023, ThermoFisher Scientific, Waltham, MA) at 37 °C, 5% CO₂, and 95% humidity. Cells were expanded until reaching 70-95% confluency at which point they were subcultured or harvested for assay use. Cells were seeded in 6-well culture plate at 3.0×10^6 cells per well in 2 mL complete growth medium and incubated with indicated concentrations of Compound 16 at 37 °C, 5% CO₂, and 95% humidity for 4 h or 24 h time. At the end of the incubation, cells were washed with PBS (Sigma) and RNA was extracted using RNeasy[®] Plus Kits (Qiagen, Germantown, MD). cDNA was synthesized using the High-Capacity cDNA Reverse Transcription Kit (Applied Biosciences, Beverly Hills, CA), and quantitative PCR was performed on a QuantStudio 3 (Applied Biosciences) using TaqMan Assays (Table A, Thermo) and TaqMan Fast Advanced Master Mix (Thermo) according to manufacturer's specifications.

Table A: TaqMan Probes	
Gene Of Interest	Assay ID
ATF4	Hs00909569_g1
DDIT3 (CHOP)	Hs00358796_g1
GPT2	Hs00370287_m1
GUSB (Endogenous Control)	Hs00939627_m1
PPP1R15A (GADD34)	Hs00169585_m1
VEGFA	Hs00900055_m1

[0355] Compound 16 unexpectedly induced the expression of PERK UPR/ISR target genes in H929 multiple myeloma cells. A figure illustrating the fold increases (compared to DMSO control) of ATF4, CHOP, GADD34, GPT2, and VEGFA is shown in Figure 4. Target genes were increased across a concentration range of 100 nM to 10 μ M.

5

Example 189. Stimulation of Multiple Myeloma Apoptosis Signaling Pathway

[0356] H929 multiple myeloma cells (catalog # CRL-9068) were obtained from the American Type Culture Collection (ATTC, Manassas, VA), grown in RPMI 1640 supplemented with 20% heat inactivated fetal bovine serum (Invitrogen, Carlsbad, CA), 1% Penicillin/Streptomycin/L-Glutamine and 0.05 mM 2-mercaptoethanol at 37 °C, 5% CO₂, and 95% humidity and maintained at 1-2 million cells per mL. RPMI8226 (catalog # CCL-155) were obtained from the American Type Culture Collection (ATTC, Manassas, VA), grown in RPMI 1640 supplemented with 10% heat inactivated fetal bovine serum (Invitrogen, Carlsbad, CA) and 1% Penicillin/Streptomycin/L-Glutamine at 37 °C, 5% CO₂, and 95% humidity and maintained at 0.1-1 million cells per mL. Cells were seeded in 6 well plates at 4 million cells per well in 2 mL complete growth medium and treated with a serial dilution of test compounds combined with either 100 nM Dexamethasone (Selleckchem, Houston, TX) or equal volume of DMSO for 24 h at 37 °C, 5% CO₂, and 95% humidity. At the end of the incubation, cells are washed with PBS supplemented with 1X Halt protease inhibitor, 1X Halt phosphatase inhibitor, 1X Sigma phosphatase inhibitor cocktail 2 and 1X EDTA and then lysed with M-PER Mammalian Protein Extraction Reagent supplemented with 3X of the inhibitor mix as described above. Cell lysates were sonicated with water bath sonicator (Qsonica, Newtown, CT) and supernatants were boiled with SDS buffer and reducing agent. Western blot was performed to quantify cleaved-Caspase 3, cleaved-Caspase 7, PARP, and beta-Actin (Cell Signaling Technology, Danvers, MA). Membranes were imaged with LI-COR Odyssey CLx Imaging System (LI-COR, Lincoln, NE).

25

[0357] Compound 16 unexpectedly induced the expression of proapoptotic proteins in H929 multiple myeloma cells. A figure illustrating cleaved PARP, cleaved Caspase 7, and cleaved Caspase 3 is shown in Figure 5. Apoptotic proteins were increased across a concentration range of 123 nM to 10 mM.

30

Example 190. Inhibition of Multiple Myeloma and B-Cell Lymphoma Cell Proliferation

[0358] H929, RPMI8226, GA-10, and DoHH-2 cells (catalog #CRL-9068) were obtained from the American Type Culture Collection (ATTC, Manassas, VA). H929 Cells were maintained in RPMI-

1640 medium supplemented with 20% heat-inactivated fetal bovine serum (catalog #A3840002, ThermoFisher Scientific, Waltham, MA), 1% Penicillin/Streptomycin /L-Glutamine (catalog #10378016, ThermoFisher Scientific, Waltham, MA), and 0.05 mM 2-mercaptoethanol (catalog #21985-023, ThermoFisher Scientific, Waltham, MA). RPMI8226, GA-10, DoHH-2 were maintained in RPMI-1640 medium supplemented with 10% heat-inactivated fetal bovine serum (catalog #A3840002, ThermoFisher Scientific, Waltham, MA) and 1% Penicillin/Streptomycin/L-Glutamine (catalog #10378016, ThermoFisher Scientific, Waltham, MA). All cells were grown at 37 °C, 5% CO₂, and 95% humidity. Cells were expanded until reaching one million five hundred thousand cells per mL at which time they were subcultured or harvested for assay use.

- 10 **[0359]** For cell proliferation assay appropriate number of cells (Forty thousand cells for H929; Twenty thousand cells for RPMI8226, and GA-10; Eight thousand cells for DoHH-2) were seeded per well in 200 µL in respective medium were dispensed into a 96-well black clear bottom plate. A serial dilution of test compound was added in triplicate and plates were incubated for 72 or 120 h at 37 °C, 5% CO₂, and 95% humidity. Several standard of care agents clinically used to treat multiple myeloma were used for combination studies (lenalidomide (catalog #S1029, Selleckchem, Houston, TX), bortezomib (catalog #S1013, Selleckchem, Houston, TX), dexamethasone (catalog #S1322, Selleckchem, Houston, TX), ibrutinib (Pharmacyclics, Sunnyvale, CA)). At the end of the incubation for H929, RPMI8226, and GA-10, 40 µL of a 440 mM solution of resazurin (Sigma, St. Louis, MO) in PBS was added to each well of the plate and plates were incubated for an additional 7 h at 37 °C, 5% CO₂, and 95% humidity. Plates were read on a Synergy2 or equivalent reader (Biotek, Winooski VT) using an excitation of 540 nm and an emission of 600 nm. At the end of the incubation of DoHH-2, cell viability was determined using CellTiter-Glo® assay (Promega, Madison, WI). Luminescence was measured using EnVision MultiLabel Reader (PerkinElmer, Waltham, MA). Data was analyzed using GraphPad Prism software (GraphPad, San Diego, CA) to calculate IC₅₀ values.

[0360] Compound 16, in combination with standard of care (SOC) agents that treat multiple myeloma or B cell lymphomas, exhibits additivity or synergy for inhibition of cell proliferation. Representative graphs are shown in Figure 6.

30 **Example 191. CCRF-CEM Xenograft Pharmacokinetic/Pharmacodynamic (PK/PD) model**

[0361] The CCRF-CEM xenograft model was performed in compliance with all the laws, regulations and guidelines of the National Institutes of Health (NIH) and with the approval of the Animal Care and Use Committee of Labcorp (Ann Arbor, MI), an AAALAC accredited facility.

Food and water were provided ad libitum. All mice were observed for clinical signs at least once daily. Female Envigo C.B-17 SCID (6-7 weeks old) were inoculated subcutaneously just below the right high axilla with ten million cells in Dulbecco's Phosphate Buffered Saline, using a 27-gauge needle and syringe. When tumor burdens reached 200 mm³ on average on day 22, mice were

5 randomly assigned into groups such that the mean tumor burden for all groups was within 10% of the overall mean tumor burden for the study population. Groups were treated on days 23-24 as follows: on day 23 vehicle control (dosed orally and IP to mimic combination group) (n=9); ASNase (Abcam, Cambridge, UK) dosed IP at 1000 U/kg/day (n=9). On day 24 vehicle control dosed orally (dosed orally and IP to mimic combination group) (n=9); Compound 16 dosed orally at 50 mg/kg (n=10)

10 and ASNase (Abcam, Cambridge, UK) dosed IP at 1000 U/kg (n=9) 2 h prior to sample harvest; Compound 16 dosed orally at 25 mg/kg (n=10) and ASNase (Abcam, Cambridge, UK) dosed IP at 1000 U/kg (n=9) 2 h prior to sample harvest at 2, 6, and 10 h post Compound 16 dose. Blood samples were collected in K2EDTA tubes and processed into plasma, snap frozen in liquid nitrogen then stored at -80 °C. Plasma samples were subjected to pharmacokinetic analysis using liquid

15 chromatography coupled with tandem mass spectrometry analysis (Cayman Chemical, Ann Arbor, MI). Tumors and pancreatic tissues were harvested and powdered over liquid nitrogen in covaris bags and stored at -80 °C. Fr tissue sample processing roughly 30 mg of tumor or pancreatic tissue was lysed in mPER lysis buffer (Thermo Fisher Scientific, Waltham, MA) supplemented with 3X Halt protease inhibitor, 3X Halt phosphatase inhibitor, 3X Sigma phosphatase inhibitor cocktail 2 and 3X EDTA on ice then homogenized using Bead Ruptor 96 (Omni, Kennesaw, GA). Samples

20 were then centrifuged at 21,000 g for 10 min at 4 °C. Cleared lysates were then transferred to ice-chilled conical bottom 96-well plates, sealed then stored at -80 °C. Next day, samples were thawed on ice followed by centrifugation at 3739 g for 10 min at 4 °C. Cleared lysates were then transferred to ice-chilled round bottom 96-well plates. Protein concentrations were determined using BCA

25 protein assay kit (Thermo Fisher Scientific, Waltham, MA). Lysates were normalized to 10 µg/µl prior to boiling in 4X SDS-sample buffer and reducing agent. Samples were resolved using SDS-PAGE then analyzed using Western blot to quantify phospho-GCN2 (Thr899) (Abcam, Cambridge, UK), total GCN2, ATF4 and beta-Actin (Cell Signaling Technology, Danvers, MA). Membranes are imaged with LI-COR Odyssey CLx Imaging System (LI-COR, Lincoln, NE). Data is analyzed using

30 GraphPad Prism software (GraphPad, San Diego, CA) to calculate % inhibition.

[0362] Compound 16, in combination with ASNase, inhibits GCN2-mediated ATF4 levels in a CCRF-CEM leukemia xenograft model. As shown in Figure 7, Compound 16 inhibited ATF4 levels by 81 to 98% compared to vehicle control when dosed at 50 mg/kg orally, and inhibited ATF4 levels by 69 to 92% compared to vehicle control when dosed at 25 mg/kg orally. Corresponding

plasma levels of Compound 16 were determined at the PD time points of 2, 6, and 10 hours post dose.

Example 192. MV-4-11 xenograft efficacy model

- 5 **[0363]** The MV-4-11 acute myeloid leukemia xenograft model was performed in compliance with all the laws, regulations, and guidelines of the National Institutes of Health (NIH) and with the approval of the Animal Care and Use Committee of Crown Bioscience (Taicang, China), an AAALAC accredited facility. Food and water were provided ad libitum. All mice were observed for clinical signs at least once daily. Female NOD/SCID (6-9 weeks old; Vital River Laboratories
- 10 Research Models and Services (Beijing, China)) were inoculated subcutaneously right front flank region with five million cells in Dulbecco's Phosphate Buffered Saline:Matrigel (1:1), using a 27-gauge needle and syringe. When tumor burdens reached 150 mm³ on average on day 7, mice were randomly assigned into groups such that the mean tumor burden for all groups was within 10% of the overall mean tumor burden for the study population. Groups were treated on days 7-21 as follows:
- 15 vehicle control (dosed orally and IP to mimic combination group (n=10); Compound 16 dosed orally at 25 mg/kg/day (n=10); Leunase (Kyowa Kirin, Japan) dosed IP at 1000 U/kg/day (n=10); Leunase (Kyowa Kirin, Japan) dosed IP at 1000 U/kg/day (n=10) and Compound 16 dosed orally at 25 mg/kg/day (n=10). Tumor volume and body weight were measured three times per week. Tumor burden (mg) was estimated from caliper measurements by the formula: tumor burden (mg=mm³) =
- 20 (length x width²)/2.
- [0364]** Compound 16, in combination with ASNase, inhibits MV-4-11 tumor growth when dosed orally. As shown in Figure 8, Compound 16 induced tumor regression when dosed at 25 mg/kg/day for 14 days in combination with Leunase dosed at 1000U/kg.

25 **EQUIVALENTS**

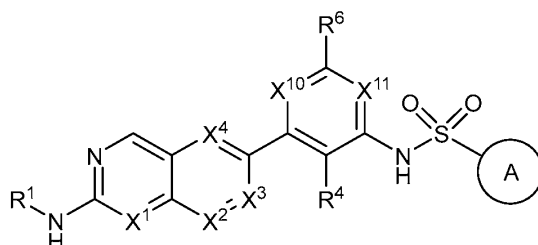
- [0365]** While specific embodiments have been discussed, the above specification is illustrative and not restrictive. Many variations of the embodiments will become apparent to those skilled in the art upon review of this specification. The full scope of what is disclosed should be determined by reference to the claims, along with their full scope of equivalents, and the specification, along with
- 30 such variations.
- [0366]** 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:



5

Formula I

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

X¹ is selected from the group consisting of CH and N;

X² and X³ are each independently selected from the group consisting of N, CH, C-O-L²-E²,
10 C-L²-E², and C-N(R²)-L²-E²,

provided that X² is selected from the group consisting of CH and N, and X³ is selected from the group consisting of CH, C-O-L²-E², C-L²-E², and C-N(R²)-L²-E²;

provided that X² is selected from the group consisting of CH, C-O-L²-E², C-L²-E², and C-N(R²)-L²-E² and X³ is selected from the group consisting of CH and N;

15 X⁴ is selected from the group consisting of CR³ and N;

X¹⁰ is selected from the group consisting of CR⁵ and N;

X¹¹ is selected from the group consisting of CR⁷ and N;

R¹ is selected from the group consisting of H, alkyl, (C=O)R¹³, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

20 wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent
25 independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

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

R³ is selected from the group consisting of H, alkyl, and halogen;

R⁴ and R⁵ are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R⁶ and R⁷ are each independently selected from the group consisting of halogen, H, and alkyl;

5 R¹³ is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and
10 heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

15 A is selected from the group consisting of a substituted 5-membered heteroaryl, a substituted 6-membered heteroaryl, a pyridone, and a substituted aryl ring;

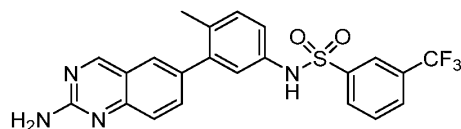
L² is selected from the group consisting of a direct bond and alkyl, wherein alkyl is optionally substituted with (E²¹)_p;

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

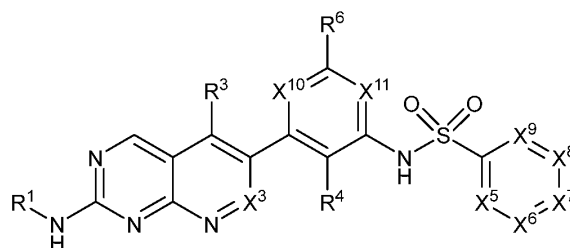
wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

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

each p is independently 0, 1 or 2; provided that the compound is not:



2. A compound represented by Formula I-A:



Formula I-A

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

- 5 X^3 is selected from the group consisting of CH, C-O-L²-E², C-L²-E², and C-N(R²)-L²-E²;
 X^5 is selected from the group consisting of CR⁸ and N;
 X^6 is selected from the group consisting of CR⁹ and N;
 X^7 is selected from the group consisting of CR¹⁰ and N;
 X^8 is selected from the group consisting of CR¹¹ and N;
 10 X^9 is selected from the group consisting of CR⁸ and N,
 provided that not more than three of X^5 , X^6 , X^7 , X^8 , and X^9 is N;
 X^{10} is selected from the group consisting of CR⁵ and N;
 X^{11} is selected from the group consisting of CR⁷ and N;
 R¹ is selected from the group consisting of H, alkyl, (C=O)R¹³, cycloalkyl, alkoxyalkyl,
 15 cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,
 wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of
 a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy,
 alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and
 heterocyclyl, and
 20 wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent
 independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine,
 aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl,
 and sulfonyl;
 R² is selected from the group consisting of H and alkyl;
 25 R³ is selected from the group consisting of H, alkyl, and halogen;
 R⁴ and R⁵ are each independently selected from the group consisting of halogen, H, alkoxy,
 alkylamino, amino, alkyl, haloalkyl and CN;
 R⁶ and R⁷ are each independently selected from the group consisting of halogen, H, and alkyl;

R⁸ is selected from the group consisting of alkoxy, alkylamino, cycloalkoxy, cycloalkylamino, halogen, H, alkyl, haloalkoxy, haloalkyl, amide, alkoxycarbonyl, hydroxyalkyl, hydroxy, and CN;

5 R⁹, R¹⁰ and R¹¹ are each independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl;

R¹³ is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,
10 wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent
15 independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

L² is selected from the group consisting of a direct bond and C₁-C₆alkyl, wherein C₁-C₆alkyl is optionally substituted with (E²¹)_p;

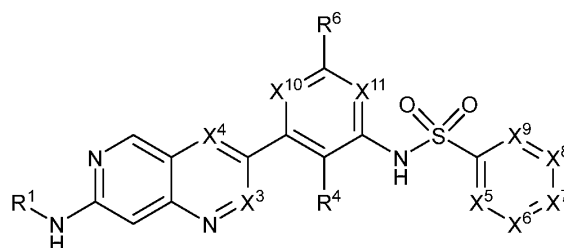
20 E² is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

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

each p is independently 0, 1 or 2.

3. A compound represented by Formula I-B:



Formula I-B

- 5 or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:
- X^3 is selected from the group consisting of CH, C-O-L²-E², C-L²-E², and C-N(R²)-L²-E²;
- X^4 is selected from the group consisting of CR³ and N;
- X^5 is selected from the group consisting of CR⁸ and N;
- X^6 is selected from the group consisting of CR⁹ and N;
- 10 X^7 is selected from the group consisting of CR¹⁰ and N;
- X^8 is selected from the group consisting of CR¹¹ and N;
- X^9 is selected from the group consisting of CR⁸ and N,
- provided that not more than three of X⁵, X⁶, X⁷, X⁸, and X⁹ is N;
- X^{10} is selected from the group consisting of CR⁵ and N;
- 15 X^{11} is selected from the group consisting of CR⁷ and N;
- R¹ is selected from the group consisting of H, alkyl, (C=O)R¹³, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,
- wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of
- a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy,
- 20 alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and
- wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl,
- 25 and sulfonyl;
- R² is selected from the group consisting of H and alkyl;
- R³ is selected from the group consisting of H, alkyl, and halogen;

R⁴ and R⁵ are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R⁶ and R⁷ are each independently selected from the group consisting of halogen, H, and alkyl;

R⁸ is selected from the group consisting of alkoxy, alkylamino, cycloalkoxy, cycloalkylamino, halogen, H, alkyl, haloalkoxy, haloalkyl, amide, alkoxycarbonyl, hydroxyalkyl, hydroxy, and CN;

R⁹, R¹⁰ and R¹¹ are each independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl;

R¹³ is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

L² is selected from the group consisting of a direct bond and C₁-C₆alkyl, wherein C₁-C₆alkyl is optionally substituted with (E²¹)_p;

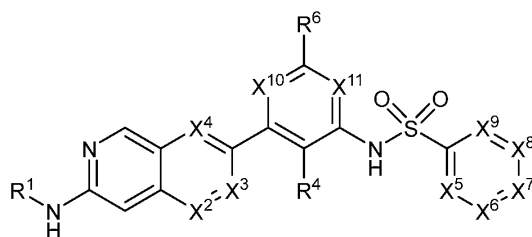
E² is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent 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, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and

each p is independently 0, 1 or 2.

4. A compound represented by Formula I-C:



Formula I-C

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

5 X² and X³ are each independently selected from the group consisting of N, CH, C-O-L²-E², C-L²-E², and C-N(R²)-L²-E²,

provided that X² is selected from the group consisting of CH and N, and X³ is selected from the group consisting of CH, C-O-L²-E², C-L²-E², and C-N(R²)-L²-E²,

10 provided that X² is selected from the group consisting of CH, C-O-L²-E², C-L²-E², and C-N(R²)-L²-E² and X³ is selected from the group consisting of CH and N;

X⁴ is selected from the group consisting of CR³ and N;

X⁵ is selected from the group consisting of CR⁸ and N;

X⁶ is selected from the group consisting of CR⁹ and N;

X⁷ is selected from the group consisting of CR¹⁰ and N;

15 X⁸ is selected from the group consisting of CR¹¹ and N;

X⁹ is selected from the group consisting of CR⁸ and N,

provided that not more than three of X⁵, X⁶, X⁷, X⁸, and X⁹ is N;

X¹⁰ is selected from the group consisting of CR⁵ and N;

X¹¹ is selected from the group consisting of CR⁷ and N;

20 R¹ is selected from the group consisting of H, alkyl, (C=O)R¹³, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and
25 heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine,

aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

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

R^3 is selected from the group consisting of H, alkyl, and halogen;

5 R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 and R^7 are each independently selected from the group consisting of halogen, H, and alkyl;

R^8 is selected from the group consisting of alkoxy, alkylamino, cycloalkoxy, cycloalkylamino, halogen, H, alkyl, haloalkoxy, haloalkyl, amide, alkoxycarbonyl, hydroxyalkyl, hydroxy, and CN;

10 R^9 , R^{10} and R^{11} are each independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl;

15 R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

20 wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

25 L^2 is selected from the group consisting of a direct bond and C₁-C₆alkyl, wherein C₁-C₆alkyl is optionally substituted with (E²¹)_p;

E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

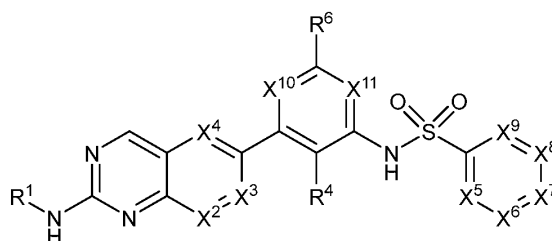
30 wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21} , at each occurrence, is independently selected from the group consisting of H, alkyl,

cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and

each p is independently 0, 1 or 2.

- 5 5. A compound represented by Formula I-D:



Formula I-D

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

- 10 X² and X³ are each independently selected from the group consisting of N, CH, C-O-L²-E², C-L²-E², and C-N(R²)-L²-E²,

provided that X² is selected from the group consisting of CH and N, and X³ is selected from the group consisting of CH, C-O-L²-E², C-L²-E², and C-N(R²)-L²-E²;

provided that X² is selected from the group consisting of CH, C-O-L²-E², C-L²-E², and C-N(R²)-L²-E² and X³ is selected from the group consisting of CH and N;

- 15 X⁴ is selected from the group consisting of CR³ and N;

X⁵ is selected from the group consisting of CR⁸ and N;

X⁶ is selected from the group consisting of CR⁹ and N;

X⁷ is selected from the group consisting of CR¹⁰ and N;

X⁸ is selected from the group consisting of CR¹¹ and N;

- 20 X⁹ is selected from the group consisting of CR⁸ and N,

provided that not more than three of X⁵, X⁶, X⁷, X⁸, and X⁹ is N;

X¹⁰ is selected from the group consisting of CR⁵ and N;

X¹¹ is selected from the group consisting of CR⁷ and N;

- 25 R¹ is selected from the group consisting of H, alkyl, (C=O)R¹³, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy,

alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

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

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 and R^7 are each independently selected from the group consisting of halogen, H, and alkyl;

R^8 is selected from the group consisting of alkoxy, alkylamino, cycloalkoxy, cycloalkylamino, halogen, H, alkyl, haloalkoxy, haloalkyl, amide, alkoxycarbonyl, hydroxyalkyl, hydroxy, and CN;

R^9 , R^{10} and R^{11} are each independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

L^2 is selected from the group consisting of a direct bond and C₁-C₆alkyl, wherein C₁-C₆alkyl is optionally substituted with (E²¹)_p;

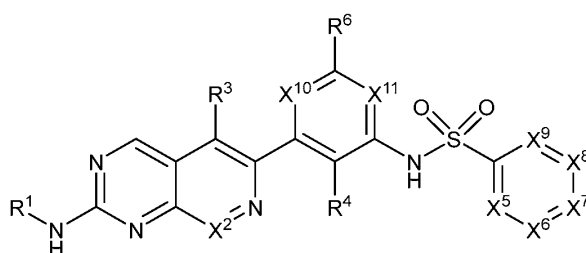
E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent 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, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and

each p is independently 0, 1 or 2.

6. A compound represented by Formula I-E:



Formula I-E

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

X^2 is selected from the group consisting of CH, C-O-L²-E², C-L²-E², and C-N(R²)-L²-E²;

X^5 is selected from the group consisting of CR⁸ and N;

X^6 is selected from the group consisting of CR⁹ and N;

X^7 is selected from the group consisting of CR¹⁰ and N;

X^8 is selected from the group consisting of CR¹¹ and N;

X^9 is selected from the group consisting of CR⁸ and N,

provided that not more than three of X⁵, X⁶, X⁷, X⁸, and X⁹ is N;

X^{10} is selected from the group consisting of CR⁵ and N;

X^{11} is selected from the group consisting of CR⁷ and N;

R¹ is selected from the group consisting of H, alkyl, (C=O)R¹³, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

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

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 and R^7 are each independently selected from the group consisting of halogen, H, and alkyl;

10 R^8 is selected from the group consisting of alkoxy, alkylamino, cycloalkoxy, cycloalkylamino, halogen, H, alkyl, haloalkoxy, haloalkyl, amide, alkoxycarbonyl, hydroxyalkyl, hydroxy, and CN;

R^9 , R^{10} and R^{11} are each independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl,

15 aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

20 wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

25 wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

L^2 is selected from the group consisting of a direct bond and C₁-C₆alkyl, wherein C₁-C₆alkyl is optionally substituted with (E²¹)_p;

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

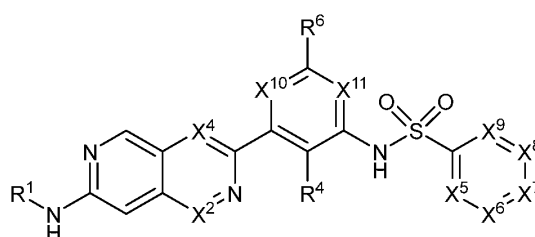
wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21} , at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and

each p is independently 0, 1 or 2.

5

7. A compound represented by Formula I-F:



Formula I-F

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

10 X^2 is selected from the group consisting of CH, C-O-L²-E², C-L²-E², and C-N(R²)-L²-E²;

X^4 is selected from the group consisting of CR³ and N;

X^5 is selected from the group consisting of CR⁸ and N;

X^6 is selected from the group consisting of CR⁹ and N;

X^7 is selected from the group consisting of CR¹⁰ and N;

15 X^8 is selected from the group consisting of CR¹¹ and N;

X^9 is selected from the group consisting of CR⁸ and N,

provided that not more than three of X⁵, X⁶, X⁷, X⁸, and X⁹ is N;

X^{10} is selected from the group consisting of CR⁵ and N;

X^{11} is selected from the group consisting of CR⁷ and N;

20 R^1 is selected from the group consisting of H, alkyl, (C=O)R¹³, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and
25 heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine,

aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

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

R^3 is selected from the group consisting of H, alkyl, and halogen;

5 R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 and R^7 are each independently selected from the group consisting of halogen, H, and alkyl;

R^8 is selected from the group consisting of alkoxy, alkylamino, cycloalkoxy, cycloalkylamino, halogen, H, alkyl, haloalkoxy, haloalkyl, amide, alkoxycarbonyl, hydroxyalkyl, hydroxy, and CN;

10 R^9 , R^{10} and R^{11} are each independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl;

15 R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

20 wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

25 L^2 is selected from the group consisting of a direct bond and C₁-C₆alkyl, wherein C₁-C₆alkyl is optionally substituted with (E²¹)_p;

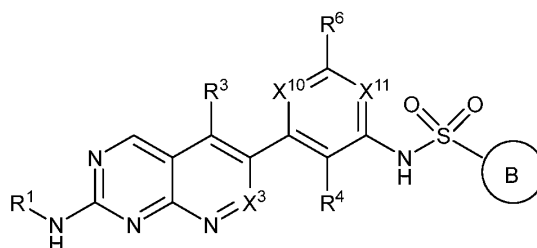
E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

30 wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent 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, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and
each p is independently 0, 1 or 2.

- 5 8. A compound represented by Formula I-G:



Formula I-G

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

- X^3 is selected from the group consisting of CH, C-O-L²-E², C-L²-E², and C-N(R²)-L²-E²;
10 X^{10} is selected from the group consisting of CR⁵ and N;
 X^{11} is selected from the group consisting of CR⁷ and N;
 R^1 is selected from the group consisting of H, alkyl, (C=O)R¹³, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of
15 a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and
wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine,
20 aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;
 R^2 is selected from the group consisting of H and alkyl;
 R^3 is selected from the group consisting of H, alkyl, and halogen;
 R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy,
25 alkylamino, amino, alkyl, haloalkyl and CN;
 R^6 and R^7 are each independently selected from the group consisting of halogen, H, and alkyl;
 R^{12} is individually and independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl,

aminocarbonyl, acylamino, halogen, cyano, haloalkyl, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, and heterocyclalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclalkyl, aryl, heteroaryl, and heteroarylalkyl,

5 wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

10 wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

B is selected from the group consisting of a five-membered heteroaryl, a six-membered heteroaryl, and a pyridone, wherein the five- or six-membered heteroaryl ring, or the pyridone is 15 optionally substituted by R^{12} at each substitutable position;

L^2 is selected from the group consisting of a direct bond and C_1 - C_6 alkyl, wherein C_1 - C_6 alkyl is optionally substituted with $(E^{21})_p$;

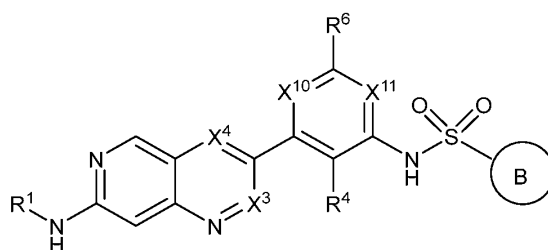
E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

20 wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent 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, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

25 and each p is independently 0, 1 or 2.

9. A compound represented by Formula I-H:



Formula I-H

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

X^3 is selected from the group consisting of CH, C-O-L²-E², C-L²-E², and C-N(R²)-L²-E²;

X^4 is selected from the group consisting of CR³ and N;

5 X^{10} is selected from the group consisting of CR⁵ and N;

X^{11} is selected from the group consisting of CR⁷ and N;

R^1 is selected from the group consisting of H, alkyl, (C=O)R¹³, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of
10 a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine,
15 aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

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

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;
20

R^6 and R^7 are each independently selected from the group consisting of halogen, H, and alkyl;

R^{12} is individually and independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, haloalkyl, alkoxy, alkylamino, H, cyanoalkyl, alkyl,
25 cycloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, and heterocyclylalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,
wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of
a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy,
30 alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine,

aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

B is selected from the group consisting of a five-membered heteroaryl, a six-membered heteroaryl, and a pyridone, wherein the five- or six-membered heteroaryl ring, or the pyridone, is optionally substituted by R^{12} at each substitutable position;

L^2 is selected from the group consisting of a direct bond and C_1 - C_6 alkyl, wherein C_1 - C_6 alkyl is optionally substituted with $(E^{21})_p$;

E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

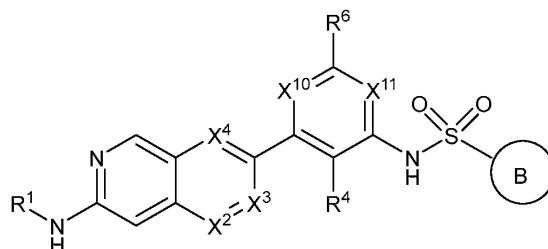
wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21} , at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

and

each p is independently 0, 1 or 2.

10. A compound represented by Formula I-J:



Formula I-J

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

X^2 and X^3 are each independently selected from the group consisting of N, CH, $C-O-L^2-E^2$, $C-L^2-E^2$, and $C-N(R^2)-L^2-E^2$,

provided that X^2 is selected from the group consisting of CH and N, and X^3 is selected from the group consisting of CH, $C-O-L^2-E^2$, $C-L^2-E^2$, and $C-N(R^2)-L^2-E^2$;

provided that X^2 is selected from the group consisting of CH, $C-O-L^2-E^2$, $C-L^2-E^2$, and $C-N(R^2)-L^2-E^2$ and X^3 is selected from the group consisting of CH and N;

X^4 is selected from the group consisting of CR^3 and N;

X¹⁰ is selected from the group consisting of CR⁵ and N;

X¹¹ is selected from the group consisting of CR⁷ and N;

R¹ is selected from the group consisting of H, alkyl, (C=O)R¹³, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclalkyl, aryl, heteroaryl, and heteroarylalkyl,

5 wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

10 wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

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

R³ is selected from the group consisting of H, alkyl, and halogen;

15 R⁴ and R⁵ are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R⁶ and R⁷ are each independently selected from the group consisting of halogen, H, and alkyl;

20 R¹² is individually and independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, haloalkyl, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, and heterocyclalkyl;

R¹³ is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclalkyl, aryl, heteroaryl, and heteroarylalkyl,

25 wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

30 wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

B is selected from the group consisting of a five-membered heteroaryl, a six-membered heteroaryl, and a pyridone, wherein the five- or six-membered heteroaryl ring, or the pyridone, is optionally substituted by R¹² at each substitutable position;

L^2 is selected from the group consisting of a direct bond and C_1 - C_6 alkyl, wherein C_1 - C_6 alkyl is optionally substituted with $(E^{21})_p$;

E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

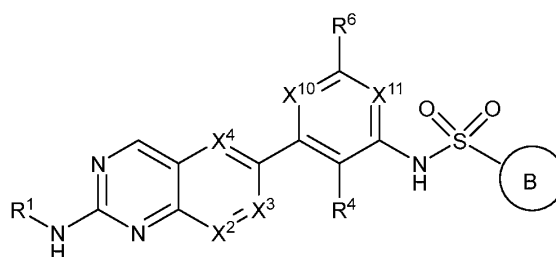
5 wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21} , at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

10 and

each p is independently 0, 1 or 2.

11. A compound represented by Formula I-K:



15

Formula I-K

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

X^2 and X^3 are each independently selected from the group consisting of N, CH, $C-O-L^2-E^2$, $C-L^2-E^2$, and $C-N(R^2)-L^2-E^2$,

20 provided that X^2 is selected from the group consisting of CH and N, and X^3 is selected from the group consisting of CH, $C-O-L^2-E^2$, $C-L^2-E^2$, and $C-N(R^2)-L^2-E^2$;

provided that X^2 is selected from the group consisting of CH, $C-O-L^2-E^2$, $C-L^2-E^2$, and $C-N(R^2)-L^2-E^2$ and X^3 is selected from the group consisting of CH and N;

X^4 is selected from the group consisting of CR^3 and N;

X^{10} is selected from the group consisting of CR^5 and N;

25 X^{11} is selected from the group consisting of CR^7 and N;

R^1 is selected from the group consisting of H, alkyl, $(C=O)R^{13}$, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

5 wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

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

10 R^3 is selected from the group consisting of H, alkyl, and halogen;

R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 and R^7 are each independently selected from the group consisting of halogen, H, and alkyl;

15 R^{12} is individually and independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, haloalkyl, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, and heterocyclylalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

20 wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

25 wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

B is selected from the group consisting of a five-membered heteroaryl, a six-membered heteroaryl, and a pyridone, wherein the five- or six-membered heteroaryl ring, or the pyridone, is
30 optionally substituted by R^{12} at each substitutable position;

L^2 is selected from the group consisting of a direct bond and C₁-C₆alkyl, wherein C₁-C₆alkyl is optionally substituted with (E²¹)_p;

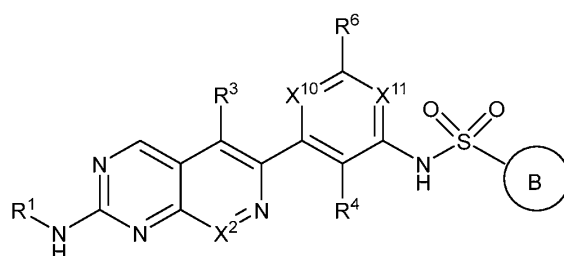
E² is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent 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, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and

each p is independently 0, 1 or 2.

12. A compound represented by Formula I-L:



Formula I-L

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

X^2 is selected from the group consisting of CH, C-O-L²-E², C-L²-E², and C-N(R²)-L²-E²;

X^{10} is selected from the group consisting of CR⁵ and N;

X^{11} is selected from the group consisting of CR⁷ and N;

R^1 is selected from the group consisting of H, alkyl, (C=O)R¹³, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

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

R^3 is selected from the group consisting of H, alkyl, and halogen;

R⁴ and R⁵ are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R⁶ and R⁷ are each independently selected from the group consisting of halogen, H, and alkyl;

R¹² is individually and independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxyalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, haloalkyl, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, and heterocyclalkyl;

R¹³ is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

B is selected from the group consisting of a five-membered heteroaryl, a six-membered heteroaryl, and a pyridone, wherein the five- or six-membered heteroaryl ring, or the pyridone, is optionally substituted by R¹² at each substitutable position;

L² is selected from the group consisting of a direct bond and C₁-C₆alkyl, wherein C₁-C₆alkyl is optionally substituted with (E²¹)_p;

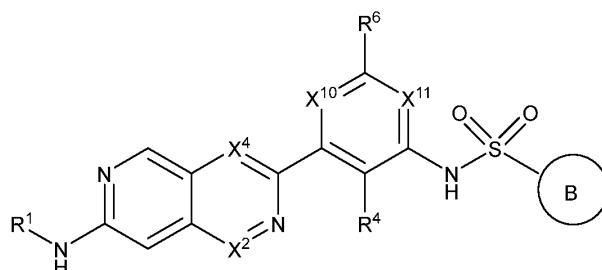
E² is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent 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, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and

each p is independently 0, 1 or 2.

13. A compound represented by Formula I-M:



Formula I-M

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

- 5 X^2 is selected from the group consisting of CH, C-O-L²-E², C-L²-E², and C-N(R²)-L²-E²;
 X^4 is selected from the group consisting of CR³ and N;
 X^{10} is selected from the group consisting of CR⁵ and N;
 X^{11} is selected from the group consisting of CR⁷ and N;
 R¹ is selected from the group consisting of H, alkyl, (C=O)R¹³, cycloalkyl, alkoxyalkyl,
 10 cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,
 wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of
 a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy,
 alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and
 heterocyclyl, and
 15 wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent
 independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine,
 aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl,
 and sulfonyl;
 R² is selected from the group consisting of H and alkyl;
 20 R³ is selected from the group consisting of H, alkyl, and halogen;
 R⁴ and R⁵ are each independently selected from the group consisting of halogen, H, alkoxy,
 alkylamino, amino, alkyl, haloalkyl and CN;
 R⁶ and R⁷ are each independently selected from the group consisting of halogen, H, and alkyl;
 R¹² is individually and independently selected from the group consisting of hydroxyalkyl,
 25 hydroxycycloalkyl, alkoxyalkyl, alkoxyalkyl, amino, aminoalkyl, aminocycloalkyl,
 aminocarbonyl, acylamino, halogen, cyano, haloalkyl, alkoxy, alkylamino, H, cyanoalkyl, alkyl,
 cycloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, and heterocyclylalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

B is selected from the group consisting of a five-membered heteroaryl, a six-membered heteroaryl, and a pyridone, wherein the five- or six-membered heteroaryl ring, or the pyridone, is optionally substituted by R^{12} at each substitutable position;

L^2 is selected from the group consisting of a direct bond and C_1 - C_6 alkyl, wherein C_1 - C_6 alkyl is optionally substituted with $(E^{21})_p$;

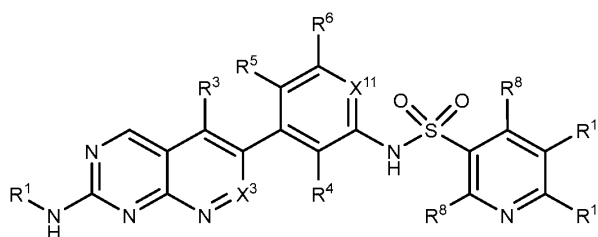
E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent 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, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and

each p is independently 0, 1 or 2.

14. A compound represented by Formula I-N:



Formula I-N

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

X^3 is selected from the group consisting of CH, C-O-L²-E², C-L²-E², and C-N(R²)-L²-E²;

X^{11} is selected from the group consisting of CR⁷ and N;

- 5 R^1 is selected from the group consisting of H, alkyl, (C=O)R¹³, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and
- 10 heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

- 15 R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 is selected from the group consisting of halogen, H, and alkyl;

- 20 R^7 is selected from the group consisting of H and F; R^8 is selected from the group consisting of alkoxy, alkylamino, cycloalkoxy, cycloalkylamino, halogen, H, alkyl, haloalkoxy, haloalkyl, amide, alkoxycarbonyl, hydroxyalkyl, hydroxycycloalkyl, hydroxy, and CN;

R^{10} and R^{11} are each independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl,

- 25 aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl; R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

- 30 wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine,

aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

L^2 is selected from the group consisting of a direct bond and C_1 - C_6 alkyl, wherein C_1 - C_6 alkyl is optionally substituted with $(E^{21})_p$;

5 E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

10 E^{21} , at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and

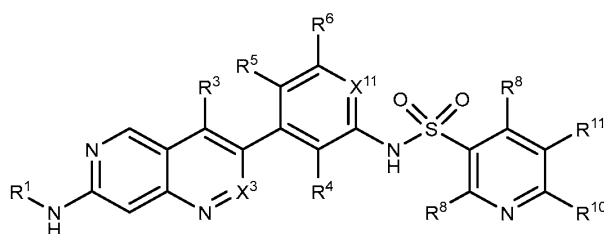
each p is independently 0, 1 or 2.

15 The compound of claim 14, wherein X^{11} is CR^7 .

15

16 The compound of claim 14, wherein X^{11} is N.

17 A compound represented by Formula I-O:



20

Formula I-O

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

X^3 is selected from the group consisting of CH, $C-O-L^2-E^2$, $C-L^2-E^2$, and $C-N(R^2)-L^2-E^2$;

X^{11} is selected from the group consisting of CR^7 and N;

25 R^1 is selected from the group consisting of H, alkyl, $(C=O)R^{13}$, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy,

alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl; R^3 is selected from the group consisting of H, alkyl, and halogen;

R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 is selected from the group consisting of halogen, H, and alkyl;

R^7 is selected from the group consisting of H and F;

R^8 is selected from the group consisting of alkoxy, alkylamino, cycloalkoxy, cycloalkylamino, halogen, H, alkyl, haloalkoxy, haloalkyl, amide, alkoxycarbonyl, hydroxyalkyl, hydroxycycloalkyl, hydroxy, and CN;

R^{10} and R^{11} are each independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl; R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

L^2 is selected from the group consisting of a direct bond and C₁-C₆alkyl, wherein C₁-C₆alkyl is optionally substituted with (E²¹)_p;

E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

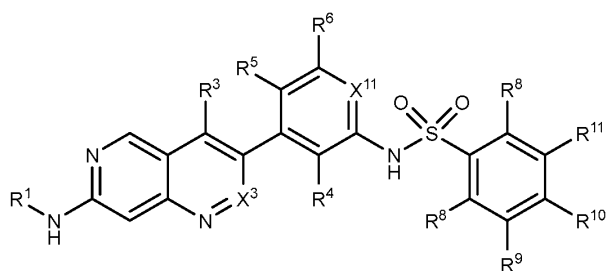
E^{21} , at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and

each p is independently 0, 1 or 2.

18. The compound of claim 17, wherein X^{11} is CR^7 .

10 19. The compound of claim 17, wherein X^{11} is N.

20. A compound represented by Formula I-P:



15 Formula I-P

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

X^3 is selected from the group consisting of CH, $C-O-L^2-E^2$, $C-L^2-E^2$, and $C-N(R^2)-L^2-E^2$;

X^{11} is selected from the group consisting of CR^7 and N;

R^1 is selected from the group consisting of H, alkyl, $(C=O)R^{13}$, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

25 wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

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

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

5 R^6 is selected from the group consisting of halogen, H, and alkyl;

R^7 is selected from the group consisting of H and F;

R^8 is selected from the group consisting of alkoxy, alkylamino, cycloalkoxy, cycloalkylamino, halogen, H, alkyl, haloalkoxy, haloalkyl, amide, alkoxycarbonyl, hydroxyalkyl, hydroxycycloalkyl, hydroxy, and CN;

10 R^9 , R^{10} , and R^{11} are each independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

20 wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

L^2 is selected from the group consisting of a direct bond and C_1 - C_6 alkyl, wherein C_1 - C_6 alkyl is optionally substituted with $(E^{21})_p$;

E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

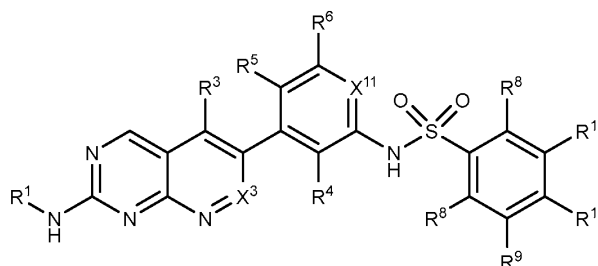
30 E^{21} , at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and

each p is independently 0, 1 or 2.

21. The compound of claim 20, wherein X^{11} is CR^7 .

22. The compound of claim 20, wherein X^{11} is N.

5 23. A compound represented by Formula I-Q:



Formula I-Q

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

10 X^3 is selected from the group consisting of CH, C-O-L²-E², C-L²-E², and C-N(R²)-L²-E²;

X^{11} is selected from the group consisting of CR^7 and N;

R^1 is selected from the group consisting of H, alkyl, (C=O)R¹³, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

15 wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

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

R^3 is selected from the group consisting of H, alkyl, and halogen;

20 R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 is selected from the group consisting of halogen, H, and alkyl;

R^7 is selected from the group consisting of H and F;

R⁸ is selected from the group consisting of alkoxy, alkylamino, cycloalkoxy, cycloalkylamino, halogen, H, alkyl, haloalkoxy, haloalkyl, amide, alkoxycarbonyl, hydroxyalkyl, hydroxycycloalkyl, hydroxy, and CN;

R⁹, R¹⁰, and R¹¹ are each independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl;

R¹³ is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

L² is selected from the group consisting of a direct bond and C₁-C₆alkyl, wherein C₁-C₆alkyl is optionally substituted with (E²¹)_p;

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

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

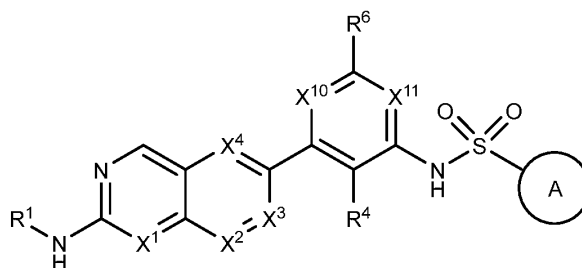
E²¹, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and

each p is independently 0, 1 or 2.

24. The compound of claim 23, wherein X¹¹ is CR⁷.

25. The compound of claim 23, wherein X¹¹ is N.

26. A compound represented by Formula I:



Formula I

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

X^1 is selected from the group consisting of CH and N;

5 X^2 and X^3 are each independently selected from the group consisting of N, CH, C-O-L²-E², C-L²-E², and C-N(R²)-L²-E²,

provided that X^2 is selected from the group consisting of CH and N, and X^3 is selected from the group consisting of CH, C-O-L²-E², C-L²-E², and C-N(R²)-L²-E²;

10 provided that X^2 is selected from the group consisting of CH, C-O-L²-E², C-L²-E², and C-N(R²)-L²-E² and X^3 is selected from the group consisting of CH and N;

X^4 is selected from the group consisting of CR³ and N;

X^{10} is selected from the group consisting of CR⁵ and N;

X^{11} is selected from the group consisting of CR⁷ and N;

15 R^1 is selected from the group consisting of H, alkyl, (C=O)R¹³, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocycl, and

20 wherein heterocycl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

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

25 R^3 is selected from the group consisting of H, alkyl, and halogen;

R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 and R^7 are each independently selected from the group consisting of halogen, H, and alkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

A is selected from the group consisting of a substituted 5-membered heteroaryl, a substituted 6-membered heteroaryl, a pyridone, and a substituted aryl ring;

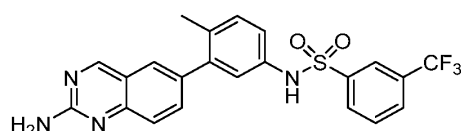
L^2 is selected from the group consisting of a direct bond and C_1 - C_6 alkyl, wherein C_1 - C_6 alkyl is optionally substituted with $(E^{21})_p$;

E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

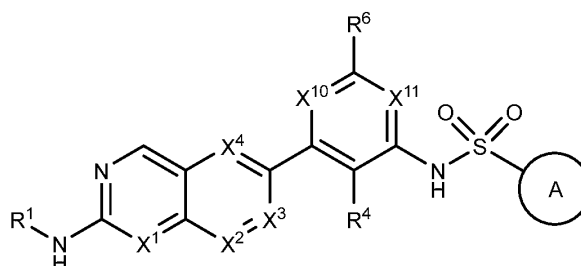
wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21} , at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and

each p is independently 0, 1 or 2; provided that the compound is not:



27. A compound represented by Formula I:



Formula I

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

- 5 X^1 is selected from the group consisting of CH and N;
 X^2 is selected from the group consisting of N, CH, C-O-L²-E², and C-L²-E²;
 X^3 is C-N(R²)-L²-E²;
 X^4 is selected from the group consisting of CR³ and N;
 X^{10} is selected from the group consisting of CR⁵ and N;
 10 X^{11} is selected from the group consisting of CR⁷ and N;
 R¹ is selected from the group consisting of H, alkyl, (C=O)R¹³, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy,
 15 alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and
 wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl,
 20 and sulfonyl;
 R² is selected from the group consisting of H and alkyl;
 R³ is selected from the group consisting of H, alkyl, and halogen;
 R⁴ and R⁵ are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;
 25 R⁶ and R⁷ are each independently selected from the group consisting of halogen, H, and alkyl;
 R¹³ is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

5 wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

A is selected from the group consisting of a substituted 5-membered heteroaryl, a substituted 10 6-membered heteroaryl, a pyridone, and a substituted aryl ring;

L^2 is selected from the group consisting of a direct bond and C_1 - C_6 alkyl, wherein C_1 - C_6 alkyl is optionally substituted with $(E^{21})_p$;

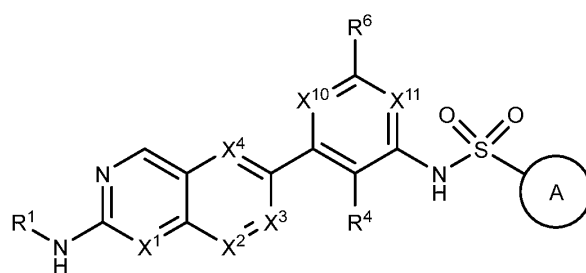
E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

15 wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent 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, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; 20 and

each p is independently 0, 1 or 2.

28. A compound represented by Formula I:



Formula I

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

X^1 is CH;

X^2 and X^3 are each independently selected from the group consisting of N, CH, C-O-L²-E², C-L²-E², and C-N(R²)-L²-E²,

provided that X^2 is selected from the group consisting of CH and N, and X^3 is selected from the group consisting of CH, C-O-L²-E², C-L²-E², and C-N(R²)-L²-E²,

5 provided that X^2 is selected from the group consisting of CH, C-O-L²-E², C-L²-E², and C-N(R²)-L²-E² and X^3 is selected from the group consisting of CH and N;

X^4 is selected from the group consisting of CR³ and N;

X^{10} is selected from the group consisting of CR⁵ and N;

X^{11} is selected from the group consisting of CR⁷ and N;

10 R^1 is selected from the group consisting of H, alkyl, (C=O)R¹³, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and

15 heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

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

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 and R^7 are each independently selected from the group consisting of halogen, H, and alkyl;

25 R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and

30 heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

A is selected from the group consisting of a substituted 5-membered heteroaryl, a substituted 6-membered heteroaryl, a pyridone, and a substituted aryl ring;

L^2 is selected from the group consisting of a direct bond and C₁-C₆alkyl, wherein C₁-C₆alkyl is optionally substituted with (E²¹)_p;

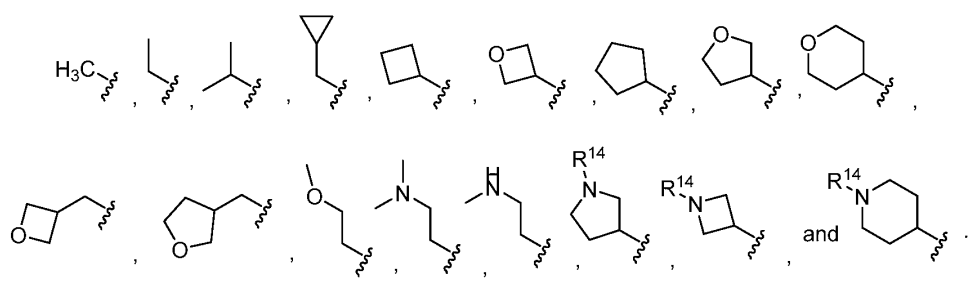
- 5 E² is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

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

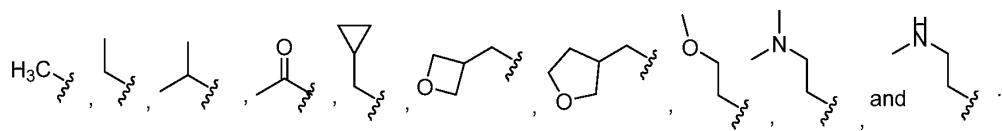
each p is independently 0, 1 or 2.

- 15 29. The compound of any one of claims 1-28, wherein R¹ is selected from the group consisting of

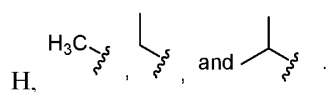


wherein each occurrence of R¹⁴ is independently selected from the group consisting of H, alkyl, alkoxyalkyl, haloalkyl, hydroxyalkyl, and cyanoalkyl.

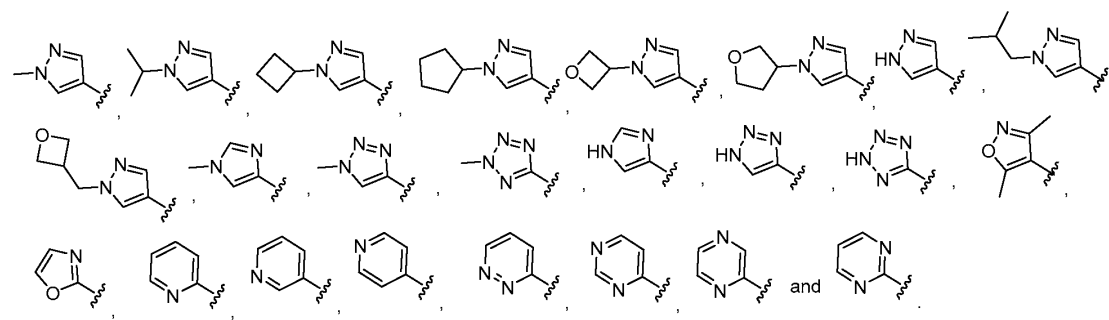
- 20 30. The compound of any of claims 1-28, wherein R¹ is selected from the group consisting of



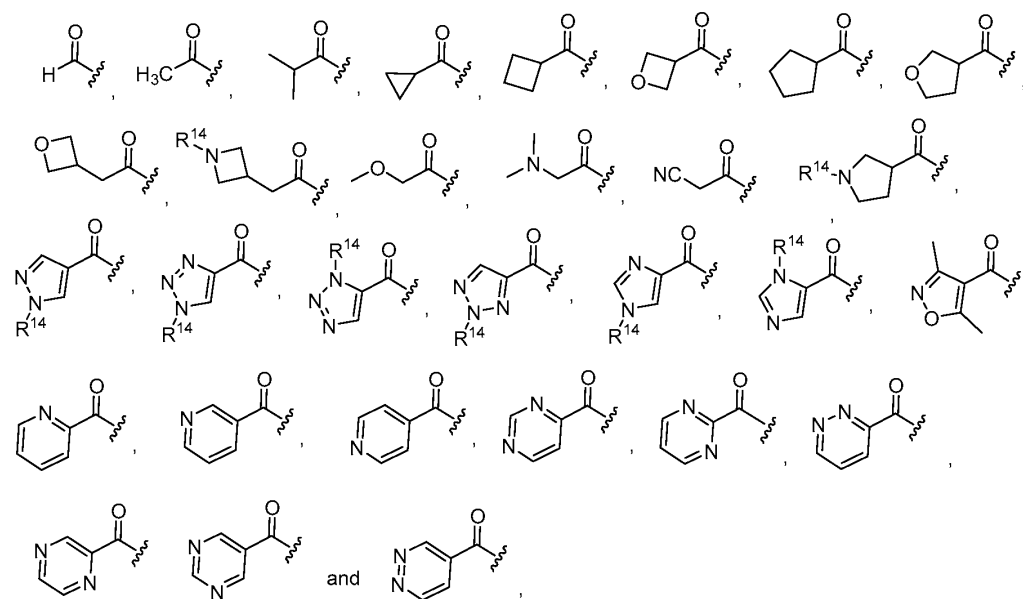
31. The compound of any one of claims 1-28, wherein R^1 is selected from the group consisting of



32. The compound of any one of claims 1-28, wherein R^1 is selected from the group consisting of



33. The compound of any one of claims 1-28, wherein R^1 is selected from the group consisting of



wherein each occurrence of R^{14} is independently selected from the group consisting of H, alkyl, alkoxyalkyl, haloalkyl, hydroxyalkyl, and cyanoalkyl.

34. The compound of any one of claims 1, 26, or 27, wherein X^1 is N.

35. The compound of any one of claims 1, 26, or 27, wherein X^1 is CH.

36. The compound of any one of claims 1-5, 8-11, or 14-20, wherein:

X^2 is selected from the group consisting of N and CH; and

X^3 is C-N(R²)-L²-E².

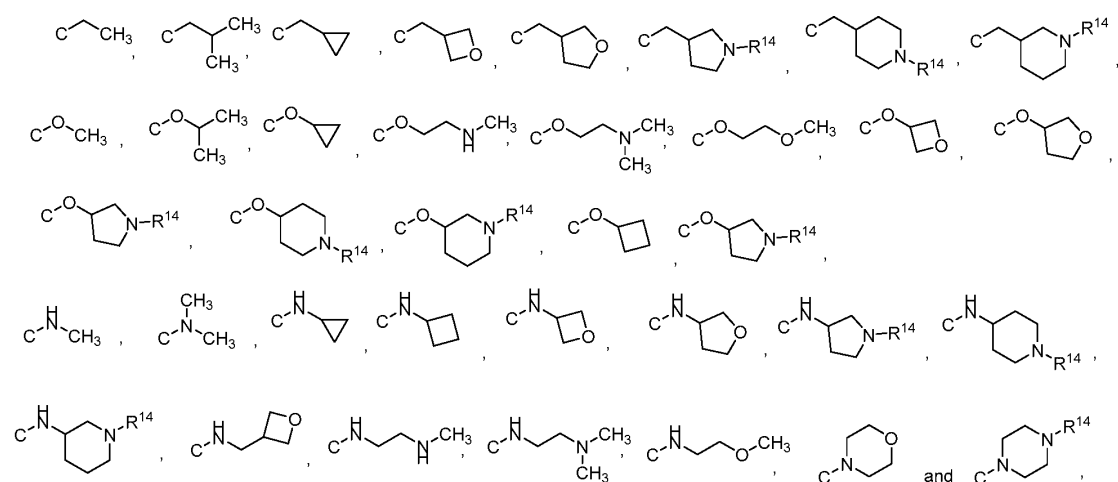
37. The compound of any one of claims 1-5, 8-11, 14-28, or 36, wherein X^3 is C-N(R²)-L²-E².

38. The compound of claim 37, wherein X^3 is CN(H)CH₃.

39. The compound of any one of claims 1-5, 8-11, or 14-28, wherein X^2 is N and X^3 is CCH₃.

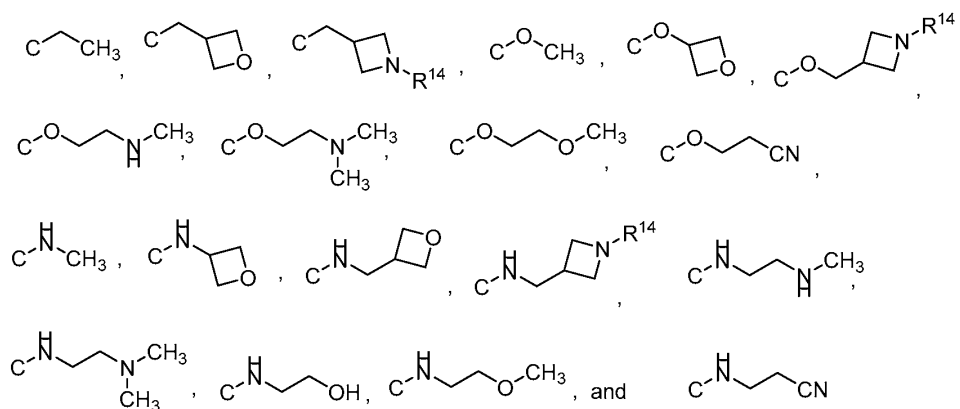
40. The compound of any one of claims 1, 4-7, 10-13, or 26-28, wherein X^2 is CH and X^3 is N.

41. The compounds of any one of claims 1, 4-7, 10-13, 26-35, wherein X^2 is selected from the group consisting of:



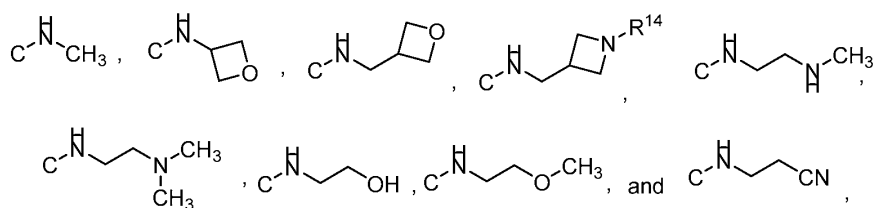
wherein each occurrence of R¹⁴ is independently selected from the group consisting of H, alkyl, alkoxyalkyl, haloalkyl, hydroxyalkyl, and cyanoalkyl.

42. The compound of any one of claims 1-5, 8-11, 14-35, wherein X^3 is selected from the group consisting of:



wherein each occurrence of R^{14} is independently selected from the group consisting of H, alkyl, alkoxyalkyl, haloalkyl, hydroxyalkyl, and cyanoalkyl.

- 5 43. The compound of any one of claims 1-5, 8-11, 14-37, wherein X^3 is selected from the group consisting of



wherein each occurrence of R^{14} is independently selected from the group consisting of H, alkyl, alkoxyalkyl, haloalkyl, hydroxyalkyl, and cyanoalkyl.

10

44. The compound of any one of claims 1-43, wherein X^4 is CR^3 .

45. The compound of any one of claims 1-44, wherein X^{10} is CR^5 and X^{11} is CR^7 .

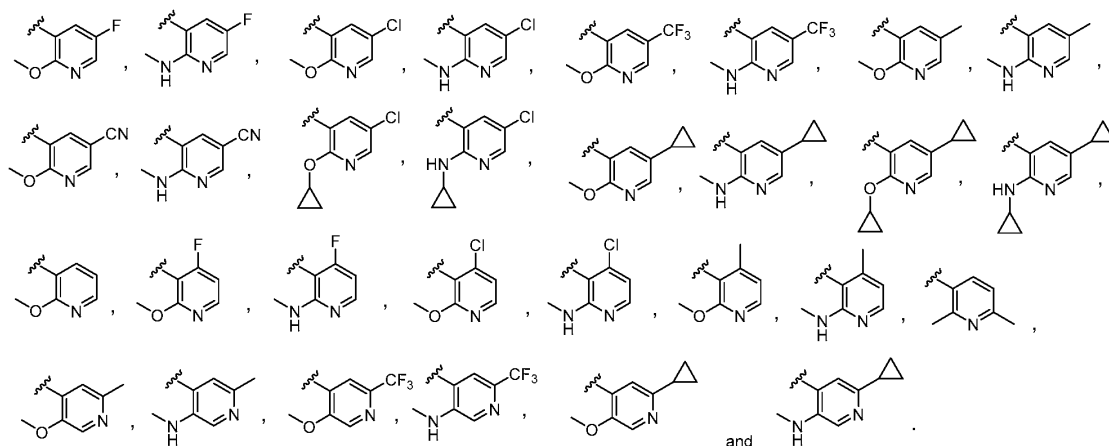
- 15 46. The compound of any one of claims 1-44, wherein X^{10} and X^{11} are N.

47. The compound of any one of claims 1-44, wherein X^{10} is CR^5 and X^{11} is N.

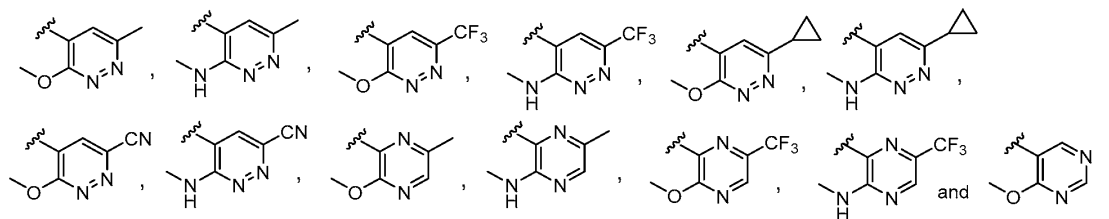
48. The compound of claim 44, wherein R^3 is selected from the group consisting of H, methyl,
20 and F.

49. The compound of any one of claims 1-48, wherein R^4 and R^5 are each independently selected from the group consisting of H, F, Cl, Me, OMe, CF_3 , and CN.
50. The compound of any one of claims 1-49, wherein R^6 and R^7 are each independently selected from the group consisting of H, F, Cl, Me.
51. The compound of any one of claims 1-49, wherein R^4 , R^5 , R^6 , and R^7 are each independently H or F, and wherein at least one of R^4 , R^5 , R^6 , and R^7 is F.
52. The compound of any one of claims 1-51, wherein:
 R^6 is F; and
 R^4 , R^5 , and R^7 are each H.
53. The compound of any one of claims 1-51, wherein:
 R^4 is F; and
 R^5 , R^6 , and R^7 are each H.
54. The compound of any one of claims 1-51, wherein:
 R^4 and R^6 are each F; and
 R^5 and R^7 are each H.
55. The compound of any one of claims 1-51, wherein:
 R^4 and R^5 are each F; and
 R^6 and R^7 are each H.
56. The compound of any one of claims 1-51, wherein:
 R^5 and R^6 are each F; and
 R^4 and R^7 are each H.

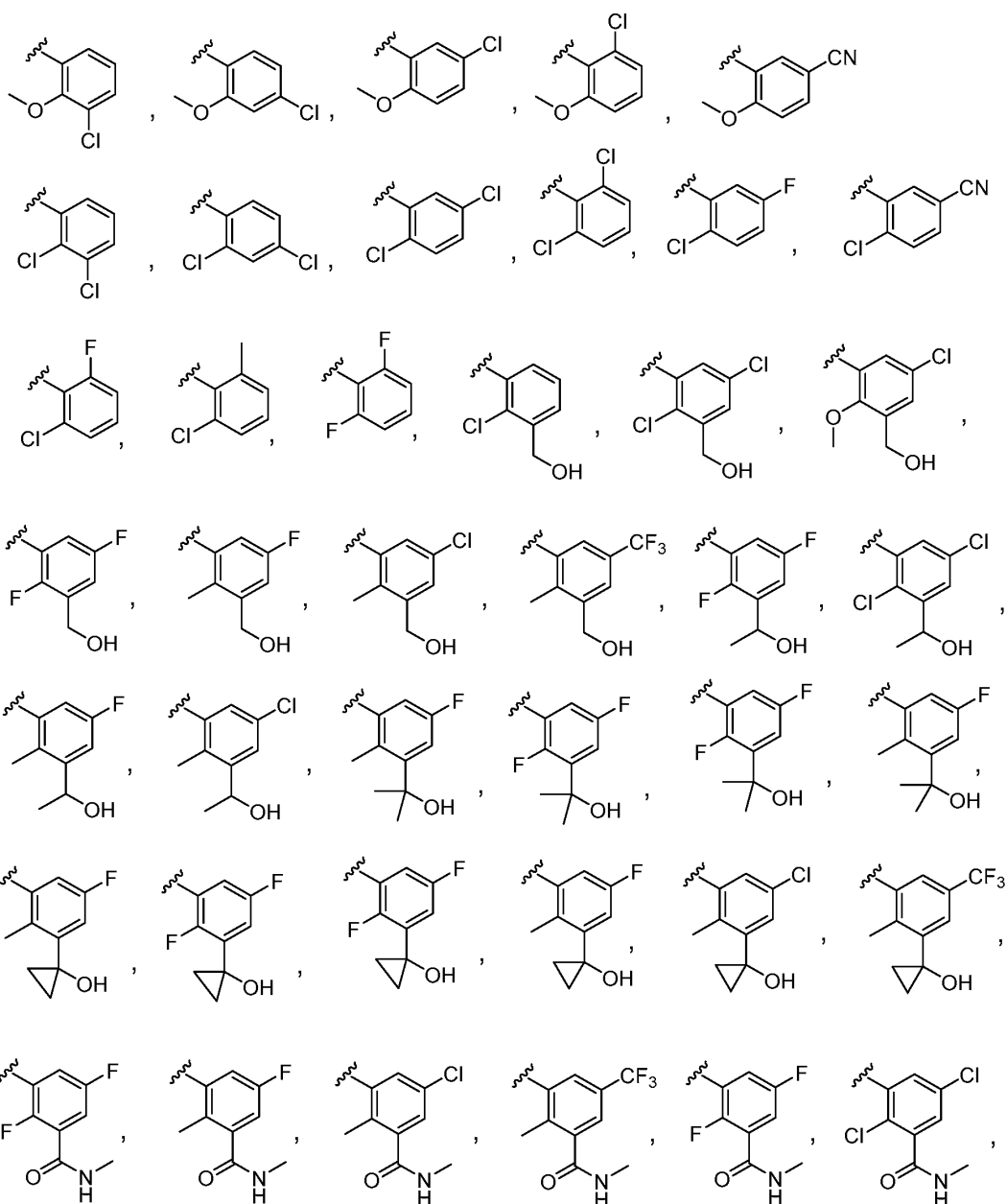
57. The compound of any one of claims 1, 8-13, or 26-56, wherein A or B is selected from the group consisting of:



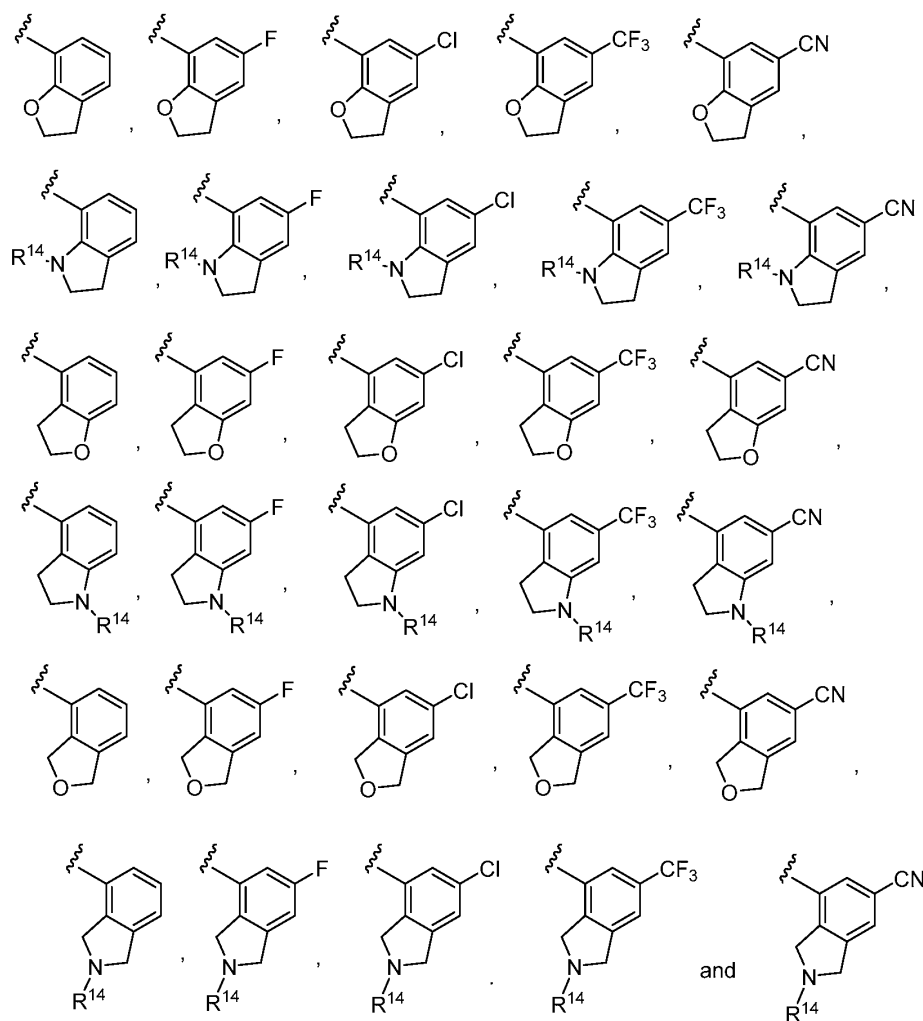
58. The compound of any one of claims 1, 8-13, or 26-56, wherein A or B is selected from the group consisting of:



59. The compound of any one of claims 1, or 26-56, wherein A is selected from the group consisting of:

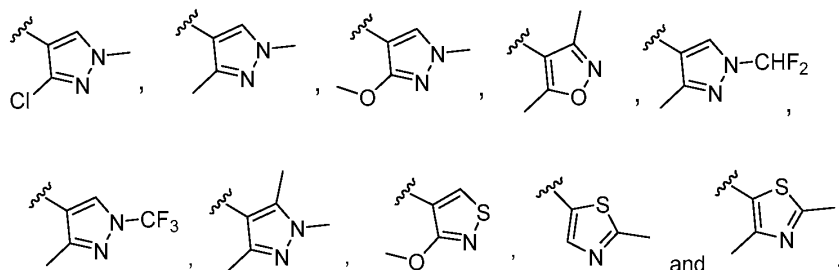


60. The compound of any one of claims 1, or 26-56, wherein A is selected from the group consisting of:

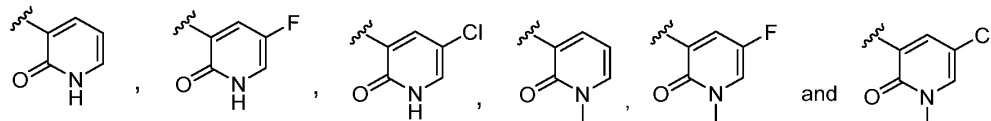


wherein each occurrence of R¹⁴ is independently selected from the group consisting of H, alkyl, alkoxyalkyl, haloalkyl, hydroxyalkyl, and cyanoalkyl.

- 5 61. The compound of any one of claims 1, 8-13, or 26-56, wherein A or B is selected from the group consisting of:

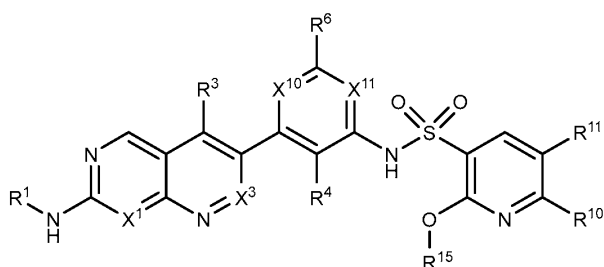


62. The compound of any one of claims 1, 8-13, or 26-56, wherein A or B is selected from the group consisting of:



5

63. A compound represented by Formula I-R:



Formula I-R

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

10 X^1 is selected from the group consisting of CH and N;

X^3 is selected from the group consisting of C-O-L²-E², C-L²-E², and C-N(R²)-L²-E²

X^{10} is selected from the group consisting of CR⁵ and N;

X^{11} is selected from the group consisting of CR^7 and N ;

R¹ is selected from the group consisting of alkyl, (C=O)R¹³, cycloalkyl, alkoxyalkyl, 15 cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl.

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

20 wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine,

aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

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

R^3 is selected from the group consisting of H, alkyl, and halogen;

5 R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 is selected from the group consisting of halogen, H, and alkyl;

R^7 is selected from the group consisting of H and F;

10 R^{10} and R^{11} are each independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxyalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxyalkyl, and heterocyclylalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, 15 cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

20 wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^{15} is selected from the group consisting of alkyl, cycloalkyl, and heterocyclyl;

25 L^2 is selected from the group consisting of a direct bond and C₁-C₆alkyl, wherein C₁-C₆alkyl is optionally substituted with (E²¹)_p;

E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

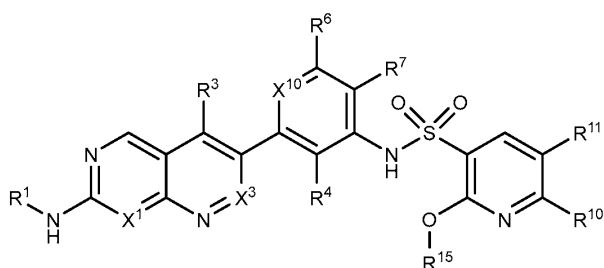
30 wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21} , at each occurrence, is independently selected from the group consisting of H, alkyl,

cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen, and

each p is independently 0, 1 or 2.

- 5 64. A compound represented by Formula I-S:



Formula I-S

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

- 10 X^1 is selected from the group consisting of CH and N;
 X^3 is selected from the group consisting of C-O-L²-E², C-L²-E², and C-N(R²)-L²-E²
 X^{10} is selected from the group consisting of CR⁵ and N;
 R^1 is selected from the group consisting of alkyl, (C=O)R¹³, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of
 15 a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and
 wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine,
 20 aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;
 R^2 is selected from the group consisting of H and alkyl;
 R^3 is selected from the group consisting of H, alkyl, and halogen;
 R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy,
 25 alkylamino, amino, alkyl, haloalkyl and CN;
 R^6 is selected from the group consisting of halogen, H, and alkyl;
 R^7 is selected from the group consisting of H and F;

R^{10} and R^{11} are each independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxyalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxyalkyl, and heterocyclalkyl;

5 R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and
10 heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

15 R^{15} is selected from the group consisting of alkyl, cycloalkyl, and heterocyclyl;

L^2 is selected from the group consisting of a direct bond and C₁-C₆alkyl, wherein C₁-C₆alkyl is optionally substituted with $(E^{21})_p$;

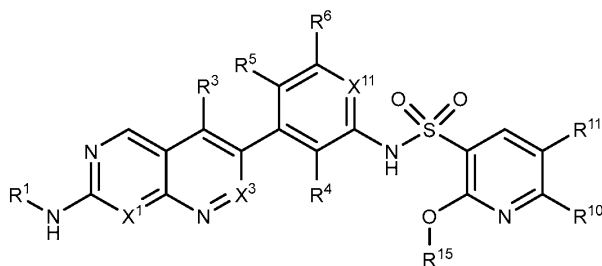
E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

20 wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent 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, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen,
25 and

each p is independently 0, 1 or 2.

65. A compound represented by Formula I-T:



Formula 1-T

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

X^1 is selected from the group consisting of CH and N;

5 X^3 is selected from the group consisting of C-O-L²-E², C-L²-E², and C-N(R²)-L²-E²

R^1 is selected from the group consisting of alkyl, (C=O)R¹³, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

10 wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

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

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

20 R^6 is selected from the group consisting of halogen, H, and alkyl;

R^7 is selected from the group consisting of H and F;

R^{10} and R^{11} are each independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxyalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxyalkyl, and heterocyclylalkyl;

25 R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

5 wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^{15} is selected from the group consisting of alkyl, cycloalkyl, and heterocyclyl;

10 L^2 is selected from the group consisting of a direct bond and C_1 - C_6 alkyl, wherein C_1 - C_6 alkyl is optionally substituted with $(E^{21})_p$;

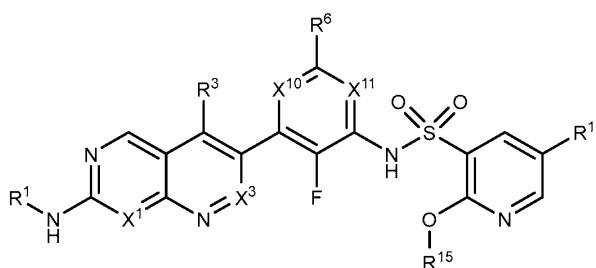
E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

15 wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent 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, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen, and

20 each p is independently 0, 1 or 2.

66. A compound represented by Formula I-U:



Formula I-U

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

X^1 is selected from the group consisting of CH and N;

X^3 is selected from the group consisting of $C-O-L^2-E^2$, $C-L^2-E^2$, and $C-N(R^2)-L^2-E^2$

X^{10} is selected from the group consisting of CR^5 and N;

X¹¹ is selected from the group consisting of CR⁷ and N;

R¹ is selected from the group consisting of alkyl, (C=O)R¹³, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

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

R³ is selected from the group consisting of H, alkyl, and halogen;

R⁵ is selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R⁶ is selected from the group consisting of halogen, H, and alkyl;

R⁷ is selected from the group consisting of H and F;

R¹¹ is selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl;

R¹³ is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R¹⁵ is selected from the group consisting of alkyl, cycloalkyl, and heterocyclyl;

L² is selected from the group consisting of a direct bond and C₁-C₆alkyl, wherein C₁-C₆alkyl is optionally substituted with (E²¹)_p;

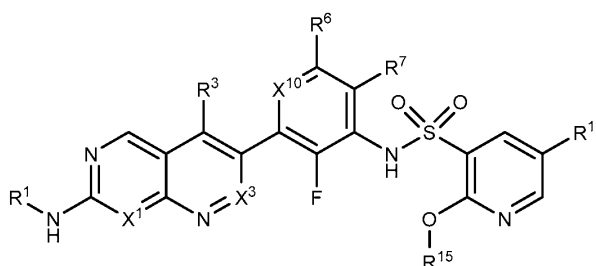
E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent 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, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen, and

each p is independently 0, 1 or 2.

67. A compound represented by Formula I-V:



Formula I-V

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

X^1 is selected from the group consisting of CH and N;

X^3 is selected from the group consisting of C-O-L²-E², C-L²-E², and C-N(R²)-L²-E²

X^{10} is selected from the group consisting of CR⁵ and N;

R^1 is selected from the group consisting of alkyl, (C=O)R¹³, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

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

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^5 is selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 is selected from the group consisting of halogen, H, and alkyl;

R^7 is selected from the group consisting of H and F;

5 R^{11} is selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, 10 cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

15 wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^{15} is selected from the group consisting of alkyl, cycloalkyl, and heterocyclyl;

20 L^2 is selected from the group consisting of a direct bond and C₁-C₆alkyl, wherein C₁-C₆alkyl is optionally substituted with (E²¹)_p;

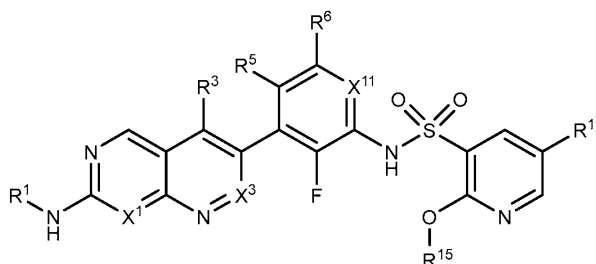
E² is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

25 wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent 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, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen, and

30 each p is independently 0, 1 or 2.

68. A compound represented by Formula I-W:



Formula I-W

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

5 X^1 is selected from the group consisting of CH and N;

X^3 is selected from the group consisting of C-O-L²-E², C-L²-E², and C-N(R²)-L²-E²

X^{11} is selected from the group consisting of CR⁷ and N;

R^1 is selected from the group consisting of alkyl, (C=O)R¹³, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

10 wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

15 wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

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

R^3 is selected from the group consisting of H, alkyl, and halogen;

20 R^5 is selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 is selected from the group consisting of halogen, H, and alkyl;

R^7 is selected from the group consisting of H and F;

25 R^{11} is selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^{15} is selected from the group consisting of alkyl, cycloalkyl, and heterocyclyl;

L^2 is selected from the group consisting of a direct bond and C₁-C₆alkyl, wherein C₁-C₆alkyl is optionally substituted with $(E^{21})_p$;

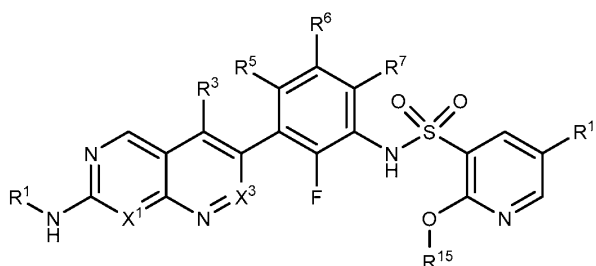
E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent 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, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen, and

each p is independently 0, 1 or 2.

69. A compound represented by Formula I-X:



Formula I-X

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

X^1 is selected from the group consisting of CH and N;

X^3 is selected from the group consisting of C-O-L²-E², C-L²-E², and C-N(R²)-L²-E²

R¹ is selected from the group consisting of alkyl, (C=O)R¹³, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

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

R³ is selected from the group consisting of H, alkyl, and halogen;

R⁵ is independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R⁶ is selected from the group consisting of halogen, H, and alkyl;

R⁷ is selected from the group consisting of H and F;

R¹¹ is selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl;

R¹³ is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R¹⁵ is selected from the group consisting of alkyl, cycloalkyl, and heterocyclyl;

L² is selected from the group consisting of a direct bond and C₁-C₆alkyl, wherein C₁-C₆alkyl is optionally substituted with (E²¹)_p;

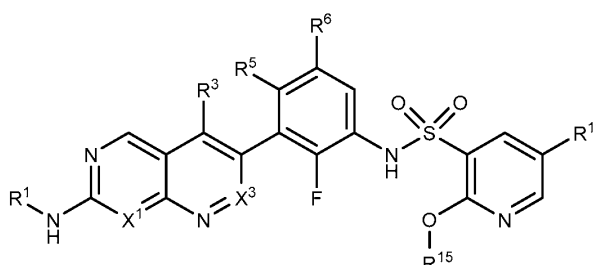
E² is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent 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, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen, and

each p is independently 0, 1 or 2.

70. A compound represented by Formula I-Y:



Formula 1-Y

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

X¹ is selected from the group consisting of CH and N;

X^3 is selected from the group consisting of C-O-L²-E², C-L²-E², and C-N(R²)-L²-E²

R¹ is selected from the group consisting of alkyl, (C=O)R¹³, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

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

R³ is selected from the group consisting of H, alkyl, and halogen;

R^5 is independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 is selected from the group consisting of halogen, H, and alkyl;

R^{11} is selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxyalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxyalkyl, and heterocyclalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^{15} is selected from the group consisting of alkyl, cycloalkyl, and heterocyclyl;

L^2 is selected from the group consisting of a direct bond and C_1 - C_6 alkyl, wherein C_1 - C_6 alkyl is optionally substituted with $(E^{21})_p$;

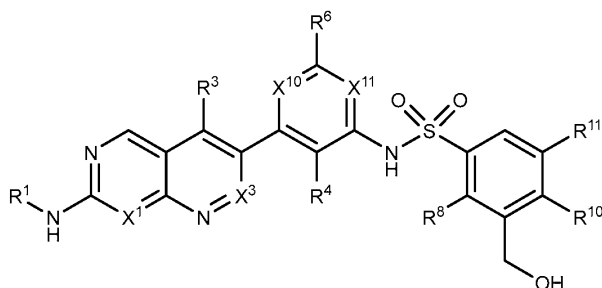
E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent 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, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen, and

each p is independently 0, 1 or 2.

71. A compound represented by Formula I-Z:



Formula I-Z

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

- 5 X^1 is selected from the group consisting of CH and N;
 X^3 is selected from the group consisting of C-O-L²-E², C-L²-E², and C-N(R²)-L²-E²
 X^{10} is selected from the group consisting of CR⁵ and N;
 X^{11} is selected from the group consisting of CR⁷ and N;
 R¹ is selected from the group consisting of alkyl, (C=O)R¹³, cycloalkyl, alkoxyalkyl,
 10 cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,
 wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of
 a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy,
 alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and
 heterocyclyl, and
 15 wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent
 independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine,
 aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl,
 and sulfonyl;
 R² is selected from the group consisting of H and alkyl;
 20 R³ is selected from the group consisting of H, alkyl, and halogen;
 R⁴ and R⁵ are each independently selected from the group consisting of halogen, H, alkoxy,
 alkylamino, amino, alkyl, haloalkyl and CN;
 R⁶ is selected from the group consisting of halogen, H, and alkyl;
 R⁷ is selected from the group consisting of H and F;
 25 R⁸ is selected from the group consisting of alkoxy, alkylamino, cycloalkoxy,
 cycloalkylamino, halogen, H, alkyl, haloalkoxy, haloalkyl, amide, alkoxycarbonyl, hydroxyalkyl,
 hydroxycycloalkyl, hydroxy, and CN;

R^{10} and R^{11} are each independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxyalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxyalkyl, and heterocyclylalkyl;

- 5 R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and
- 10 heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

- 15 L^2 is selected from the group consisting of a direct bond and C_1 - C_6 alkyl, wherein C_1 - C_6 alkyl is optionally substituted with $(E^{21})_p$;

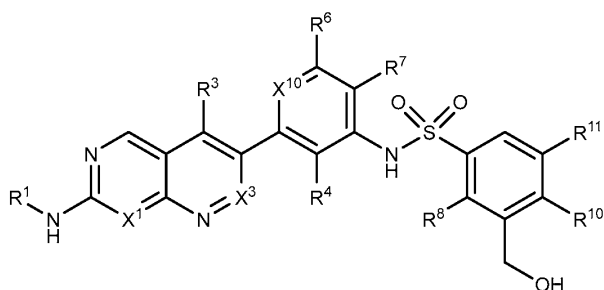
E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

- wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent
- 20 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, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen, and

- 25 each p is independently 0, 1 or 2.

72. A compound represented by Formula I-AA:



Formula I-AA

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

X^1 is selected from the group consisting of CH and N;

X^3 is selected from the group consisting of C-O-L²-E², C-L²-E², and C-N(R²)-L²-E²

5 X^{10} is selected from the group consisting of CR⁵ and N;

R^1 is selected from the group consisting of alkyl, (C=O)R¹³, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

10 wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

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

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

20 R^6 is selected from the group consisting of halogen, H, and alkyl;

R^7 is selected from the group consisting of H and F;

R^8 is selected from the group consisting of alkoxy, alkylamino, cycloalkoxy, cycloalkylamino, halogen, H, alkyl, haloalkoxy, haloalkyl, amide, alkoxycarbonyl, hydroxyalkyl, hydroxycycloalkyl, hydroxy, and CN

25 R^{10} and R^{11} are each independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

5 L^2 is selected from the group consisting of a direct bond and C_1 - C_6 alkyl, wherein C_1 - C_6 alkyl is optionally substituted with $(E^{21})_p$;

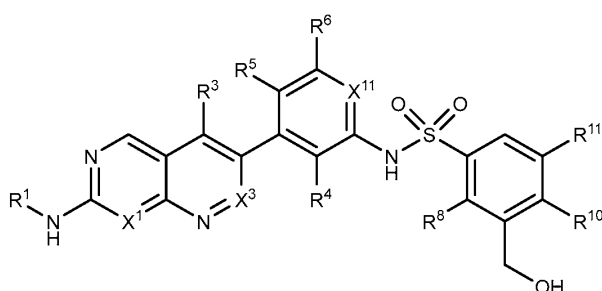
E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

10 wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent 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, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen, and

15 each p is independently 0, 1 or 2.

73. A compound represented by Formula I-AB:



Formula I-AB

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

X^1 is selected from the group consisting of CH and N;

X^3 is selected from the group consisting of $C-O-L^2-E^2$, $C-L^2-E^2$, and $C-N(R^2)-L^2-E^2$

X^{11} is selected from the group consisting of CR^7 and N;

25 R^1 is selected from the group consisting of alkyl, $(C=O)R^{13}$, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy,

alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

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

R³ is selected from the group consisting of H, alkyl, and halogen;

R⁴ and R⁵ are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R⁶ is selected from the group consisting of halogen, H, and alkyl;

R⁷ is selected from the group consisting of H and F;

R⁸ is selected from the group consisting of alkoxy, alkylamino, cycloalkoxy, cycloalkylamino, halogen, H, alkyl, haloalkoxy, haloalkyl, amide, alkoxycarbonyl, hydroxyalkyl, hydroxycycloalkyl, hydroxy, and CN

R¹¹ is selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclalkyl;

R¹³ is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

L² is selected from the group consisting of a direct bond and C₁-C₆alkyl, wherein C₁-C₆alkyl is optionally substituted with (E²¹)_p;

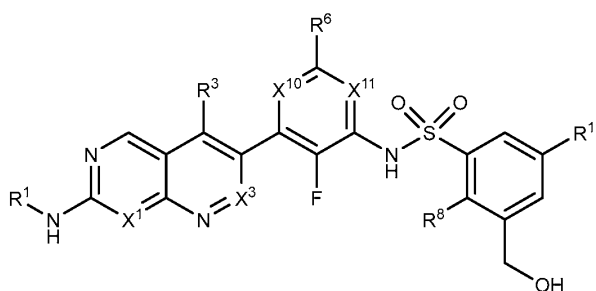
E² is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent 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, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen, and

each p is independently 0, 1 or 2.

74. A compound represented by Formula I-AC:



Formula I-AC

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

X^1 is selected from the group consisting of CH and N;

X^3 is selected from the group consisting of C-O-L²-E², C-L²-E², and C-N(R²)-L²-E²

15 X^{10} is selected from the group consisting of CR⁵ and N;

X^{11} is selected from the group consisting of CR⁷ and N;

R^1 is selected from the group consisting of alkyl, (C=O)R¹³, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

20 wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

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

R^3 is selected from the group consisting of H, alkyl, and halogen;

R⁵ is selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R⁶ is selected from the group consisting of halogen, H, and alkyl;

R⁷ is selected from the group consisting of H and F;

5 R⁸ is selected from the group consisting of alkoxy, alkylamino, cycloalkoxy, cycloalkylamino, halogen, H, alkyl, haloalkoxy, haloalkyl, amide, alkoxycarbonyl, hydroxyalkyl, hydroxycycloalkyl, hydroxy, and CN

10 R¹¹ is selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclalkyl;

R¹³ is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclalkyl, aryl, heteroaryl, and heteroarylalkyl,

15 wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

20 wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

L² is selected from the group consisting of a direct bond and C₁-C₆alkyl, wherein C₁-C₆alkyl is optionally substituted with (E²¹)_p;

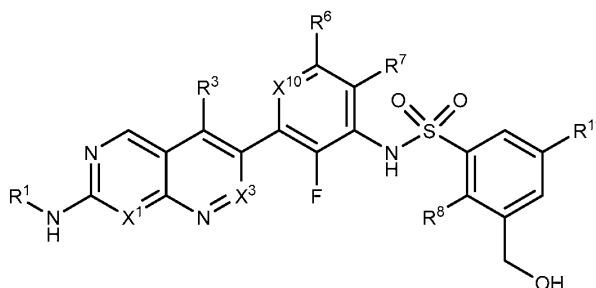
25 E² is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

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

each p is independently 0, 1 or 2.

75. A compound represented by Formula I-AD:



Formula I-AD

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

5 X¹ is selected from the group consisting of CH and N;

X³ is selected from the group consisting of C-O-L²-E², C-L²-E², and C-N(R²)-L²-E²

X¹⁰ is selected from the group consisting of CR⁵ and N;

R¹ is selected from the group consisting of alkyl, (C=O)R¹³, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

10 wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

15 wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

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

R³ is selected from the group consisting of H, alkyl, and halogen;

20 R⁵ is selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R⁶ is selected from the group consisting of halogen, H, and alkyl;

R⁷ is selected from the group consisting of H and F;

25 R⁸ is selected from the group consisting of alkoxy, alkylamino, cycloalkoxy, cycloalkylamino, halogen, H, alkyl, haloalkoxy, haloalkyl, amide, alkoxyalkyl, hydroxyalkyl, hydroxycycloalkyl, hydroxy, and CN

R¹¹ is selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxyalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano,

alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclalkyl, aryl, heteroaryl, and heteroarylalkyl,

5 wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

10 wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

L^2 is selected from the group consisting of a direct bond and C₁-C₆alkyl, wherein C₁-C₆alkyl is optionally substituted with $(E^{21})_p$;

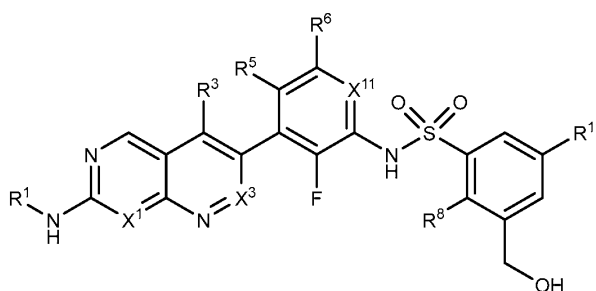
15 E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

20 E^{21} , at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen, and

each p is independently 0, 1 or 2.

25 76. A compound represented by Formula I-AE:



Formula I-AE

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

X^1 is selected from the group consisting of CH and N;

X^3 is selected from the group consisting of C-O-L²-E², C-L²-E², and C-N(R²)-L²-E²

X^{11} is selected from the group consisting of CR⁷ and N;

R^1 is selected from the group consisting of alkyl, (C=O)R¹³, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

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

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^5 is selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 is selected from the group consisting of halogen, H, and alkyl;

R^7 is selected from the group consisting of H and F;

R^8 is selected from the group consisting of alkoxy, alkylamino, cycloalkoxy, cycloalkylamino, halogen, H, alkyl, haloalkoxy, haloalkyl, amide, alkoxycarbonyl, hydroxyalkyl, hydroxycycloalkyl, hydroxy, and CN;

R^{11} is selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine,

aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

L^2 is selected from the group consisting of a direct bond and C_1 - C_6 alkyl, wherein C_1 - C_6 alkyl is optionally substituted with $(E^{21})_p$;

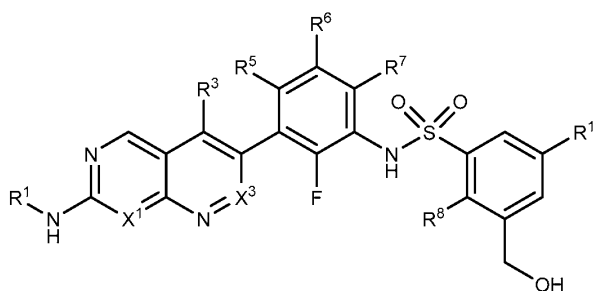
5 E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

10 E^{21} , at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen, and

each p is independently 0, 1 or 2.

15 77. A compound represented by Formula I-AF:



Formula I-AF

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

X^1 is selected from the group consisting of CH and N;

20 X^3 is selected from the group consisting of $C-O-L^2-E^2$, $C-L^2-E^2$, and $C-N(R^2)-L^2-E^2$

R^1 is selected from the group consisting of alkyl, $(C=O)R^{13}$, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy,

25 alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine,

aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

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

R^3 is selected from the group consisting of H, alkyl, and halogen;

5 R^5 is selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 is selected from the group consisting of halogen, H, and alkyl;

R^7 is selected from the group consisting of H and F;

10 R^8 is selected from the group consisting of alkoxy, alkylamino, cycloalkoxy, cycloalkylamino, halogen, H, alkyl, haloalkoxy, haloalkyl, amide, alkoxy carbonyl, hydroxyalkyl, hydroxycycloalkyl, hydroxy, and CN;

R^{11} is selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxy cycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, 15 heterocyclyl, alkoxy carbonyl, and heterocyclalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, 20 alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, 25 and sulfonyl;

L^2 is selected from the group consisting of a direct bond and C₁-C₆alkyl, wherein C₁-C₆alkyl is optionally substituted with (E²¹)_p;

E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

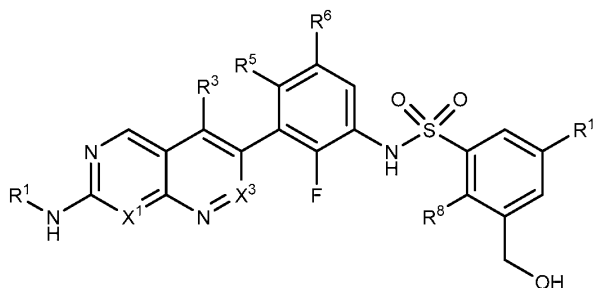
30 wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21} , at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen, and

each p is independently 0, 1 or 2.

5

78. A compound represented by Formula I-AG:



Formula I-AG

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

10 X^1 is selected from the group consisting of CH and N;

X^3 is selected from the group consisting of C-O-L²-E², C-L²-E², and C-N(R²)-L²-E²

R^1 is selected from the group consisting of alkyl, (C=O)R¹³, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl, wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of

15 a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, 20 aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

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

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^5 is selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, 25 haloalkyl and CN;

R^6 is selected from the group consisting of halogen, H, and alkyl;

R⁸ is selected from the group consisting of alkoxy, alkylamino, cycloalkoxy, cycloalkylamino, halogen, H, alkyl, haloalkoxy, haloalkyl, amide, alkoxycarbonyl, hydroxyalkyl, hydroxycycloalkyl, hydroxy, and CN

5 R¹¹ is selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl;

R¹³ is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,
10 wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent
15 independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

L² is selected from the group consisting of a direct bond and C₁-C₆alkyl, wherein C₁-C₆alkyl is optionally substituted with (E²¹)_p;

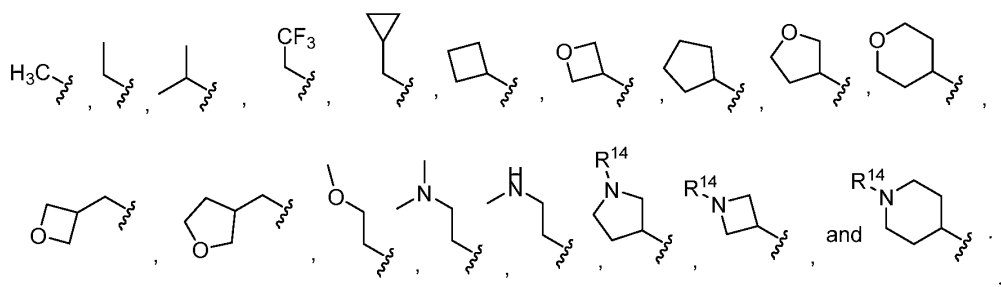
20 E² is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

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

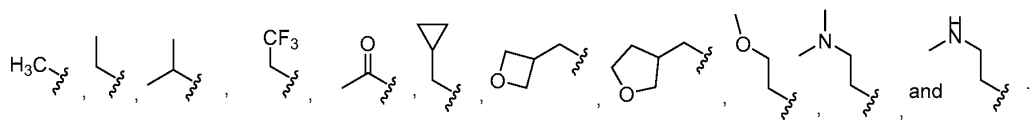
each p is independently 0, 1 or 2.

30 79. The compound of any one of claims 63-78, wherein R¹ is selected from the group consisting of

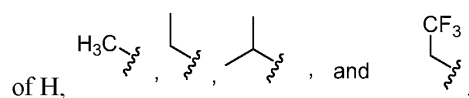


wherein each occurrence of R¹⁴ is independently selected from the group consisting of H, alkyl, alkoxyalkyl, haloalkyl, hydroxyalkyl, and cyanoalkyl.

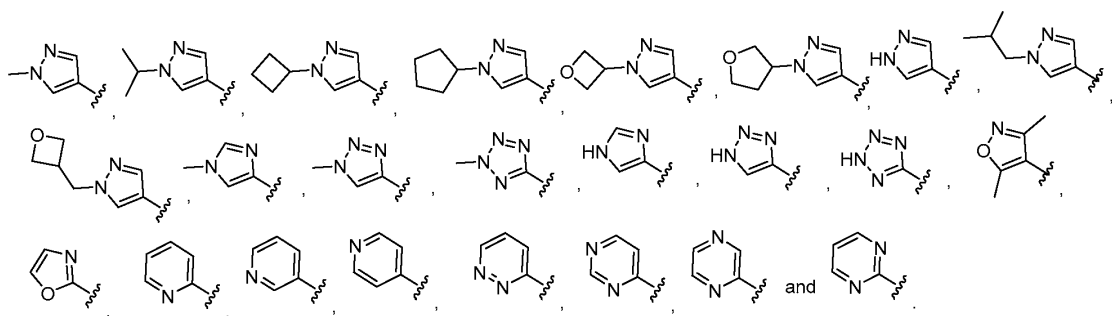
80. The compound of any of claims 63-78, wherein R¹ is selected from the group consisting of



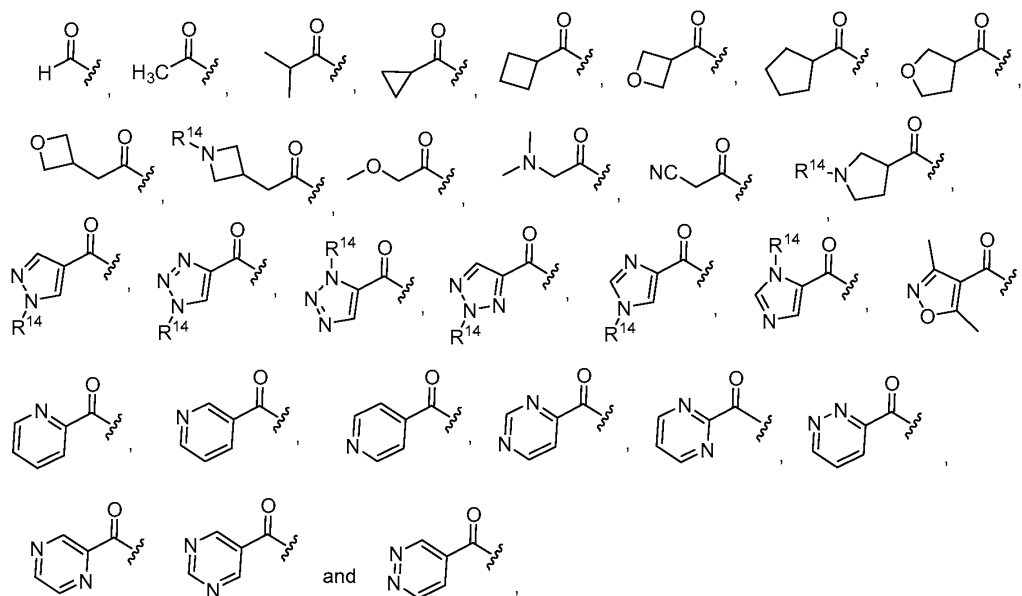
81. The compound of any one of claims 63-78, wherein R¹ is selected from the group consisting



10 82. The compound of any one of claims 63-78, wherein R¹ is selected from the group consisting
of



83. The compound of any one of claims 63-78, wherein R¹ is selected from the group consisting of



wherein each occurrence of R¹⁴ is independently selected from the group consisting of H, alkyl, alkoxyalkyl, haloalkyl, hydroxyalkyl, and cyanoalkyl.

5 84. The compound of any one of claims 63-83, wherein X¹ is N.

85. The compound of any one of claims 63-83, wherein X¹ is CH.

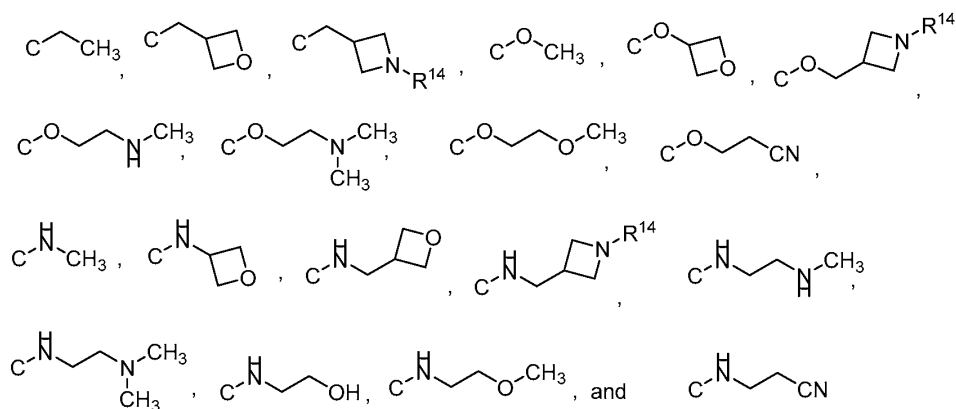
86. The compound of any one of claims 63-85, wherein X³ is C-N(R²)-L²-E².

10

87. The compound of claim 86, wherein X³ is CN(H)CH₃.

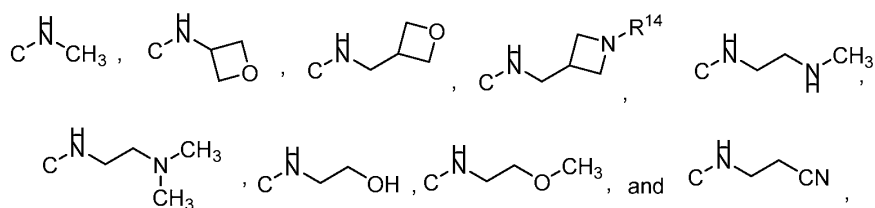
88. The compound of any one of claims 63-85, wherein X³ is CCH₃.

15 89. The compound of any one of claims 63-85, wherein X³ is selected from the group consisting of:



wherein each occurrence of R^{14} is independently selected from the group consisting of H, alkyl, alkoxyalkyl, haloalkyl, hydroxyalkyl, and cyanoalkyl.

- 5 90. The compound of any one of claims 63-85, wherein X^3 is selected from the group consisting of



wherein each occurrence of R^{14} is independently selected from the group consisting of H, alkyl, alkoxyalkyl, haloalkyl, hydroxyalkyl, and cyanoalkyl.

10

91. The compound of any one of claims 63-68 and 71-76, wherein X^{10} is N and X^{11} is CR^7 .
92. The compound of any one of claims 63-68 and 71-76, wherein X^{10} and X^{11} are N.
- 15 93. The compound of any one of claims 63-68 and 71-76, wherein X^{10} is CR^5 and X^{11} is N.
94. The compound of any one of claims 63, 68, and 71-76, wherein R^3 is H, C_1 - C_6 alkyl, and halogen.
- 20 95. The compound of any one of claims 63, 68, 71-76, and 94, wherein R^3 is H.

96. The compound of any one of claims 63, 68, 71-76, and 94, wherein R³ is Me.
97. The compound of any one of claims 63, 68, 71-76, and 94, wherein R³ is F.
- 5 98. The compound of any one of claims 63, 68, 71-76, and 94, wherein R³ is Cl.
99. The compound of any one of claims 63-65, 71-73, and 79-98, wherein R⁴ is selected from the group consisting of H, F, Cl, Me, OMe, CF₃, and CN.
- 10 100. The compound of any one of claims 63-99, wherein R⁵ is selected from the group consisting of H, F, Cl, Me, OMe, CF₃, and CN.
101. The compound of any one of claims 63-100, wherein R⁶ and R⁷ are each independently selected from the group consisting of H, F, Cl, Me.
- 15 102. The compound of any one of claims 63-101, wherein R⁴, R⁵, R⁶, and R⁷ are each independently H or F, and wherein at least one of R⁴, R⁵, R⁶, and R⁷ is F.
103. The compound of any one of claims 63-65, 71-73, and 79-102, wherein:
20 R⁶ is F; and
R⁴, R⁵, and R⁷ are each H.
104. The compound of any one of claims 63-102, wherein:
R⁴ is F; and
25 R⁵, R⁶, and R⁷ are each H.
105. The compound of any one of claims 63-102, wherein:
R⁴ and R⁶ are each F; and
R⁵ and R⁷ are each H.
30
106. The compound of any one of claims 63-102, wherein:
R⁴ and R⁵ are each F; and
R⁶ and R⁷ are each H.

107. The compound of any one of claims 63-65, 71-73, and 79-102, wherein:

R⁵ and R⁶ are each F; and

R⁴ and R⁷ are each H.

5 108. The compound of any one of claims 63-107, wherein R¹⁵ is selected from the group consisting of C₁-C₆ alkyl, C₃-C₆ cycloalkyl, and C₃-C₆ heterocyclyl.

109. The compound of any one of claims 63-108, wherein R¹⁵ is cyclopropyl.

10 110. The compound of any one of claims 63-108, wherein R¹⁵ is Me.

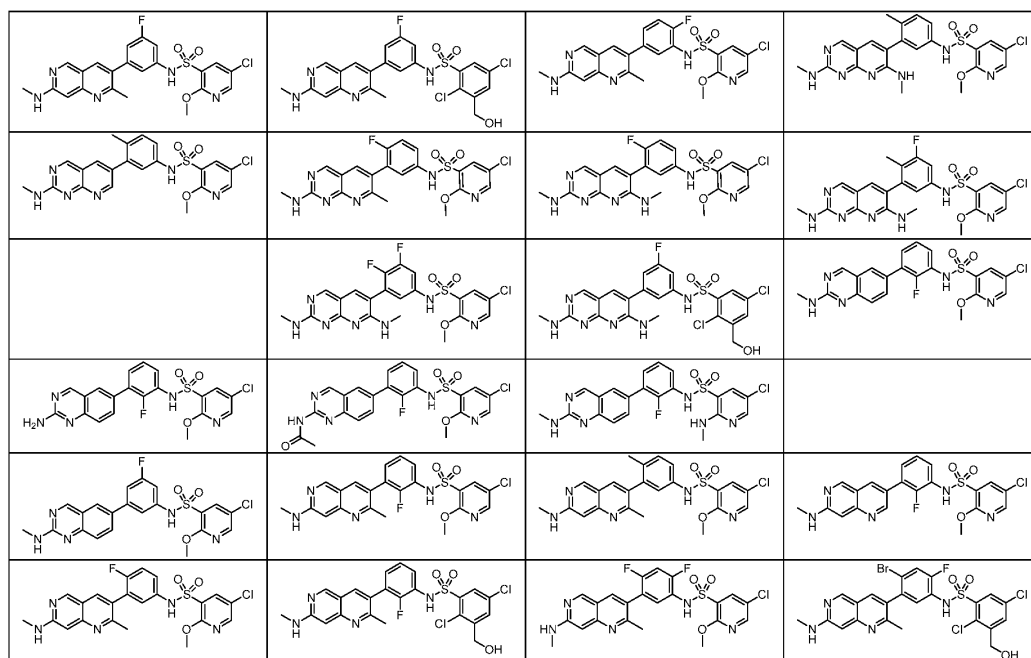
111. The compound of any one of claims 63-108, wherein R¹⁵ is oxetanyl.

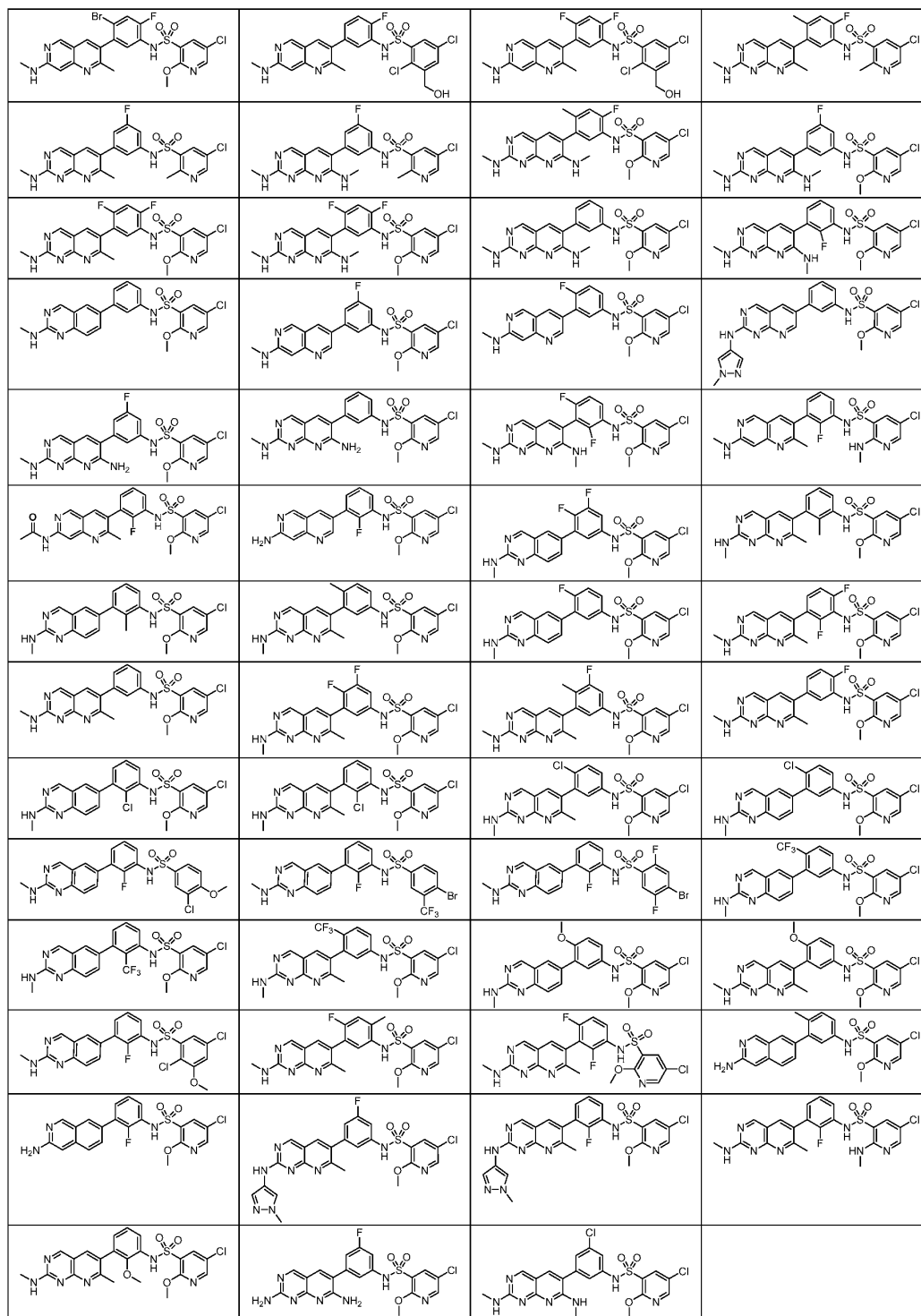
112. The compound of any one of claims 63-108, wherein R¹⁵ is oxetan-2-yl.

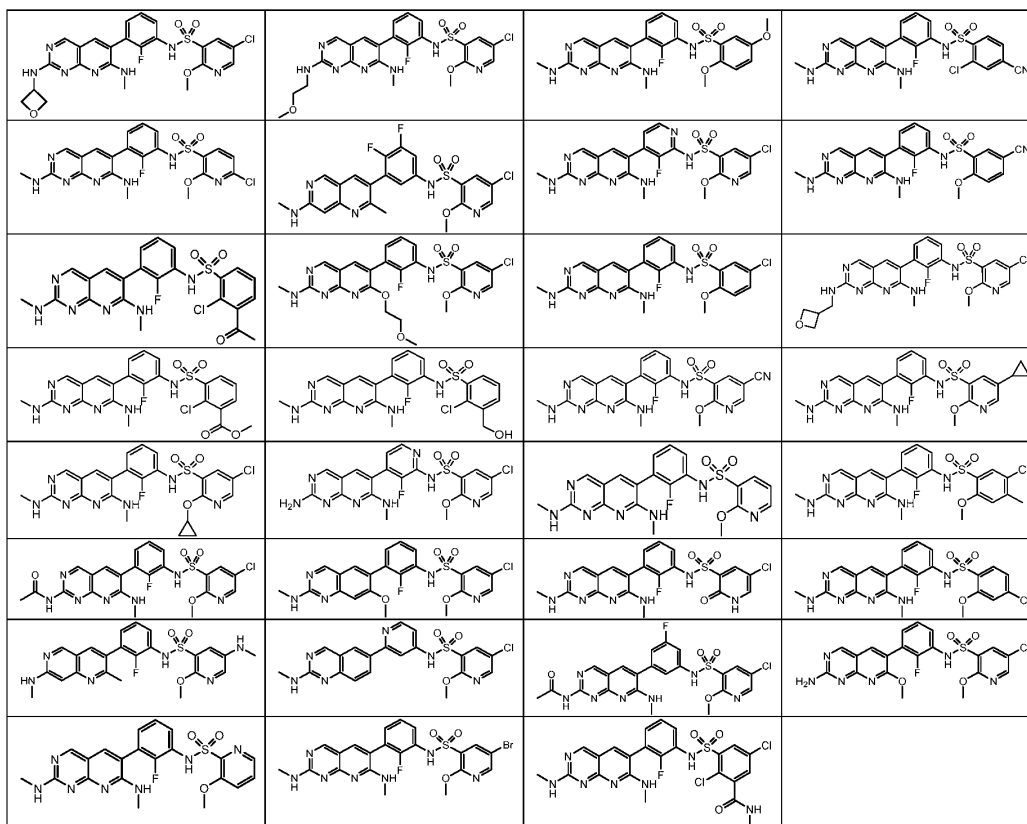
15

113. The compound of any one of claims 63-108, wherein R¹⁵ is oxetan-3-yl.

114. A compound selected from the group consisting of:







and pharmaceutically acceptable salts, enantiomers, stereoisomers, and tautomers thereof.

115. A pharmaceutical composition comprising a compound according to any one of claims 1-114,
5 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

116. A method of treating a disease caused by a dysregulation of an integrated stress response
and/or an unfolded protein response in a patient in need thereof, comprising administering to the
patient a therapeutically effective amount of the compound of any one of claims 1-114, or a
10 pharmaceutically acceptable salt thereof, or of the pharmaceutical composition of claim 115.

117. The method of claim 116, wherein the dysregulation of the integrated stress response and/or
an unfolded protein response is caused by a kinase selected from the group consisting of PERK
kinase and GCN2 kinase.

15

118. The method of claim 116 or 117, wherein the dysregulation of the integrated stress response and/or the unfolded protein response is caused by GCN2 kinase.

119. The method of claim 116 or 117, wherein the dysregulation of the integrated stress response
5 and/or the unfolded protein response is caused by PERK kinase.

120. A method of modulating the activity of GCN2 kinase in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of the compound of any one of claims 1-114, or a pharmaceutically acceptable salt thereof, or of the pharmaceutical composition of claim
10 115.

121. A method of activating GCN2 kinase in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of the compound of any one of claims 1-114, or a pharmaceutically acceptable salt thereof, or of the pharmaceutical composition of claim 115.

122. A method of modulating the activity of PERK kinase in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of the compound of any one of claims 1-114, or a pharmaceutically acceptable salt thereof, or of the pharmaceutical composition of claim
15 115.

123. A method of activating PERK kinase in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of the compound of any one of claims 1-114, or a pharmaceutically acceptable salt thereof, or of the pharmaceutical composition of claim 115.
20

124. A method of inhibiting GCN2 kinase and inhibiting PERK kinase in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of the compound of any one of claims 1-114, or a pharmaceutically acceptable salt thereof, or of the pharmaceutical composition of claim 115.
25

125. A method of inhibiting the activity of GCN2 kinase in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of the compound of any one of claims 1-114, or a pharmaceutically acceptable salt thereof, or of the pharmaceutical composition of claim
30 115.

126. A method of inhibiting the activity of PERK kinase in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of the compound of any one of claims 1-114, or a pharmaceutically acceptable salt thereof, or of the pharmaceutical composition of claim 115.
- 5
127. 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 1-114, or a pharmaceutically acceptable salt thereof, or of the pharmaceutical composition of claim 115.
- 10
128. The method of claim 126, wherein the cancer is selected from the group consisting of colorectal cancer, lung cancer, mesothelioma, pancreatic cancer, pharyngeal cancer, laryngeal cancer, esophagus cancer, gastric, duodenal cancer, small intestinal cancer, breast cancer, ovarian cancer, testis tumor, prostate, liver cancer, thyroid cancer, renal cancer, uterine cancer, gestational choriocarcinoma, brain tumor, retinoblastoma, skin cancer, melanoma, sarcoma, fibrosarcoma,
- 15
- malignant bone tumor, urinary bladder cancer, hematologic cancer, leukemia, acute myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myeloid leukemia, multiple myeloma, B-cell lymphoma, Follicular lymphoma, mantle cell lymphoma, diffuse large B cell lymphoma, T-cell lymphoma, erythroleukemia, histiocytic lymphoma, waldenstrom macroglobulinemia, light chain amyloidosis, and malignant lymphoma.
- 20
129. The method of claim 127 or 128, wherein the cancer is leukemia.
130. The method of claim 127 or 128, wherein the cancer is acute myeloid leukemia.
- 25
131. The method of claim 127 or 128, wherein the cancer is acute lymphoblastic leukemia.
132. The method of claim 127 or 128, wherein the cancer is fibrosarcoma.
133. The method of claim 127 or 128, wherein the cancer is multiple myeloma.
- 30
134. The method of claim 127 or 128, wherein the cancer is lymphoma.
135. The method of claim 127 or 128, wherein the cancer is B-cell lymphoma.

136. The method of claim 127 or 128, wherein the cancer is T cell lymphoma.

137. A method of treating amyloidosis in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of the compound of any one of claims 1-114, or a
5 pharmaceutically acceptable salt thereof, or of the pharmaceutical composition of claim 115.

138. A method of treating light chain amyloidosis in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of the compound of any one of claims 1-114, or a pharmaceutically acceptable salt thereof, or of the pharmaceutical composition of claim
10 115.

139. A method of treating a disease selected from a GCN2 associated disease and a PERK associated disease, in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of the compound of any one of claims 1-114, or a pharmaceutically
15 acceptable salt thereof, or of the pharmaceutical composition of claim 115.

140. The method of claim 139, wherein the disease is a GCN2 associated disease.

141. The method of claim 139, wherein the disease is a PERK associated disease.
20

142. The method of any one of claims 139-141, wherein the disease is a cancer.

143. The method of claim 142, wherein the cancer is selected from the group consisting of colorectal cancer, lung cancer, mesothelioma, pancreatic cancer, pharyngeal cancer, laryngeal
25 cancer, esophagus cancer, gastric, duodenal cancer, small intestinal cancer, breast cancer, ovarian cancer, testis tumor, prostate, liver cancer, thyroid cancer, renal cancer, uterine cancer, gestational choriocarcinoma, brain tumor, retinoblastoma, skin cancer, melanoma, sarcoma, fibrosarcoma, malignant bone tumor, urinary bladder cancer, hematologic cancer, leukemia, acute myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myeloid leukemia,
30 multiple myeloma, B-cell lymphoma, Follicular lymphoma, Mantle cell lymphoma, diffuse large B cell lymphoma, T-cell lymphoma, erythroleukemia, histocytic lymphoma, waldenstrom macroglobulinemia, and malignant lymphoma.

144. The method of claim 142 or 143, wherein the cancer is leukemia.

145. The method of claim 142 or 143, wherein the cancer is acute myeloid leukemia.
146. The method of claim 142 or 143, wherein the cancer is acute lymphoblastic leukemia.
- 5 147. The method of claim 142 or 143, wherein the cancer is fibrosarcoma.
148. The method of claim 142 or 143, wherein the cancer is multiple myeloma.
149. The method of claim 142 or 143, wherein the cancer is lymphoma.
- 10 150. The method of claim 142 or 143, wherein the cancer is B-cell lymphoma.
151. The method of claim 142 or 143, wherein the cancer is T cell lymphoma.
- 15 152. The method of claim 139, wherein the disease is amyloidosis.
153. The method of claim 139, wherein the disease is light chain amyloidosis.
154. A method of treating a disease selected from a GCN2 associated disease and a PERK
20 associated disease, in a patient in need thereof, comprising administering to the patient a
therapeutically effective amount of a compound according to any one of claims 1-114, or a
pharmaceutically acceptable salt thereof, and a therapeutically effective amount of one or more
therapeutic agents.
- 25 155. The method of claim 154, wherein the disease is a GCN2 associated disease.
156. The method of claim 154, wherein the disease is a PERK associated disease.
157. The method of any one of claims 154-156, wherein the disease is a cancer.
- 30 158. The method of claim 157, wherein the cancer is selected from the group consisting of
colorectal cancer, lung cancer, mesothelioma, pancreatic cancer, pharyngeal cancer, laryngeal
cancer, esophagus cancer, gastric, duodenal cancer, small intestinal cancer, breast cancer, ovarian
cancer, testis tumor, prostate, liver cancer, thyroid cancer, renal cancer, uterine cancer, gestational

choriocarcinoma, brain tumor, retinoblastoma, skin cancer, melanoma, sarcoma, fibrosarcoma, malignant bone tumor, urinary bladder cancer, hematologic cancer, leukemia, acute myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myeloid leukemia, multiple myeloma, B-cell lymphoma, Follicular lymphoma, mantle cell lymphoma, diffuse large B cell lymphoma, T-cell lymphoma, erythroleukemia, histiocytic lymphoma, waldenstrom
5 macroglobulinemia, light chain amyloidosis, and malignant lymphoma.

159. The method of claim 157 or 158, wherein the cancer is leukemia.

10 160. The method of claim 157 or 158, wherein leukemia is acute myeloid leukemia.

161. The method of claim 157 or 158, wherein leukemia is acute lymphoblastic leukemia.

162. The method of claim 157 or 158, wherein the cancer is fibrosarcoma.

15

163. The method of claim 157 or 158, wherein the cancer is multiple myeloma.

164. The method of claim 157 or 158, wherein the cancer is lymphoma.

20 165. The method of claim 157 or 158, wherein the cancer is B-cell lymphoma.

166. The method of claim 157 or 158, wherein the cancer is T cell lymphoma.

167. The method of claim 154, wherein the disease is amyloidosis.

25

168. The method of claim 154, wherein the disease is light chain amyloidosis.

169. The method of any one of claims 154-168, wherein the one or more therapeutic agents is selected from the group consisting of an IMiD agent, a proteasome inhibitor, a steroid, an anti-CD38
30 agent, an anti-CD20 agent, a Bcl-2 inhibitor, a PI3K inhibitor, a bi-specific antibody, a nucleoside analog, a BTK inhibitor, a DNA alkylating agent, an EZH2 inhibitor, an anthracycline, a topoisomerase inhibitor, a platin, a tyrosine kinase inhibitor, an HDAC inhibitor, a nuclear export inhibitor, an anti-microtubule agent, L-asparaginase, pegylated asparaginase, a PERK inhibitor, a

mTOR inhibitor, an immunomodulatory agent, a MAPK pathway inhibitor, a MEK inhibitor, an ERK inhibitor, and a Ras inhibitor.

170. The method of any one of claims 154-168, wherein the one or more therapeutic agents is
5 selected from the group consisting of L-asparaginase, pegaspargase, calaspargase pegol – mnkl, bortezomib, carfilzomib, ixazomib, thalidomide, pomalidomide, lenalidomide, dexamethasone, prednisone, daratumumab, daratumumab / hyaluronidase, isatuximab, rituximab, obinutuzumab, venetoclax, idelalisib, copanlisib, duvelisib, umbralisib, gemcitabine, cytarabine, ibrutinib, acalabrutinib, zanubrutinib, bendamustine, cyclophosphamide, tazemetostat, doxorubicin,
10 daunorubicin, etoposide, oxaloplatin, carboplatin, cisplatinbosutinib, dasatinib, imatinib, nilotinib, ponatinib, panobinostat, selinexor, vincristine, JZP-458, eryaspase, PF745 (JZP-341), asparaginase *Erwinia chrysanthemi* (crisantaspase), *Escherichia coli* asparaginase (colaspace), an anti-PD1 agent, an anti-PDL1 agent, and an anti-CTLA4 agent.
171. The compound of any one of claims 1-114, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 115, for use in treating a disease caused by a dysregulation of an integrated stress response and/or the unfolded protein response in a patient in need thereof.
172. The use of claim 171, wherein the dysregulation of the integrated stress response and/or the
20 unfolded protein response is caused by a kinase selected from the group consisting of PERK kinase and GCN2 kinase.
173. The use of claim 171 or 172, wherein the dysregulation of the integrated stress response and/or the unfolded protein response is caused by GCN2 kinase.
25
174. The use of claim 171 or 172, wherein the dysregulation of the integrated stress response and/or the unfolded protein response is caused by PERK kinase.
175. The compound of any one of claims 1-114, or a pharmaceutically acceptable salt thereof, or
30 the pharmaceutical composition of claim 115, for use in modulating the activity of GCN2 kinase in a patient in need thereof.

176. The compound of any one of claims 1-114, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 115, for use in activating GCN2 kinase in a patient in need thereof.

5 177. The compound of any one of claims 1-114, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 115, for use in modulating the activity of PERK kinase in a patient in need thereof.

178. The compound of any one of claims 1-114, or a pharmaceutically acceptable salt thereof, or
10 the pharmaceutical composition of claim 115, for use in activating PERK kinase in a patient in need thereof.

179. The compound of any one of claims 1-114, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 115, for use in inhibiting GCN2 kinase and inhibiting
15 PERK kinase in a patient in need thereof.

180. The compound of any one of claims 1-114, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 115, for use in modulating the activity of GCN2 kinase in a
20 patient in need thereof.

181. The compound of any one of claims 1-114, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 115, for use in inhibiting the activity of PERK kinase in a patient in need thereof.

25 182. The compound of any one of claims 1-114, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 115, for use in treating a cancer in a patient in need thereof.

183. The use of claim 182, wherein the cancer is selected from the group consisting of colorectal cancer, lung cancer, mesothelioma, pancreatic cancer, pharyngeal cancer, laryngeal cancer,
30 esophagus cancer, gastric, duodenal cancer, small intestinal cancer, breast cancer, ovarian cancer, testis tumor, prostate, liver cancer, thyroid cancer, renal cancer, uterine cancer, gestational choriocarcinoma, brain tumor, retinoblastoma, skin cancer, melanoma, sarcoma, fibrosarcoma, malignant bone tumor, urinary bladder cancer, hematologic cancer, leukemia, acute myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myeloid leukemia,

multiple myeloma, B-cell lymphoma, Follicular lymphoma, mantle cell lymphoma, diffuse large B cell lymphoma, T-cell lymphoma, erythroleukemia, histocytic lymphoma, waldenstrom macroglobulinemia, and malignant lymphoma.

5 184. The use of claim 182 or 183, wherein the cancer is leukemia.

185. The use of claim 182 or 183, wherein the cancer is acute myeloid leukemia.

186. The use of claim 182 or 183, wherein the cancer is acute lymphoblastic leukemia.

10

187. The use of claim 182 or 183, wherein the cancer is fibrosarcoma.

188. The use of claim 182 or 183, wherein the cancer is multiple myeloma.

15 189. The use of claim 182 or 183, wherein the cancer is lymphoma.

190. The use of claim 182 or 183, wherein the cancer is B-cell lymphoma.

191. The use of claim 182 or 183, wherein the cancer is T cell lymphoma.

20

192. The compound of any one of claims 1-114, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 115, for use in treating amyloidosis in a patient in need thereof.

25 193. The compound of any one of claims 1-114, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 115, for use in treating light chain amyloidosis in a patient in need thereof.

194. The compound of any one of claims 1-114, or a pharmaceutically acceptable salt thereof, or
30 the pharmaceutical composition of claim 115, for use in treating a disease selected from a GCN2 associated disease and a PERK associated disease, in a patient in need thereof.

195. The use of claim 194, wherein the disease is a GCN2 associated disease.

196. The use of claim 194, wherein the disease is a PERK associated disease.
197. The use of any one of claims 194-196, wherein the disease is a cancer.
- 5 198. The use of claim 197, wherein the cancer is selected from the group consisting of colorectal cancer, lung cancer, mesothelioma, pancreatic cancer, pharyngeal cancer, laryngeal cancer, esophagus cancer, gastric, duodenal cancer, small intestinal cancer, breast cancer, ovarian cancer, testis tumor, prostate, liver cancer, thyroid cancer, renal cancer, uterine cancer, gestational choriocarcinoma, brain tumor, retinoblastoma, skin cancer, melanoma, sarcoma, fibrosarcoma,
- 10 malignant bone tumor, urinary bladder cancer, hematologic cancer, leukemia, acute myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myeloid leukemia, multiple myeloma, B-cell lymphoma, Follicular lymphoma, mantle cell lymphoma, diffuse large B cell lymphoma, T-cell lymphoma, erythroleukemia, histiocytic lymphoma, waldenstrom macroglobulinemia, and malignant lymphoma.
- 15 199. The use of claim 197 or 198, wherein the cancer is leukemia.
200. The use of claim 197 or 198, wherein the cancer is acute myeloid leukemia.
- 20 201. The use of claim 197 or 198, wherein the cancer is acute lymphoblastic leukemia.
202. The use of claim 197 or 198, wherein the cancer is fibrosarcoma.
203. The method of claim 197 or 198, wherein the cancer is multiple myeloma.
- 25 204. The method of claim 197 or 198, wherein the cancer is lymphoma.
205. The method of claim 197 or 198, wherein the cancer is B-cell lymphoma.
- 30 206. The method of claim 197 or 198, wherein the cancer is T cell lymphoma.
207. The use of claim 194, wherein the disease is amyloidosis.
208. The use of claim 194, wherein the disease is light chain amyloidosis.

209. The compound of any one of claims 1-114, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 115, for use in treating a disease selected from a GCN2 associated disease and a PERK associated disease, in a patient in need thereof.
- 5 210. The use of claim 209, wherein the disease is a GCN2 associated disease.
211. The use of claim 209, wherein the disease is a PERK associated disease.
212. The use of any one of claims 209-211, wherein the disease is a cancer.
- 10 213. The use of claim 212, wherein the cancer is selected from the group consisting of colorectal cancer, lung cancer, mesothelioma, pancreatic cancer, pharyngeal cancer, laryngeal cancer, esophagus cancer, gastric, duodenal cancer, small intestinal cancer, breast cancer, ovarian cancer, testis tumor, prostate, liver cancer, thyroid cancer, renal cancer, uterine cancer, gestational
- 15 choriocarcinoma, brain tumor, retinoblastoma, skin cancer, melanoma, sarcoma, fibrosarcoma, malignant bone tumor, urinary bladder cancer, hematologic cancer, leukemia, acute myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myeloid leukemia, multiple myeloma, B-cell lymphoma, Follicular lymphoma, mantle cell lymphoma, diffuse large B cell lymphoma, T-cell lymphoma, erythroleukemia, histocytic lymphoma, waldenstrom
- 20 macroglobulinemia, and malignant lymphoma.
214. The use of claim 212 or 213, wherein the cancer is leukemia.
215. The use of claim 212 or 213, wherein leukemia is acute myeloid leukemia.
- 25 216. The use of claim 212 or 213, wherein leukemia is acute lymphoblastic leukemia.
217. The use of claim 212 or 213, wherein the cancer is fibrosarcoma.
- 30 218. The method of claim 212 or 213, wherein the cancer is multiple myeloma.
219. The method of claim 212 or 213, wherein the cancer is lymphoma.
220. The method of claim 212 or 213, wherein the cancer is B-cell lymphoma.

221. The method of claim 212 or 213, wherein the cancer is T cell lymphoma.
222. The use of claim 209, wherein the disease is amyloidosis.
- 5 223. The method of claim 209, wherein the disease is light chain amyloidosis.
224. The use of any one of claims 209-223, wherein the one or more therapeutic agents is selected from the group consisting of an IMiD agent, a proteasome inhibitor, a steroid, an anti-CD38 agent, an anti-CD20 agent, a Bcl-2 inhibitor, a PI3K inhibitor, a Bi-specific antibody, a nucleoside analog, a
10 BTK inhibitor, a DNA alkylating agent, an EZH2 inhibitor, an anthracycline, a topoisomerase inhibitor, a platin, a tyrosine kinase inhibitor, a HDAC inhibitor, a nuclear export inhibitor, an anti-microtubule agent, L-asparaginase, pegylated asparaginase, a PERK inhibitor, a mTOR inhibitor, an immunomodulatory agent, a MAPK pathway inhibitor, a MEK inhibitor, an ERK inhibitor, and a Ras inhibitor.
- 15 225. The use of any one of claims 209-223, wherein the one or more therapeutic agents is selected from the group consisting of L-asparaginase, pegaspargase, calaspargase pegol – mnkl, bortezomib, carfilzomib, ixazomib, thalidomide, pomalidomide, lenalidomide, dexamethasone, prednisone, daratumumab, daratumumab / hyaluronidase, isatuximab, rituximab, obinutuzumab, venetoclax,
20 idelalisib, copanlisib, duvelisib, umbralisib, gemcitabine, cytarabine, ibrutinib, acalabrutinib, zanubrutinib, bendamustine, cyclophosphamide, tazemetostat, doxorubicin, daunorubicin, etoposide, oxaloplatin, carboplatin, cisplatinbosutinib, dasatinib, imatinib, nilotinib, ponatinib, panobinostat, selinexor, vincristine, JZP-458, eryaspase, PF745 (JZP-341), asparaginase *Erwinia chrysanthemi* (crisantaspase), *Escherichia coli* asparaginase (colaspase), an anti-PD1 agent, an anti-PDL1 agent,
25 and an anti-CTLA4 agent.