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(54) Title: HETEROCYCLIC COMPOUNDS AS KINASE INHIBITORS

(57) Abstract: Heterocyclic compounds as CDK4 or CDK6 or other CDK inhibitors are provided. The compounds may find use as therapeutic agents for the treatment of diseases and may find particular use in oncology.

HETEROCYCLIC COMPOUNDS AS KINASE INHIBITORS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 63/183,529, filed on May 3, 2021, the content of which is incorporated herein by reference in its entirety.

FIELD OF INVENTION

[0002] This disclosure relates generally to therapeutics which play a crucial role in the control of the cell cycle and more particularly, compounds that inhibit cyclin-dependent kinases (CDK). The disclosure also provides pharmaceutically acceptable compositions comprising compounds of the present disclosure and methods of using said compositions in the treatment of diseases associated with these pathways.

BACKGROUND

[0003] The cell cycle is a period between the successive divisions of a cell. During this period, the contents of the cell must be accurately replicated. The processes that permit the cell to divide are very precisely controlled by a multitude of enzymatic reactions amongst which the protein kinase-triggered protein phosphorylation plays a major role. In eukaryotes, there are four main stages/phases of cell cycle namely the Gap-1 (G1) phase, Synthesis (S) phase, Gap-2 (G2) and Mitosis (M) phases. An extended phase of Gap-1 phase is coined as Gap-0 (G0) phase or Resting phase (Cancers 2014, 6, 2224-2242).

[0004] Uncontrolled proliferation is the hallmark of cancer and other proliferative disorders and abnormal cell cycle regulation is, therefore, common in these diseases. Cyclin-dependent kinases (CDK) constitute a heterodimeric family of serine/threonine protein kinases involved in cell cycle and transcription. They include two main groups: cell cycle CDK and transcriptional CDK. The functionality of CDK depends on specific interactions with regulatory proteins named cyclins which form heterodimeric complexes with their partners. These complexes are important regulators of the cellular processes, especially in the cell cycle progression.

[0005] The human proteome contains 20 CDK along with 29 cyclins. CDK1, CDK2, CDK4 and CDK6 are generally considered cell cycle CDK, whereas CDK7, CDK8, CDK9 and CDK11 are mainly involved in transcription regulation (Genome Biol 2014;15(6):122, Nat Cell Biol 2009;11(11):1275-6). CDK5 is the prototype of atypical CDK: it is activated by

the non-cyclin proteins p35 (or Cdk5R1) and p39 (or Cdk5R2) and has unique post-mitotic functions in neuronal biology, angiogenesis and cell differentiation. Proliferative signals induce the transition from the G0 or G1 phases into S phase through the activation of the structurally related CDK4 and CDK6 [Development, 2013;140 (15):3079-93, Biochem Pharmacol 2012;84(8):985-93, Nature 2014;510(7505):393-6]. The binding of cyclin D to CDK4 and to CDK6 promotes the phosphorylation of the transcriptional repressor retinoblastoma protein (RB1).

[0006] CDK hyperactivity is often observed in cancer, reflecting their prominent role in cell cycle and transcription regulation. In cancer cells, the process of cell division becomes unregulated, resulting in uncontrolled growth that leads to the development of a tumor. A number of mechanisms contribute to the dysregulation of the cell cycle in malignant cells, including the amplification and hyperactivity of CDK4/6, or their genomic instability, which might cause CDK4/6 to become oncogenic drivers of cell replication. Usurping these mechanisms, cancer cells can continue to replicate by triggering the G1 to S phase transition. This process appears to be facilitated by a shortening of the G1 phase. In a cancer cell, CDK4/6 antagonizes intrinsic tumor suppression mechanisms including cell senescence and apoptosis, which further augments the growth of a tumor. Cancer cells also upregulate other CDK and cyclins and decrease suppressive mechanisms such as intrinsic CDK inhibitors and tumor suppressor proteins. The overall effect of this type of cell cycle dysregulation is malignant cell proliferation and the development of cancer (Clinical Breast Cancer, 2016, 1526-8209).

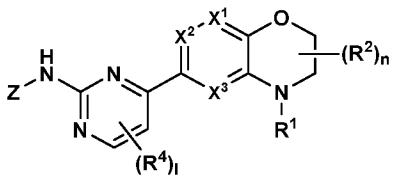
[0007] Several CDK inhibitors have been reported (such as in WO2011101409 and WO2011101417) or clinically developed. Flavopiridol and R-Roscovitine (Seliciclib), were the first generation of pan-CDK inhibitors with anti-tumor activity attributed to down-regulation of CDK9-mediated anti-apoptotic proteins, especially Mcl-1. Recently, a new generation of CDK inhibitors have been developed, advanced to clinical trials, and approved for certain types of cancer. Dinaciclib, a selective inhibitor of CDK1, CDK2, CDK5, and CDK9, was directed towards refractory chronic lymphocytic leukemia while palbociclib was tested against advanced estrogen receptor (ER)-positive breast cancer as a selective inhibitor of CDK4 and CDK6. The development of more selective second and third generation CDK inhibitors, including specific CDK4/6 inhibitors, has led to a renewed enthusiasm for manipulating the cyclin D1-CDK4/6 axis in cancer treatment. There are three FDA-approved CDK4/6 inhibitors presently: Palbociclib, Ribociclib and Abemaciclib.

[0008] The development of therapies, including monotherapies, for treatment of proliferative disorders using a therapeutic targeted generically at CDK, or specifically at dual inhibition of CDK4 and CDK6, is therefore potentially highly desirable.

[0009] There is still a need for new CDK4/6 inhibitors. Compounds for the treatment of hyper-proliferative diseases preferably have at least one advantageous property selected from selectivity, potency, stability, pharmacodynamic properties and safety profile. In this regard, a novel class of CDK4/6 inhibitors is provided herein.

BRIEF SUMMARY

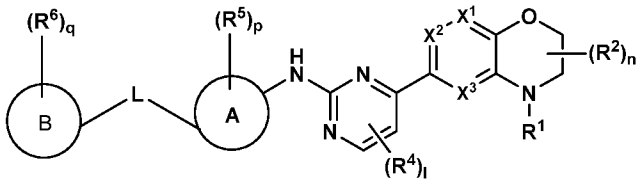
[0010] In one aspect, provided is a compound of Formula (J):



(J),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein X^1, X^2, X^3, Z, R^1, R^2, R^3, R^4, l, m, and n are as detailed herein.

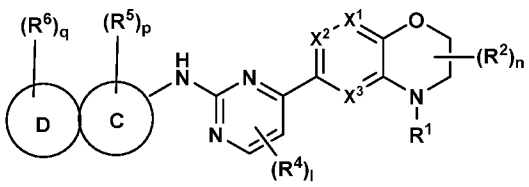
[0011] In some embodiments, provided is a compound of Formula (I):



(I),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein X^1, X^2, X^3, A, B, L, R^1, R^2, R^3, R^4, R^5, R^6, l, n, p, and q are as detailed herein.

[0012] In some embodiments, provided is a compound of Formula (II):



(II),

or a stereoisomer or tautome thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein X^1, X^2, X^3, C, D, R^1, R^2, R^3, R^4, R^5, R^6, l, n, p, and q are as detailed herein.

[0013] In another aspect, provided is a method of treating cancer in an individual in need thereof comprising administering to the individual a therapeutically effective amount of a compound as detailed herein. Also provided is a method of modulating CDK4/6 in an individual, comprising administering to the individual a compound detailed herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing. Also provided is a method of modulating CDK4/6 and one or more of CDK1, CDK2, and CDK9 in an individual, comprising administering to the individual a compound detailed herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing. Also provided is a method of inhibiting CDK4/6 in a cell, comprising administering a compound detailed herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, to the cell. Also provided is a method of inhibiting CDK4/6 and one or more of CDK1, CDK2, and CDK9 in a cell, comprising administering a compound detailed herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, to the cell. In some embodiments of the methods detailed herein, the methods comprise administration of a compound detailed herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, as a monotherapy.

[0014] In another aspect, provided is a pharmaceutical composition comprising a compound detailed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient. Kits comprising a compound detailed herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, are also provided. Kits may optionally include instructions for use, such as instructions for use in any of the methods detailed herein, for example, for use in the treatment of cancer. A compound as detailed herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, is also provided for the manufacture of a medicament for the treatment of cancer.

DETAILED DESCRIPTION

Definitions

[0015] As used in the present specification, the following words, phrases and symbols are generally intended to have the meanings as set forth below, except to the extent that the context in which they are used indicates otherwise.

[0016] The term "about" refers to a variation of ±1%, ±3%, ±5%, or ±10% of the value specified. For example, "about 50" can in some embodiments includes a range of from 45 to 55. For integer ranges, the term "about" can include one or two integers greater than and/or less than a recited integer at each end of the range. Unless indicated otherwise herein, the term "about" is intended to include values, e.g., weight percentages, proximate to the recited range that are equivalent in terms of the functionality of the individual ingredient, the composition, or the embodiment. Also, the singular forms "a" and "the" include plural references unless the context clearly dictates otherwise. Thus, e.g., reference to "the compound" includes a plurality of such compounds and includes reference to one or more compounds and equivalents thereof known to those skilled in the art.

[0017] "Alkyl" refers to an unbranched or branched saturated hydrocarbon chain. As used herein, alkyl has 1 to 20 carbon atoms (C_{1-20} alkyl or C_1-C_{20} alkyl), 1 to 8 carbon atoms (C_{1-8} alkyl or C_1-C_8 alkyl), 1 to 6 carbon atoms (C_{1-6} alkyl or C_1-C_6 alkyl), or 1 to 4 carbon atoms (C_{1-4} alkyl or C_1-C_4 alkyl). Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl, and 3-methylpentyl. When an alkyl residue having a specific number of carbons is named by chemical name or identified by molecular formula, all positional isomers having that number of carbons may be encompassed; thus, for example, "butyl" includes n-butyl (i.e. $-(CH_2)_3CH_3$), sec-butyl (i.e. $-CH(CH_3)CH_2CH_3$), iso-butyl (i.e. $-CH_2CH(CH_3)_2$) and tert-butyl (i.e. $-C(CH_3)_3$); and "propyl" includes n-propyl (i.e. $-(CH_2)_2CH_3$) and isopropyl (i.e. $-CH(CH_3)_2$).

[0018] "Haloalkyl" refers to an unbranched or branched alkyl group as defined above, wherein one or more (e.g., 1 to 6 or 1 to 3) hydrogen atoms are replaced by a halogen. For example, where a residue is substituted with more than one halogen, it may be referred to by using a prefix corresponding to the number of halogen moieties attached. Dihaloalkyl and trihaloalkyl refer to alkyl substituted with two ("di") or three ("tri") halo groups, which may

be, but are not necessarily, the same halogen. Examples of haloalkyl include difluoromethyl (-CHF_2) and trifluoromethyl (-CF_3).

[0019] "Alkenyl" as used herein refers to an unsaturated linear or branched hydrocarbon chain or combination thereof, having at least one site of olefinic unsaturation (*i.e.*, having at least one moiety of the formula C=C). The alkenyl group may be in "cis" or "trans" configurations, or alternatively in "E" or "Z" configurations. Particular alkenyl groups are those having 2 to 20 carbon atoms (C_{2-20} alkenyl or C_2-C_{20} alkenyl), having 2 to 8 carbon atoms (C_{2-8} alkenyl or C_2-C_8 alkenyl), having 2 to 6 carbon atoms (C_{2-6} alkenyl or C_2-C_6 alkenyl), or having 2 to 4 carbon atoms (C_{2-4} alkenyl or C_2-C_4 alkenyl). Examples of alkenyl include, but are not limited to, groups such as ethenyl (or vinyl), prop-1-enyl, prop-2-enyl (or allyl), 2-methylprop-1-enyl, but-1-enyl, but-2-enyl, but-3-enyl, buta-1,3-dienyl, 2-methylbuta-1,3-dienyl, homologs and isomers thereof, and the like.

[0020] "Alkylene" as used herein refers to the same residues as alkyl, but having bivalency. Particular alkylene groups are those having 1 to 6 carbon atoms (C_{1-6} alkylene or C_1-C_6 alkylene), 1 to 5 carbon atoms (C_{1-5} alkylene or C_1-C_5 alkylene), 1 to 4 carbon atoms (C_{1-4} alkylene or C_1-C_4 alkylene) or 1 to 3 carbon atoms (C_{1-3} alkylene or C_1-C_3 alkylene). Examples of alkylene include, but are not limited to, groups such as methylene (-CH_2-), ethylene (-CH_2CH_2-), propylene (-$CH_2CH_2CH_2$-), butylene (-$CH_2CH_2CH_2CH_2$-), and the like.

[0021] "Alkoxy" refers to the group "-O-alkyl". Examples of alkoxy groups include, without limitation, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, tert-butoxy, sec-butoxy, npentoxy, n-hexoxy and 1,2-dimethylbutoxy.

[0022] "Alkynyl" as used herein refers to an unsaturated linear or branched hydrocarbon chain or combination thereof, having at least one site of acetylenic unsaturation (*i.e.*, having at least one moiety of the formula C≡C). Particular alkynyl groups are those having 2 to 20 carbon atoms (C_{2-20} alkynyl or C_2-C_{20} alkynyl), having 2 to 8 carbon atoms (C_{2-8} alkynyl or C_2-C_8 alkynyl), having 2 to 6 carbon atoms (C_{2-6} alkynyl or C_2-C_6 alkynyl), or having 2 to 4 carbon atoms (C_{2-4} alkynyl or C_2-C_4 alkynyl). Examples of alkynyl include, but are not limited to, groups such as ethynyl (or acetylenyl), prop-1-ynyl, prop-2-ynyl (or propargyl), but-1-ynyl, but-2-ynyl, but-3-ynyl, homologs and isomers thereof, and the like.

[0023] "Aryl" refers to and includes polyunsaturated aromatic hydrocarbon groups. Aryl may contain additional fused rings (*e.g.*, from 1 to 3 rings). In one variation, the aryl group contains from 6 to 14 annular carbon atoms ("C_6-C_{14} aryl"),. Examples of aryl groups

include, but are not limited to, phenyl, naphthyl, and anthryl. Aryl, however, does not encompass or overlap in any way with heteroaryl defined below. If one or more aryl groups are fused with a heteroaryl, the resulting ring system is heteroaryl. If one or more aryl groups are fused with a heterocyclyl, the resulting ring system is heterocyclyl.

[0024] "Carbonyl" refers to the group C=O.

[0025] "Cycloalkyl" refers to a saturated or partially unsaturated cyclic alkyl group having a single ring or multiple rings including fused, bridged and spiro ring systems. The term "cycloalkyl" includes cycloalkenyl groups (i.e., the cyclic group having at least one double bond) and carbocyclic fused ring systems having at least one sp^3 carbon atom (i.e., at least one non-aromatic ring). As used herein, cycloalkyl has from 3 to 20 ring carbon atoms (C_{3-20} cycloalkyl or C_3-C_{20} cycloalkyl), 3 to 12 ring carbon atoms (C_{3-12} cycloalkyl or C_3-C_{12} cycloalkyl), 3 to 10 ring carbon atoms (C_{3-10} cycloalkyl or C_3-C_{10} cycloalkyl), 3 to 8 ring carbon atoms (C_{3-8} cycloalkyl or C_3-C_8 cycloalkyl), or 3 to 6 ring carbon atoms (C_{3-6} cycloalkyl or C_3-C_6 cycloalkyl). Monocyclic groups include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl. Further, the term cycloalkyl is intended to encompass any non-aromatic cyclic alkyl ring which may be fused to an aryl ring, regardless of the attachment to the remainder of the molecule.

[0026] "Halo" or "halogen" refers to elements of the Group 17 series having atomic number 9 to 85. Preferred halo groups include fluoro, chloro, bromo and iodo.

[0027] "Heteroaryl" refers to an aromatic group having a single ring, multiple rings or multiple fused rings, with one or more ring heteroatoms independently selected from nitrogen, oxygen, and sulfur. As used herein, heteroaryl includes 1 to 20 ring carbon atoms, 3 to 12 ring carbon atoms, or 3 to 8 carbon ring atoms, and 1 to 5 ring heteroatoms, 1 to 4 ring heteroatoms, 1 to 3 ring heteroatoms, 1 to 2 ring heteroatoms, or 1 ring heteroatom independently selected from nitrogen, oxygen and sulfur. In certain instances, heteroaryl includes 5- to 12- membered, 5- to 10- membered ring systems, 5- to 7- membered ring systems, or 5- to 6- membered ring systems, each independently having 1 to 4 ring heteroatoms, 1 to 3 ring heteroatoms, 1 to 2 ring heteroatoms, or 1 ring heteroatom independently selected from nitrogen, oxygen and sulfur. Any aromatic ring, having a single or multiple fused rings, containing at least one heteroatom, is considered a heteroaryl regardless of the attachment to the remainder of the molecule (i.e., through any one of the fused rings). Heteroaryl does not encompass or overlap with aryl as defined above.

[0028] "Heterocyclyl" refers to a saturated or partially unsaturated cyclic alkyl group, with one or more ring heteroatoms independently selected from nitrogen, oxygen and sulfur. The term "heterocyclyl" includes heterocycloalkenyl groups (i.e., the heterocyclyl group having at least one double bond), bicyclic heterocyclic groups, such as bridged-heterocyclyl groups, fused-heterocyclyl groups and spiro-heterocyclyl groups. A heterocyclyl may be a single ring or multiple rings wherein the multiple rings may be fused, bridged or spiro, and may comprise one or more (e.g., 1 to 3) oxo (=O) or N-oxide ($-O^-$) moieties. Any non-aromatic ring containing at least one heteroatom is considered a heterocyclyl, regardless of the attachment (i.e., can be bound through a carbon atom or a heteroatom). Further, the term heterocyclyl is intended to encompass any non-aromatic ring containing at least one heteroatom, which ring may be fused to an aryl or heteroaryl ring, regardless of the attachment to the remainder of the molecule. As used herein, heterocyclyl has 2 to 20 ring carbon atoms, 2 to 12 ring carbon atoms, 2 to 10 ring carbon atoms, 2 to 8 ring carbon atoms, 3 to 12 ring carbon atoms, 3 to 8 ring carbon atoms, or 3 to 6 ring carbon atoms; and 1 to 5 ring heteroatoms, 1 to 4 ring heteroatoms, 1 to 3 ring heteroatoms, 1 to 2 ring heteroatoms, or 1 ring heteroatom independently selected from nitrogen, sulfur or oxygen. In certain instances, heteroaryl includes 3- to 12- membered, 5- to 10- membered ring systems, 5- to 7-membered ring systems, or 5- to 6- membered ring systems, each independently having 1 to 4 ring heteroatoms, 1 to 3 ring heteroatoms, 1 to 2 ring heteroatoms, or 1 ring heteroatom independently selected from nitrogen, oxygen and sulfur. The term "heterocyclyl" also includes "spiroheterocyclyl" when there are two positions for substitution on the same carbon atom. In certain embodiments, the term "bicyclic heterocyclic" encompasses fused-heterocyclyl groups.

[0029] "Oxo" refers to the moiety =O.

[0030] "Optionally substituted" unless otherwise specified means that a group may be unsubstituted or substituted by one or more (e.g., 1, 2, 3, 4 or 5) of the substituents listed for that group in which the substituents may be the same of different, provided that the group's normal valence is not exceeded. In one embodiment, an optionally substituted group has one substituent. In another embodiment, an optionally substituted group has two substituents. In another embodiment, an optionally substituted group has three substituents. In another embodiment, an optionally substituted group has four substituents. In some embodiments, an optionally substituted group has 1 to 2, 2 to 5, 3 to 5, 2 to 3, 2 to 4, 3 to 4, 1 to 3, 1 to 4 or 1 to 5 substituents.

[0031] As used herein "CDK" refers to one or more cyclin-dependent kinases. CDK4/6 refers to both CDK4 and CDK6. Thus, inhibitors of CDK4/6 inhibit both CDK4 and CDK6.

[0032] A "pharmaceutically acceptable carrier" refers to an ingredient in a pharmaceutical formulation, other than an active ingredient, which is nontoxic to a subject. A pharmaceutically acceptable carrier includes, but is not limited to, a buffer, excipient, stabilizer, or preservative.

[0033] As used herein, "treatment" or "treating" is an approach for obtaining beneficial or desired results including clinical results. For example, beneficial or desired results include, but are not limited to, one or more of the following: decreasing symptoms resulting from the disease, increasing the quality of life of those suffering from the disease, decreasing the dose of other medications required to treat the disease, delaying the progression of the disease, and/or prolonging survival of individuals. In reference to cancers or other unwanted cell proliferation, beneficial or desired results include shrinking a tumor (reducing tumor size); decreasing the growth rate of the tumor (such as to suppress tumor growth); reducing the number of cancer cells; inhibiting, retarding or slowing to some extent and preferably stopping cancer cell infiltration into peripheral organs; inhibiting (slowing to some extent and preferably stopping) tumor metastasis; inhibiting tumor growth; preventing or delaying occurrence and/or recurrence of tumor; and/or relieving to some extent one or more of the symptoms associated with the cancer. In some embodiments, beneficial or desired results include preventing or delaying occurrence and/or recurrence, such as of unwanted cell proliferation.

[0034] As used herein, "delaying development of a disease" means to defer, hinder, slow, retard, stabilize, and/or postpone development of the disease (such as cancer). This delay can be of varying lengths of time, depending on the history of the disease and/or individual being treated. As is evident to one skilled in the art, a sufficient or significant delay can, in effect, encompass prevention, in that the individual does not develop the disease. For example, a late stage cancer, such as development of metastasis, may be delayed.

[0035] As used herein, an "effective dosage" or "effective amount" of compound or salt thereof or pharmaceutical composition is an amount sufficient to effect beneficial or desired results. For prophylactic use, beneficial or desired results include results such as eliminating or reducing the risk, lessening the severity of, or delaying the onset of the disease, including biochemical, histological and/or behavioral symptoms of the disease, its complications and

intermediate pathological phenotypes presenting during development of the disease. For therapeutic use, beneficial or desired results include ameliorating, palliating, lessening, delaying or decreasing one or more symptoms resulting from the disease, increasing the quality of life of those suffering from the disease, decreasing the dose of other medications required to treat the disease, enhancing effect of another medication such as via targeting, delaying the progression of the disease, and/or prolonging survival. In reference to cancers or other unwanted cell proliferation, an effective amount comprises an amount sufficient to cause a tumor to shrink and/or to decrease the growth rate of the tumor (such as to suppress tumor growth) or to prevent or delay other unwanted cell proliferation. In some embodiments, an effective amount is an amount sufficient to delay development. In some embodiments, an effective amount is an amount sufficient to prevent or delay occurrence and/or recurrence. An effective amount can be administered in one or more administrations, in the case of cancer, the effective amount of the drug or composition may: (i) reduce the number of cancer cells; (ii) reduce tumor size; (iii) inhibit, retard, slow to some extent and preferably stop cancer cell infiltration into peripheral organs; (iv) inhibit (i.e., slow to some extent and preferably stop) tumor metastasis; (v) inhibit tumor growth; (vi) prevent or delay occurrence and/or recurrence of tumor; and/or (vii) relieve to some extent one or more of the symptoms associated with the cancer. An effective dosage can be administered in one or more administrations. For purposes of this disclosure, an effective dosage of compound or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or pharmaceutical composition is an amount sufficient to accomplish prophylactic or therapeutic treatment either directly or indirectly. It is intended and understood that an effective dosage of a compound or salt thereof, or pharmaceutical composition may or may not be achieved in conjunction with another drug, compound, or pharmaceutical composition. Thus, an "effective dosage" may be considered in the context of administering one or more therapeutic agents, and a single agent may be considered to be given in an effective amount if, in conjunction with one or more other agents, a desirable result may be or is achieved.

[0036] As used herein, the term "individual" is a mammal, including humans. An individual includes, but is not limited to, human, bovine, horse, feline, canine, rodent, or primate. In some embodiments, the individual is human. The individual (such as a human) may have advanced disease or lesser extent of disease, such as low tumor burden. In some embodiments, the individual is at an early stage of a proliferative disease (such as cancer). In

some embodiments, the individual is at an advanced stage of a proliferative disease (such as an advanced cancer).

[0037] As used herein, by "pharmaceutically acceptable" or "pharmacologically acceptable" is meant a material that is not biologically or otherwise undesirable, e.g., the material may be incorporated into a pharmaceutical composition administered to a patient without causing any significant undesirable biological effects or interacting in a deleterious manner with any of the other components of the composition in which it is contained. Pharmaceutically acceptable carriers or excipients have preferably met the required standards of toxicological and manufacturing testing and/or are included on the Inactive Ingredient Guide prepared by the U.S. Food and Drug administration.

[0038] "Pharmaceutically acceptable salts" are those salts which retain at least some of the biological activity of the free (non-salt) compound and which can be administered as drugs or pharmaceuticals to an individual. Such salts, for example, include: (1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, oxalic acid, propionic acid, succinic acid, maleic acid, tartaric acid and the like; (2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base. Acceptable organic bases include ethanolamine, diethanolamine, triethanolamine and the like. Acceptable inorganic bases include aluminum hydroxide, calcium hydroxide, potassium hydroxide, sodium carbonate, sodium hydroxide, and the like. Further examples of pharmaceutically acceptable salts include those listed in Berge et al., Pharmaceutical Salts, J. Pharm. Sci. 1977 Jan;66(1):1-19. Pharmaceutically acceptable salts can be prepared in situ in the manufacturing process, or by separately reacting a purified compound of the disclosure in its free acid or base form with a suitable organic or inorganic base or acid, respectively, and isolating the salt thus formed during subsequent purification.

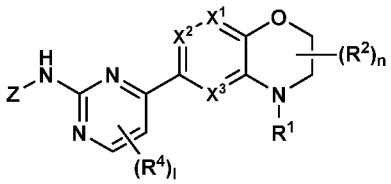
[0039] The term "excipient" as used herein means an inert or inactive substance that may be used in the production of a drug or pharmaceutical, such as a tablet containing a compound of the disclosure as an active ingredient. Various substances may be embraced by the term excipient, including without limitation any substance used as a binder, disintegrant, coating, compression/encapsulation aid, cream or lotion, lubricant, solutions for parenteral administration, materials for chewable tablets, sweetener or flavoring, suspending/gelling

agent, or wet granulation agent. Binders include, e.g., carbomers, povidone, xanthan gum, etc.; coatings include, e.g., cellulose acetate phthalate, ethylcellulose, gellan gum, maltodextrin, enteric coatings, etc.; compression/encapsulation aids include, e.g., calcium carbonate, dextrose, fructose dc (dc="directly compressible"), honey dc, lactose (anhydrate or monohydrate; optionally in combination with aspartame, cellulose, or microcrystalline cellulose), starch dc, sucrose, etc.; disintegrants include, e.g., croscarmellose sodium, gellan gum, sodium starch glycolate, etc.; creams or lotions include, e.g., maltodextrin, carrageenans, etc.; lubricants include, e.g., magnesium stearate, stearic acid, sodium stearyl fumarate, etc.; materials for chewable tablets include, e.g., dextrose, fructose dc, lactose (monohydrate, optionally in combination with aspartame or cellulose), etc.; suspending/gelling agents include, e.g., carrageenan, sodium starch glycolate, xanthan gum, etc.; sweeteners include, e.g., aspartame, dextrose, fructose dc, sorbitol, sucrose dc, etc.; and wet granulation agents include, e.g., calcium carbonate, maltodextrin, microcrystalline cellulose, etc.

[0040] It is understood that embodiments, aspects and variations described herein also include "consisting" and/or "consisting essentially of" embodiments, aspects and variations.

Compounds

[0041] In one aspect, provided is a compound of Formula (J):



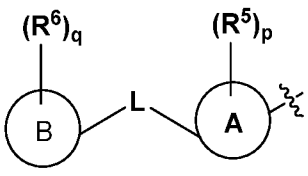
(J),

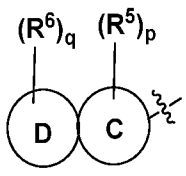
or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein:

X^1 is CR^3 or N;

X^2 is CR^3 or N;

X^3 is CR^3 or N;

Z is 

or 

, wherein

A is C_3-C_6 cycloalkyl, 4- to 7-membered heterocyclyl, 5- to 7-membered heteroaryl, or C_6 aryl, each of which is optionally substituted with one or more R^5;

L is a bond, -$CR^{11}R^{12}$-, -O-, -S-, -$S(O)_2$-, -C(O)-, -NR^{10}-, -$S(O)_2NR^{10}$-, or -$NR^{10}SO_2$-;

B is hydrogen, C_3-C_6 cycloalkyl, 3- to 7-membered heterocyclyl, 5- to 7-membered heteroaryl, or C_6 aryl, each of which is optionally substituted with one or more R^6;

C is C_3-C_6 cycloalkyl, 5- to 7-membered heterocyclyl, 5- to 7-membered heteroaryl, or C_6 aryl, each of which is optionally substituted with one or more R^5, wherein C is fused to D; and

D is C_3-C_6 cycloalkyl, 3- to 7-membered heterocyclyl, 5- to 7-membered heteroaryl, or C_6 aryl, each of which is optionally substituted with one or more R^6;

R^1 is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_8 alkoxy, C_3-C_{12} cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 10-membered heteroaryl, C_6-C_{14} aryl, -(C_1-C_3 alkylene)(C_3-C_{12} cycloalkyl), -(C_1-C_3 alkylene)(3- to 12-membered heterocyclyl), -$C(O)R^{10}$, -(C_1-C_3 alkylene)(5- to 10-membered heteroaryl) or -(C_1-C_3 alkylene)(C_6-C_{14} aryl), wherein R^1 is independently optionally substituted with one or more substituents selected from the group consisting of halogen, oxo, -OR^{13}, -$NR^{13}R^{14}$, -$C(O)R^{13}$, -CN, C_3-C_8 cycloalkyl, and C_1-C_6 alkyl optionally substituted with one or more substituents selected from the group consisting of oxo, -OH and halogen;

each R^2 is independently C_2-C_6 alkenyl, C_2-C_6 alkynyl, -OH, oxo, -$NR^{11}R^{12}$, -CN, -$C(O)R^{10}$, -$C(O)NR^{11}R^{12}$, halogen, or C_1-C_6 alkyl optionally substituted with one or more substituents selected from the group consisting of –CN, -OH or halogen, or

two R^2 or R^1 and R^2 are taken together with the atom or atoms to which they are attached to form a C_3-C_6 cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 10-membered heteroaryl, or C_6-C_{14} aryl, each of which is independently optionally substituted with one or more substituents selected from the group consisting of C_1-C_6 alkyl, -OH, oxo, and halogen;

each of R^3 and R^4 is independently hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, -CN, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, halogen or -OH;

each R^5 is independently C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, oxo, -CN, -OR^{10}, -SR^{10}, -$NR^{11}R^{12}$, -$C(O)R^{10}$, -$C(O)NR^{11}R^{12}$, -$OC(O)NR^{11}R^{12}$, -$NR^{10}C(O)R^{11}$, -$NR^{10}C(O)NR^{11}R^{12}$, -$S(O)R^{10}$, -$S(O)_2R^{10}$, -$NR^{10}S(O)_2R^{11}$, -$S(O)_2NR^{11}R^{12}$, C_3-C_6 cycloalkyl, 3- to 12-membered heterocyclyl, -(C_1-C_3 alkylene)OR^{10}, -(C_1-C_3 alkylene)SR^{10}, -(C_1-C_3 alkylene)$NR^{11}R^{12}$, -(C_1-C_3 alkylene)$C(O)R^{10}$, -(C_1-C_3 alkylene)$C(O)NR^{11}R^{12}$, -(C_1-C_3 alkylene)$NR^{10}C(O)R^{11}$, -(C_1-C_3 alkylene)$NR^{10}C(O)NR^{11}R^{12}$, -(C_1-C_3 alkylene)$S(O)_2R^{10}$, -(C_1-C_3 alkylene)$NR^{10}S(O)_2R^{11}$, -(C_1-C_3 alkylene)$NR^{10}S(O)_2NR^{11}R^{12}$, -($C_1$-$C_3$ alkylene)$S(O)_2NR^{11}R^{12}$, -(C_1-C_3 alkylene)(C_3-C_6 cycloalkyl), -(C_1-C_3 alkylene)(3- to 12-membered heterocyclyl), wherein each R^5 is independently optionally substituted with one or more substituents selected from the group consisting of halogen, oxo, -OR^{13}, -$NR^{13}R^{14}$, -$C(O)R^{13}$, -CN, -(C_1-C_3 alkylene)OR^{13}, -(C_1-C_3 alkylene)$NR^{13}R^{14}$, -(C_1-C_3 alkylene)$C(O)R^{13}$, C_3-C_8 cycloalkyl, and C_1-C_6 alkyl optionally substituted with one or more substituents selected from the group consisting of oxo, -OH, and halogen,

or any two R^5 are taken together with the atom or atoms to which they are attached to form a C_3-C_6 cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 10-membered heteroaryl, or C_6-C_{14} aryl;

each R^6 is independently oxo or R^7, or any two R^6 are taken together with the atom or atoms to which they are attached to form a C_3-C_6 cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 10-membered heteroaryl, or C_6-C_{14} aryl;

each R^7 is independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 6-membered heterocyclyl, -OR^{10}, -$NR^{11}R^{12}$, -$NR^{10}C(O)R^{11}$, -$NR^{10}C(O)NR^{11}R^{12}$, -$S(O)_2R^{10}$, -$NR^{10}S(O)_2R^{11}$, -$S(O)_2NR^{11}R^{12}$, -$C(O)R^{10}$, -$C(O)NR^{11}R^{12}$, -(C_1-C_3 alkylene)CN, -(C_1-C_3 alkylene)OR^{10}, -(C_1-C_3 alkylene)SR^{10}, -(C_1-C_3 alkylene)$NR^{11}R^{12}$, -(C_1-C_3 alkylene)CF_3, -(C_1-C_3 alkylene)$C(O)R^{10}$, -(C_1-C_3 alkylene)$C(O)NR^{11}R^{12}$, -(C_1-C_3 alkylene)$NR^{10}C(O)R^{11}$, -(C_1-C_3 alkylene)$NR^{10}C(O)NR^{11}R^{12}$, -(C_1-C_3 alkylene)$S(O)_2R^{10}$, -(C_1-C_3 alkylene)$NR^{10}S(O)_2R^{11}$, -(C_1-C_3 alkylene)$S(O)_2NR^{11}R^{12}$, -(C_1-C_3 alkylene)(C_3-C_6 cycloalkyl), or -(C_1-C_3 alkylene)(3- to 6-membered heterocyclyl), wherein each R^7 is independently optionally substituted with one or more substituents selected from the group consisting of halogen, oxo, -OR^{13}, -$NR^{13}R^{14}$, -$C(O)R^{13}$, -CN, -(C_1-C_3 alkylene)OR^{13}, -(C_1-C_3 alkylene)$NR^{13}R^{14}$, -(C_1-C_3 alkylene)$C(O)R^{13}$, C_3-C_8 cycloalkyl, and C_1-C_6 alkyl optionally substituted with one or more substituents selected from the group consisting of oxo, -OH, and halogen;

each R^{10} is independently hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, -(C_1-C_3 alkylene)(C_3-C_6 cycloalkyl), C_6-C_{14} aryl, 5- to 6-membered heteroaryl or 3- to 6-membered heterocyclyl, each of which is independently optionally substituted with one or more substituents selected from the group consisting of halogen, oxo, -CN, -OR^{15}, -$NR^{15}R^{16}$, and C_1-C_6 alkyl optionally substituted with one or more substituents selected from the group consisting of halogen, -OH, and oxo;

R^{11} and R^{12} are each independently hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, -(C_1-C_3 alkylene)(C_3-C_6 cycloalkyl), C_6-C_{14} aryl, 5- to 6-membered heteroaryl or 3- to 6-membered heterocyclyl, each of which is independently optionally substituted with one or more substituents selected from the group consisting of halogen, oxo, -CN, -OR^{15}, -$NR^{15}R^{16}$, and C_1-C_6 alkyl optionally substituted with one or more substituents selected from the group consisting of halogen, -OH, and oxo,

or R^{11} and R^{12} are taken together with the atom to which they attached to form a 3- to 6- membered heterocyclyl optionally substituted with one or more substituents selected from the group consisting of halogen, oxo, and C_1-C_6 alkyl optionally substituted with one or more substituents selected from the group consisting of halogen, -OH, and oxo;

R^{13} and R^{14} are each independently hydrogen or C_1-C_6 alkyl, wherein the C_1-C_6 alkyl is optionally substituted with one or more substituents selected from the group consisting of halogen, -OR^{15}, -$NR^{15}R^{16}$, and oxo,

or R^{13} and R^{14} are taken together with the atom to which they attached to form a 3- to 6- membered heterocyclyl optionally substituted with one or more substituents selected from the group consisting of halogen, oxo, and C_1-C_6 alkyl optionally substituted with one or more substituents selected from the group consisting of halogen, -OH, and oxo; and

R^{15} and R^{16} are each independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl are each independently optionally substituted with one or more substituents selected from the group consisting of halogen, -OH, and oxo,

or R^{15} and R^{16} are taken together with the atom to which they attached to form a 3- to 6- membered heterocyclyl optionally substituted with one or more substituents selected from the group consisting of halogen, oxo, and C_1-C_6 alkyl optionally substituted with one or more substituents selected from the group consisting of halogen, -OH, and oxo;

l is 0, 1, or 2;

p and q are each independently 0, 1, 2 or 3; and

n is 0, 1, 2, 3 or 4,

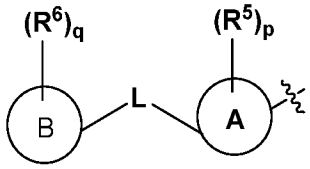
provided that at least one of (1), (2), (3), and (4) applies:

(1) at least one of X^1, X^2, and X^3 is N or CR^3, wherein R^3 is -CN,

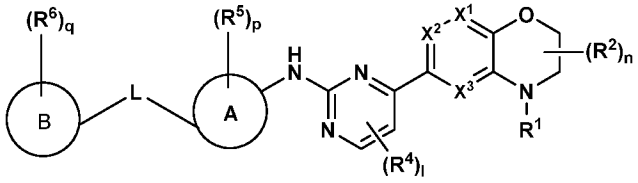
(2) *l* is 1 and R^4 is -CN,

(3) at least one R^2 is C_1-C_6 alkyl substituted with one or more halogen,

(4) two R^2 or R^1 and R^2 are taken together with the atom or atoms to which they are attached to form a C_3-C_6 cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 10-membered heteroaryl, or C_6-C_{14} aryl, each of which is independently optionally substituted with one or more substituents selected from the group consisting of C_1-C_6 alkyl, -OH, oxo, and halogen.

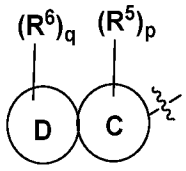
[0042] In some embodiments of a compound of Formula (J), Z is 

and provides a compound of Formula (I):

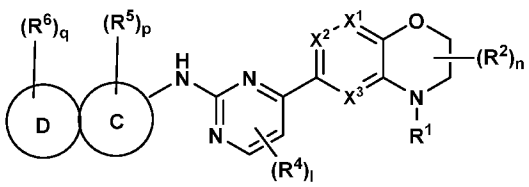


(I),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein X^1, X^2, X^3, A, B, L, R^1, R^2, R^3, R^4, R^5, R^6, l, m, n, p, and q are as detailed herein for Formula (J).

[0043] In some embodiments of a compound of Formula (J), Z is 

and provides a compound of Formula (II):



(II),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein X^1, X^2, X^3, C, D, R^1, R^2, R^3, R^4, R^5, R^6, l, n, p, and q are as detailed herein for Formula (J).

[0044] In some embodiments of a compound of Formula (J) or any related formula where applicable, X^1 is N. In some embodiments, X^1 is CR^3. In some embodiments, X^1 is CR^3, wherein R^3 is -CN. In some embodiments, X^2 is N. In some embodiments, X^2 is CR^3. In some embodiments, X^2 is CR^3, wherein R^3 is -CN. In some embodiments, X^3 is N. In some embodiments, X^3 is CR^3. In some embodiments, X^3 is CR^3, wherein R^3 is -CN.

[0045] In some embodiments of a compound of Formula (J) or any related formula where applicable, each R^3 is independently C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, halogen, or –OH. In some embodiments, each R^3 is independently C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy or halogen. In some embodiments, each R^3 is independently fluoro, chloro, methyl, trifluoromethyl, trifluoromethoxy, methoxy, and cyclopropyl. In some embodiments, R^3 is halogen.

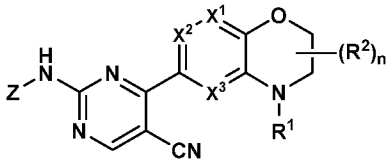
[0046] In some embodiments of a compound of Formula (J) or any related formula where applicable, at least one of X^1, X^2, and X^3 is N or CR^3, wherein R^3 is -CN.

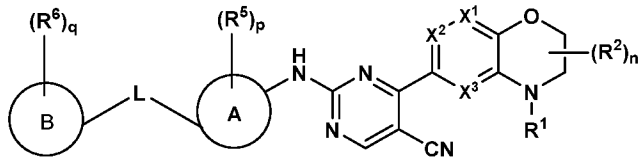
[0047] In some embodiments of a compound of Formula (J) or any related formula where applicable, is *l* is 0. In some embodiments, *l* is 1 or 2. In some embodiments, *l* is 1. In some embodiments, *l* is 2.

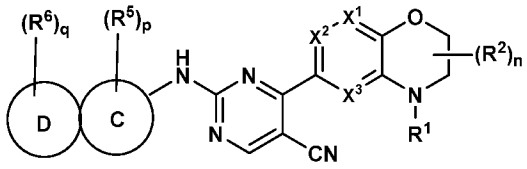
[0048] In some embodiments of a compound of Formula (J) or any related formula where applicable, each R^4 is independently C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, halogen, or –OH. In some embodiments, each R^4 is independently C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy or halogen. In some embodiments, each R^4 is independently fluoro, chloro, methyl, trifluoromethyl, trifluoromethoxy, methoxy, and cyclopropyl. In some embodiments, R^4 is halogen. In some embodiments, *l* is 1 and R^4 is halogen.

[0049] In some embodiments of a compound of Formula (J) or any related formula where applicable, *l* is 1 and R^4 is -CN.

[0050] In some embodiments, a compound of Formula (J) is of Formula (J-1), (I-1), or (II-1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.


(J-1),


(I-1),

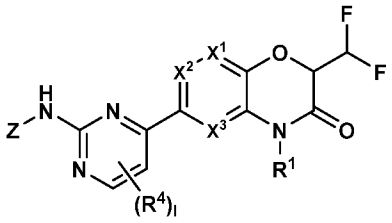

(II-1).

[0051] In some embodiments of a compound of Formula (J) or any related formula where applicable, n is 0. In some embodiments, n is 1. In some embodiments, n is 2. In some embodiments, n is 3. In some emboidments, n is 4. In some embodiments, n is 0 or 1. In some embodiments, n is 0, 1, or 2. In some embodiments, n is 0, 1, 2, or 3. In some emboidments, n is 1, 2, or 3.

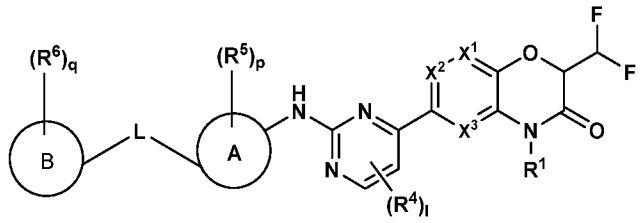
[0052] In some embodiments of a compound of Formula (J) or any related formula where applicable, each R^2 is independently C_1-C_6 alkyl, oxo, -C(O)R^{10}, or -CN. In some embodiments, each R^2 is independently C_1-C_6 alkyl, oxo, or halogen. In some embodiments, each R^2 is oxo. In some embodiments, each R^2 is independently -N$R^{11}R^{12}$. In some embodiments, each R^2 is –CN. In some embodiments, each R^2 is independently -C(O)R^{10}. In some embodiments, R^2 is -C(O)R^{10}, wherein R^{10} is C_1-C_6 alkyl such as methyl. In some embodiments, R^2 is –C(O)N$R^{11}R^{12}$. In some embodiments, R^2 is halogen, such as fluoro. In some embodiments, R^2 is C_1-C_6 alkyl, such methyl. In some embodiments, R^2 is H. In some embodiments, each R^2 is independently oxo or C_1-C_6 alkyl such as methyl. In some embodiments, each R^2 is independently oxo or C_1-C_6 alkyl such as methyl; and n is 1 or 2. In some embodiments, each R^2 is independently oxo or C_1-C_6 alkyl such as methyl; and n is 1. In some embodiments, each R^2 is independently oxo or C_1-C_6 alkyl such as methyl; and n is 2. In some embodiments, R^2 is C_1-C_6 alkyl such as methyl. In some embodiments, R^2 is C_1-C_6 alkyl such as methyl; and n is 1. In some embodiments, each R^2 is independently -C(O)R^{10}, wherein R^{10} is C_1-C_6 alkyl such as methyl. In some embodiments, each R^2 is independently -C(O)R^{10}, wherein R^{10} is C_1-C_6 alkyl such as methyl; and n is 1. In some embodiments, each R^2 is oxo; and n is 1 or 2. In some embodiments, each R^2 is oxo; and n is 1. In some embodiments, each R^2 is oxo; and n is 2. In some embodiments, each R^2 is independently oxo or -CN. In some embodiments, each R^2 is independently oxo or -CN; and n is 2. In some embodiments, R^2 is independently methyl, oxo, -C(O)CH_3, or -CN. In some

embodiments, In some embodiments, one R^2 is oxo and one R^2 is C_1-C_6 alkyl substituted with one or more halogen; and n is 2.

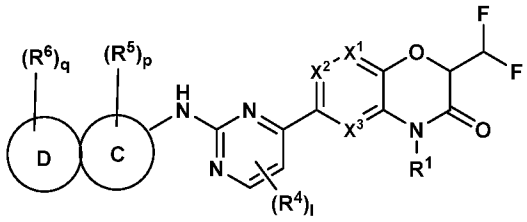
[0053] In some embodiments, a compound of Formula (J) is of Formula (J-2), (I-2), or (II-2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.



(J-2),



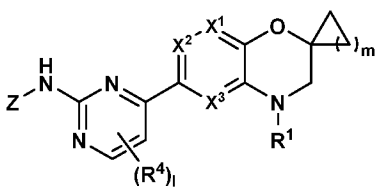
(I-2),



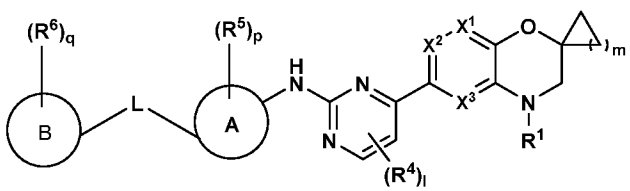
(II-2).

[0054] In some embodiments of a compound of Formula (J) or any related formula where applicable, two R^2 are taken together with the atom or atoms to which they are attached to form a C_3-C_6 cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 10-membered heteroaryl, or C_6-C_{14} aryl, each of which is independently optionally substituted with one or more substituents selected from the group consisting of C_1-C_6 alkyl, -OH, oxo, and halogen. In some embodiments, two R^2 are attached to a same carbon atom and are taken together with the atom to form a C_3-C_6 cycloalkyl.

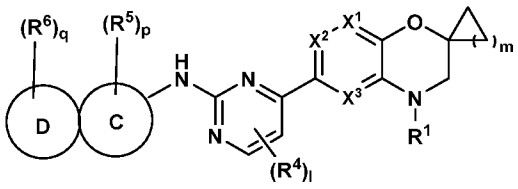
[0055] In some embodiments, a compound of Formula (J) is of Formula (J-3), (I-3), or (II-3), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.



(J-3),

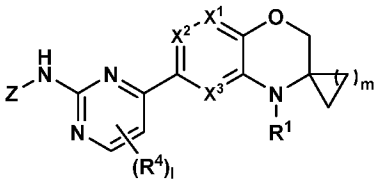


(I-3),

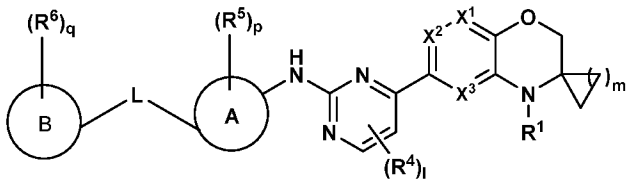


(II-3), wherein m is 1, 2, 3, or 4.

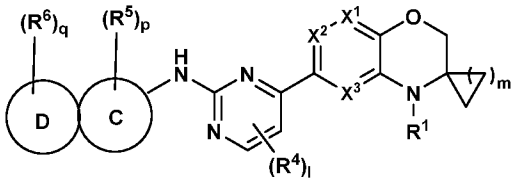
[0056] In some embodiments, a compound of Formula (J) is of Formula (J-4), (I-4), or (II-4), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.



(J-4),

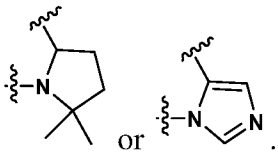


(I-4),



(II-4), wherein m is 1, 2, 3, or 4.

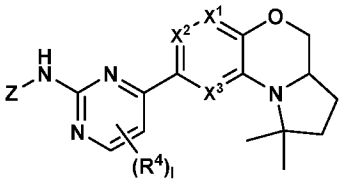
[0057] In some embodiments of a compound of Formula (J) or any related formula where applicable, R^1 and R^2 are taken together with the atoms to which they are attached to form a C_3-C_6 cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 10-membered heteroaryl, or C_6-C_{14} aryl, each of which is independently optionally substituted with one or more substituents selected from the group consisting of C_1-C_6 alkyl, -OH, oxo, and halogen. In some embodiments, R^1 and R^2 are taken together with the atoms to which they are attached to form



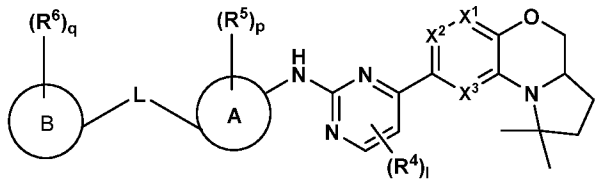
or

.

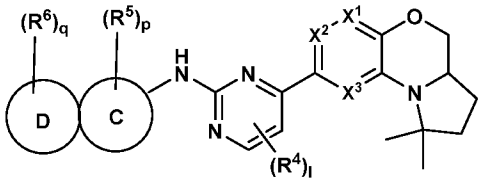
[0058] In some embodiments, a compound of Formula (J) is of Formula (J-5), (I-5), or (II-5), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.



(J-5),

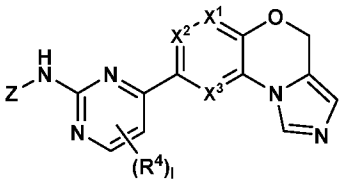


(I-5),

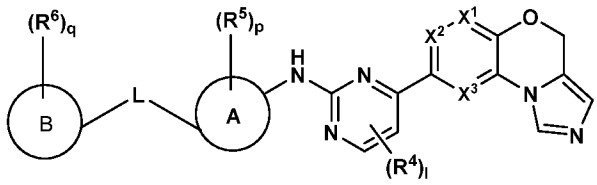


(II-5).

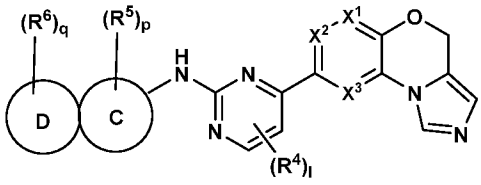
[0059] In some embodiments, a compound of Formula (J) is of Formula (J-6), (I-6), or (II-6), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.



(J-6),



(I-6),

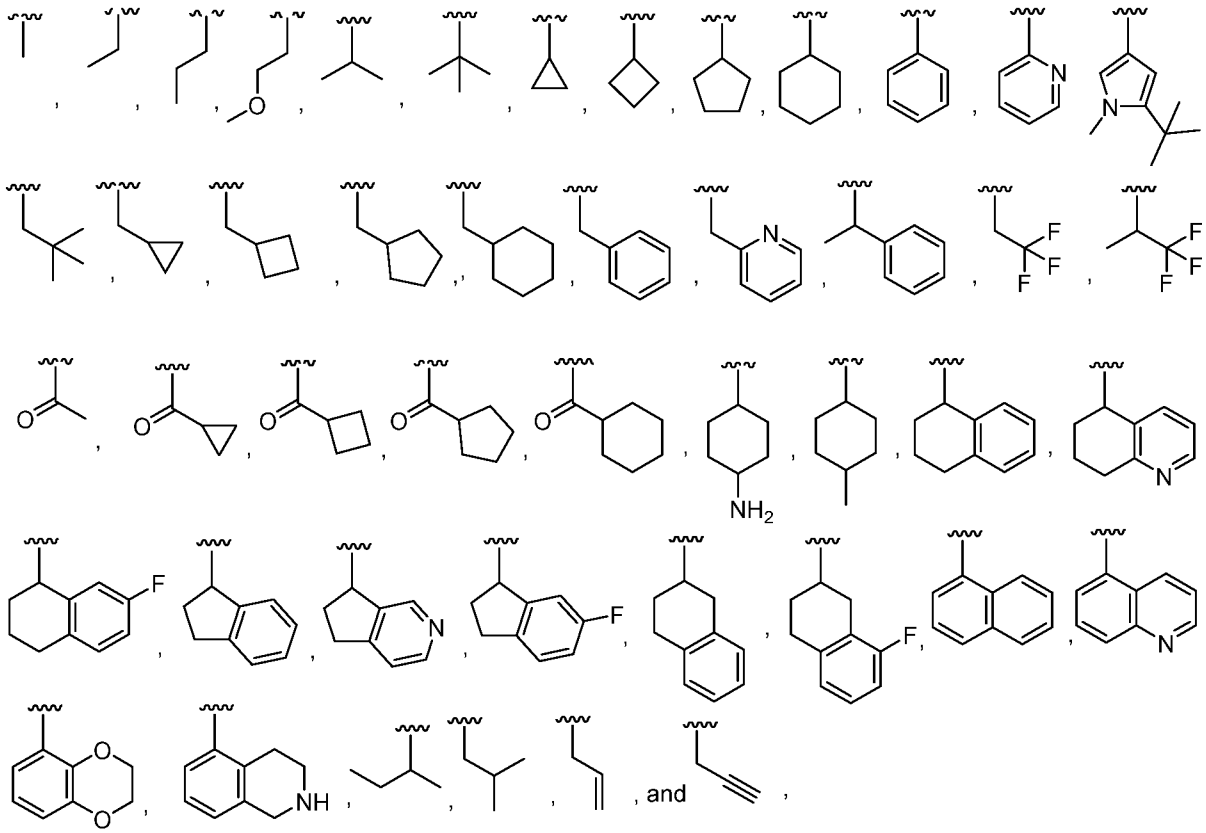


(II-6).

[0060] In some embodiments of a compound of Formula (J) or any related formula where applicable, R^1 is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_8 alkoxy, C_3-C_6 cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 10-membered heteroaryl, C_6-C_{14} aryl, -C(O)R^{10}, -(C_1-C_3 alkylene)(C_3-C_6 cycloalkyl), -(C_1-C_3 alkylene)(3- to 12-membered heterocyclyl), -(C_1-C_3 alkylene)(5- to 10-membered heteroaryl) or -(C_1-C_3 alkylene)(C_6-C_{14} aryl), each of which is independently optionally substituted with one or more substituents selected from the group consisting of halogen, oxo, -OR^{13}, -N$R^{13}R^{14}$, -C(O)R^{13}, -CN, C_3-C_8 cycloalkyl, and C_1-C_6 alkyl optionally substituted with one or more substituents selected from the group consisting of oxo, -OH or halogen. In some embodiments, R^1 is hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 10-membered heteroaryl, C_6-C_{14} aryl, -C(O)R^{10}, -(C_1-C_3 alkylene)(C_3-C_6 cycloalkyl), -(C_1-C_3 alkylene)(3- to 12-membered heterocyclyl), -(C_1-C_3 alkylene)(5- to 10-membered heteroaryl) or -(C_1-C_3 alkylene)(C_6-C_{14} aryl), each of which is unsubstituted. In some embodiments, R^1 is C_2-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_8 alkoxy, C_3-C_6 cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 10-membered heteroaryl, C_6-C_{14} aryl, -(C_1-C_3 alkylene)(C_3-C_6 cycloalkyl), -C(O)R^{10}, or -(C_1-C_3 alkylene)(C_6-C_{14} aryl), each of which independently optionally substituted with one or more substituents selected from the group consisting of halogen, oxo, -OR^{13}, -N$R^{13}R^{14}$, -C(O)R^{13}, -CN, C_3-C_8

cycloalkyl, and C_1-C_6 alkyl optionally substituted with one or more substituents selected from the group consisting of oxo, -OH or halogen. In some embodiments, R^1 is C_2-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_8 alkoxy, C_3-C_6 cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 10-membered heteroaryl, C_6-C_{14} aryl, or -C(O)R^{10}, each of which independently optionally substituted with one or more substituents selected from the group consisting of halogen, oxo, -OR^{13}, -$NR^{13}R^{14}$, -C(O)R^{13}, -CN, C_3-C_8 cycloalkyl, and C_1-C_6 alkyl optionally substituted with one or more substituents selected from the group consisting of oxo, -OH or halogen. In some embodiments, R^1 is hydrogen, C_1-C_6 alkyl, -C(O)R^{10}, -(C_1-C_3 alkylene)(C_3-C_6 cycloalkyl), -(C_1-C_3 alkylene)(5- to 10-membered heteroaryl), or C_3-C_6 cycloalkyl, each of which is optionally substituted with halogen, oxo, -NH_2. In some embodiments, R^1 is methyl, ethyl, n-propyl, isopropyl, cyclopropyl, cyclopentyl, cyclohexyl or cyclopropyl-methyl. In some embodiments, R^1 is isopropyl. In some embodiments, R^1 is C_1-C_6 alkyl. In some embodiments, R^1 is C_2-C_6 alkyl.

[0061] In some embodiments of a compound of Formula (J) or any related formula where applicable, R^1 is selected from the group consisting of



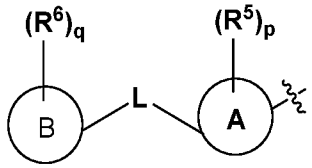
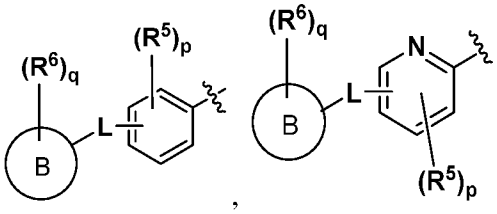
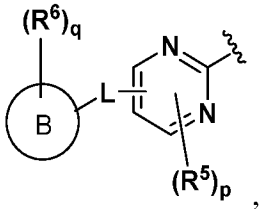
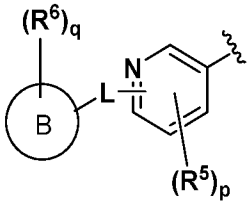
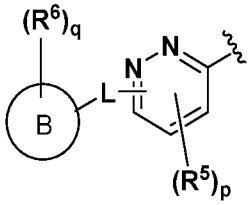
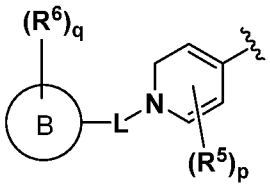
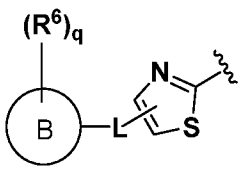
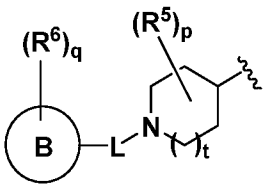
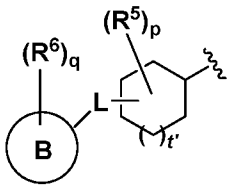
wherein the wavy lines denote attachment points to the rest of the molecule.

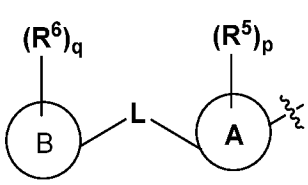
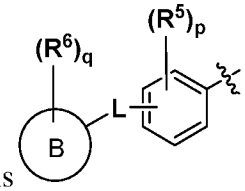
[0062] In some embodiments of a compound of Formula (J) or any related formula where applicable, A is C_3-C_6 cycloalkyl, 4- to 7-membered heterocyclyl, 5- to 7-membered heteroaryl or C_6 aryl, each of which is unsubstituted. In some embodiments, A is C_3-C_6 cycloalkyl, 4- to 7-membered heterocyclyl, 5- to 7-membered heteroaryl or C_6 aryl, each of which is optionally substituted with one or more R^5. In some embodiments, A is C_6 aryl optionally substituted with one or more R^5. In some embodiments, A is phenyl optionally substituted with one or more R^5. In some embodiments, A is 5- to 7-membered heteroaryl optionally substituted with one or more R^5. In some embodiments, A is selected from the group consisting of pyridinyl, pyrimidinyl, pyrazolyl, thiazolyl, oxazolyl, isooxazolyl or imidazolyl, each of which is optionally substituted with one or more R^5. In some embodiments, A is 4- to 7-membered heterocyclyl optionally substituted with one or more R^5. In some embodiments, A is piperidinyl, pyrrolidinyl, azetidinyl, dihydropyridine, or pyridone, each of optionally substituted with one or more R^5. In some embodiments, A is C_3-C_6 cycloalkyl optionally substituted with one or more R^5. In some embodiments, A is cyclohexyl or cyclopentyl, each of which is optionally substituted with one or more R^5. In some embodiments, A is phenyl, pyridinyl, pyrimidinyl, pyrazolyl, thiazolyl, oxazolyl, isooxazolyl, imidazolyl, piperidinyl, pyrrolidinyl, azetidinyl, pyridone, cyclohexyl, or cyclopentyl, each of which is unsubstituted. In some embodiments of a compound of Formula (I), A is phenyl, pyridinyl, pyrimidinyl, pyrazolyl, thiazolyl, oxazolyl, isooxazolyl, imidazolyl, piperidinyl, pyrrolidinyl, azetidinyl, dihydropyridine, pyridone, cyclohexyl, or cyclopentyl, each of which is optionally substituted with one or more R^5.

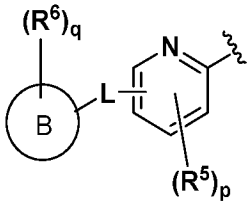
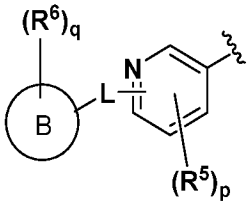
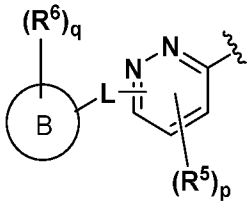
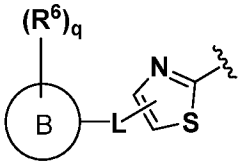
[0063] In some embodiments of a compound of Formula (J) or any related formula where applicable, B is hydrogen, C_3-C_6 cycloalkyl, 3- to 7-membered heterocyclyl, 5- to 7-membered heteroaryl, or C_6 aryl, each of which is optionally substituted with one or more R^6. In some embodiments, B is C_3-C_6 cycloalkyl, 3- to 7-membered heterocyclyl, 5- to 7-membered heteroaryl, or C_6 aryl, each of which is unsubstituted. In some embodiments, B is hydrogen. In some embodiments, B is 3- to 7-membered heterocyclyl optionally substituted with one or more R^6. In some embodiments, B is diazepanyl, azepanyl, piperazinyl, piperidinyl, pyrrolidinyl or azetidinyl, each of which is optionally substituted with one or more R^6. In some embodiments, B is 5- to 7-membered heteroaryl optionally substituted with one or more R^6. In some embodiments, B is imidazolyl or pyrazolyl, each of which is optionally substituted with one or more R^6. In some embodiments, B is phenyl optionally substituted with one or more R^6. In some embodiments, B is C_3-C_6 cycloalkyl optionally

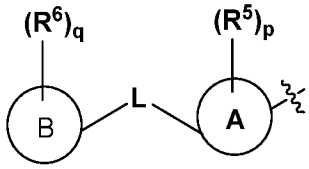
substituted with one or more R^6. In some embodiments, B is cyclopentyl, cyclohexyl, or cycloheptyl, each of which is optionally substituted with one or more R^6. In some embodiments, B is hydrogen, diazepanyl, azepanyl, piperazinyl, piperidinyl, pyrrolidinyl, azetidinyl, imidazolyl, pyrazolyl, phenyl, cyclopentyl, cyclohexyl, or cycloheptyl, each of which is unsubstituted. In some embodiments of a compound of Formula (I), B is hydrogen, diazepanyl, azepanyl, piperazinyl, piperidinyl, pyrrolidinyl, azetidinyl, imidazolyl, pyrazolyl, phenyl, cyclopentyl, cyclohexyl, or cycloheptyl, each of which is optionally substituted with one or more R^6.

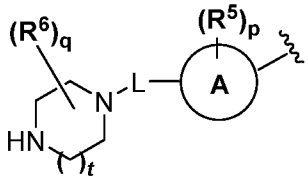
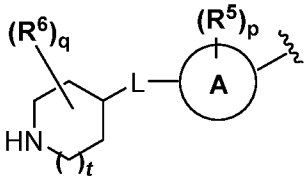
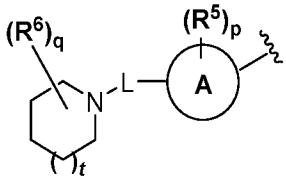
[0064] In some embodiments of a compound of Formula (J) or any related formula where applicable, L is a bond, -CH_2-, -NH-, -O-, -S-, -$S(O)_2$-, -CO-, -NCH_3-, -$S(O)_2NH$-,or –$NHS(O)_2$-. In some embodiments of a compound of Formula (I), L is a bond, -CH_2-, -NH-, -O-, or –S-. In some embodiments, L is a bond. In some embodiments, L is -CH_2-. In some embodiments, L is -NH-. In some embodiments, L is -S-. In some embodiments, L is -O-. In some embodiments, L is –$S(O)_2$-. In some embodiments, L is –C(O)-. In some embodiments, L is -NCH_3-. In some embodiments, L is –$NHS(O)_2$-. In some embodiments, L is -$CR^{11}R^{12}$-. In some embodiments, L is -NR^{10}-. In some embodiments, L is -$NR^{10}S(O)_2$-. In some embodiments, L is –$S(O)_2NR^{10}$-. In some embodiments, L is –$S(O)_2NH$-. In some embodiments, L is – $NHS(O)_2$-.

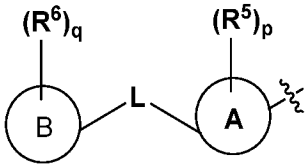
[0065] In some embodiments of a compound of Formula (J) or any related formula where applicable, Z is  which is  ,  ,  ,  ,  ,  ,  , or  , wherein t is 0, 1, or 2; and t'

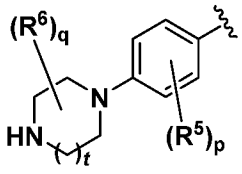
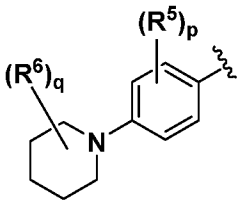
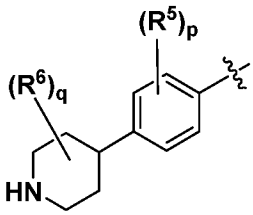
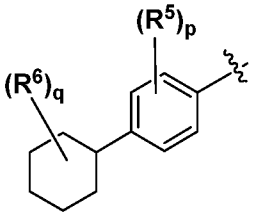
is 0 or 1. In some embodiments, Z is  which is  ,

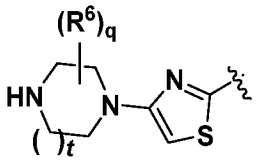
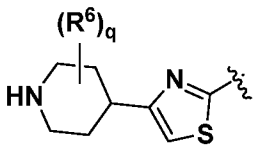
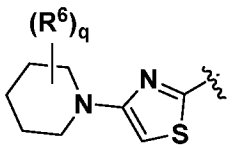
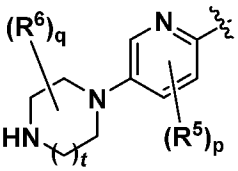
 ,  ,  , or  , wherein

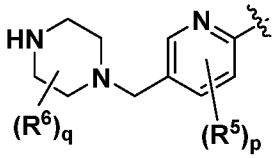
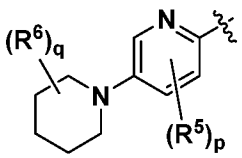
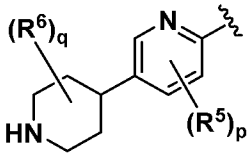
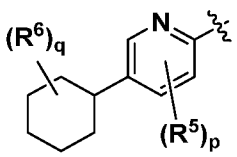
t is 0, 1, or 2; and t' is 0 or 1. In some embodiments, Z is  which is

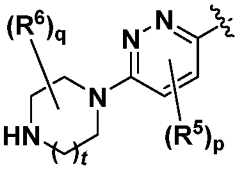
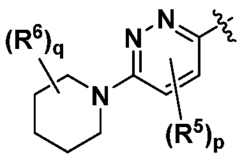
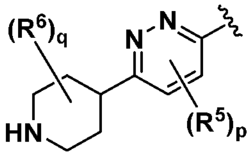
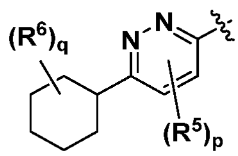
 ,  , or  , wherein t is 0, 1,

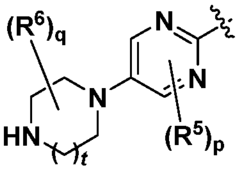
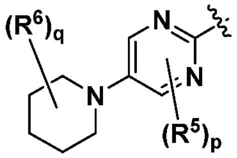
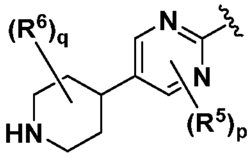
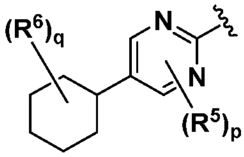
or 2; and t' is 0 or 1. In some embodiments, Z is  which is

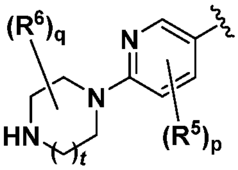
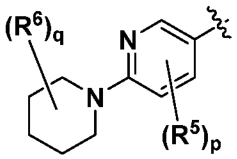
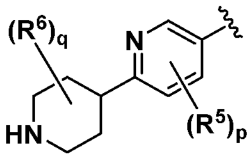
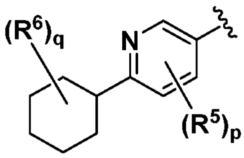
 ,  ,  ,  ,

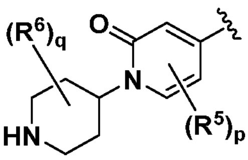
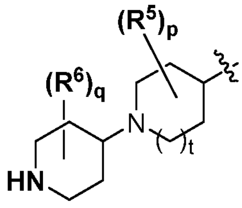
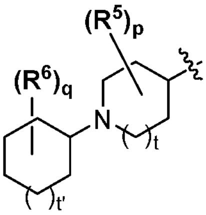
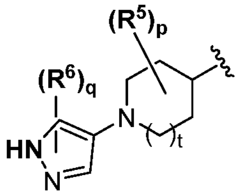
 ,  ,  ,  ,

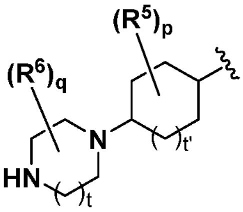
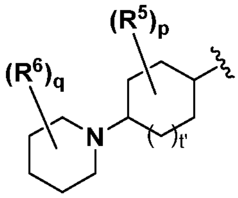
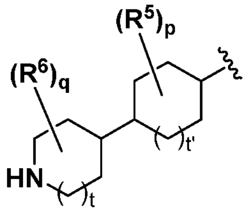
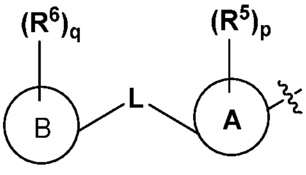
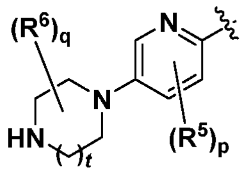
 ,  ,  ,  ,

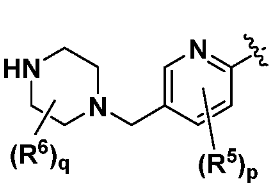
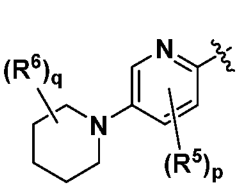
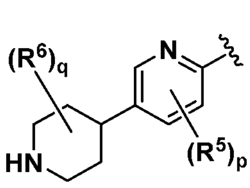
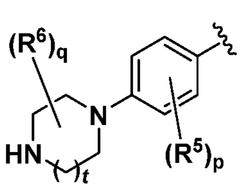
 ,  ,  ,  ,

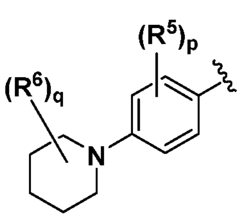
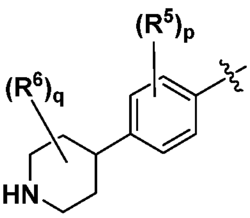
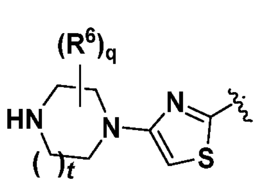
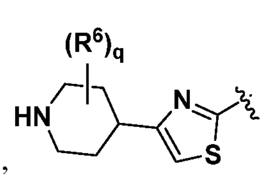
 ,  ,  ,  ,

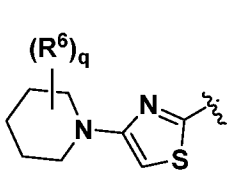
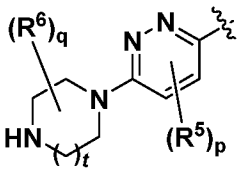
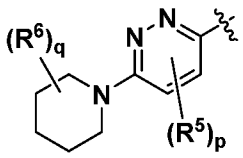
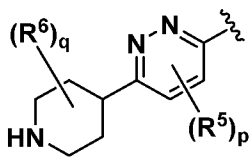
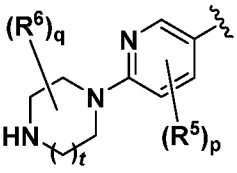
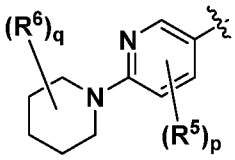
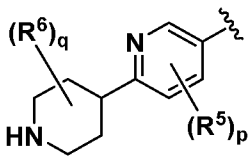
 ,  ,  ,  ,

 ,  ,  ,  ,

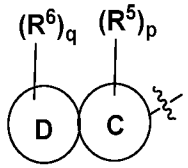
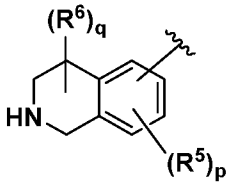
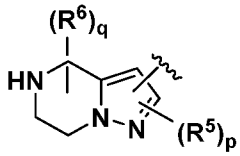
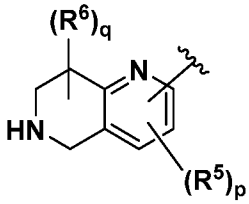
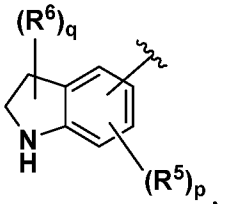
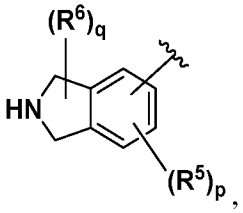
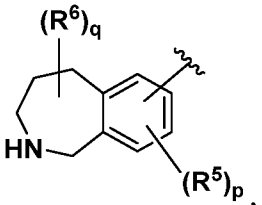
 ,  , or  , wherein t is 0, 1, or 2; and t' is 0 or 1. In some embodiments, Z is  which is  ,

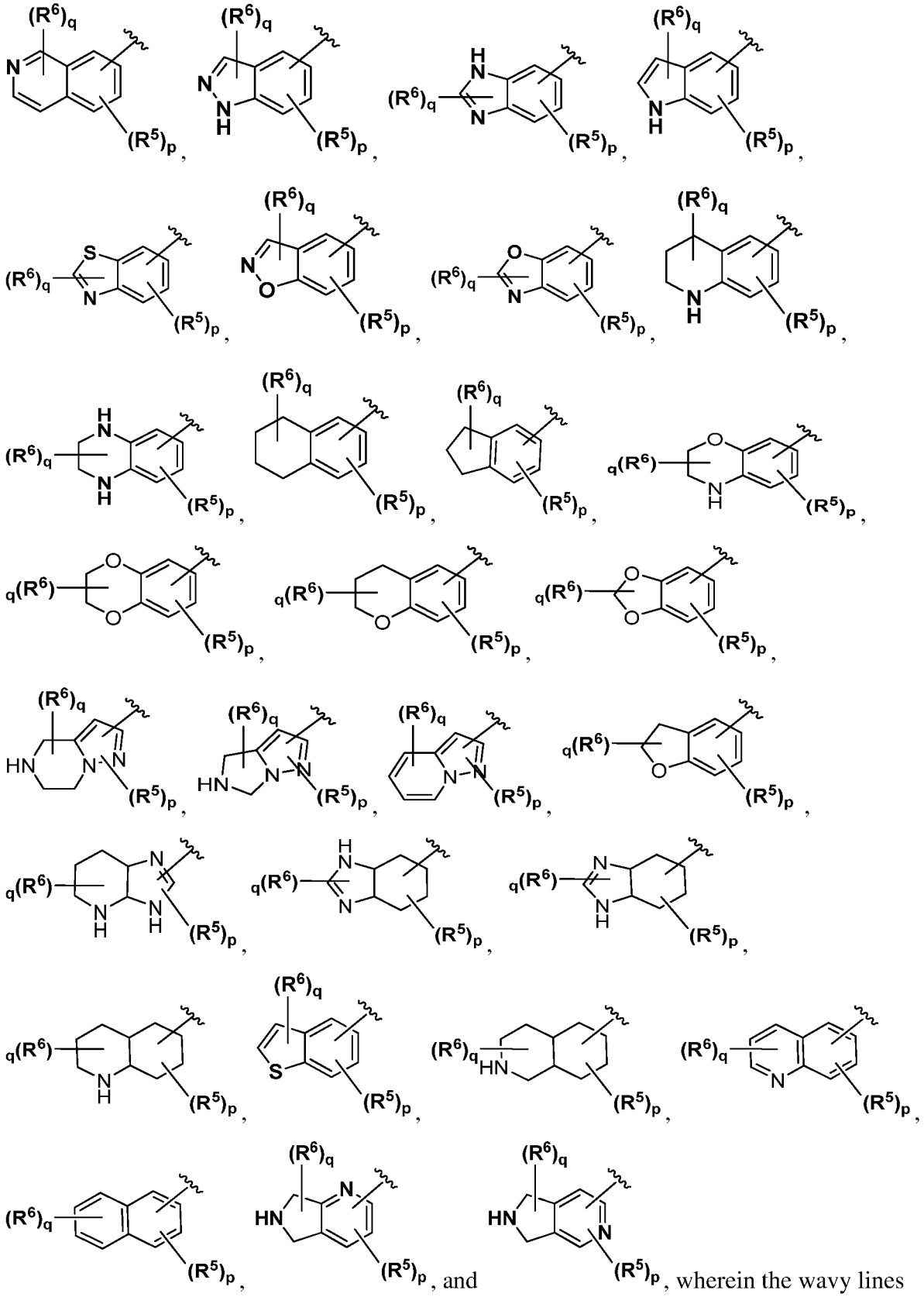
 ,  ,  ,  ,

 ,  ,  ,  ,







 , wherein t is 0, 1, or 2. In some embodiments, t is 0. In some embodiments, t is 1. In some embodiments, t is 2. In some embodiments, t' is 0. In some embodiments, t' is 1. In some embodiments, t is 1 and t' is 1.

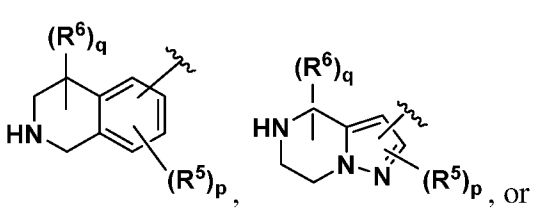
[0066] In some embodiments of a compound of Formula (J) or any related formula where applicable, D is fused with C to form a 7- to 12- membered bicyclic ring having at least one aromatic ring, wherein C and D are optionally substituted with one or more R^5 and R^6. In some embodiments, D is fused with C to form a 7- to 12- membered bicyclic ring having at least one aromatic ring and at least one heteroatom selected from the group consisting of N, O, and S, wherein C and D are optionally substituted with with one or more R^5 and R^6. In some embodiments, D is fused with C to form a 7- to 12- membered bicyclic ring having at least one aromatic ring and at least one nitrogen atom, wherein C and D are optionally substituted with with one or more R^5 and R^6. In some embodiments, D is fused with C to form a 7- to 12- membered bicyclic ring having at least one aromatic ring and at least one nitrogen atom, wherein C and D are optionally substituted with with one or more R^5 and R^6.

[0067] In some embodiments of a compound of Formula (J) or any related formula where applicable, Z is  which is 








, and , wherein the wavy lines

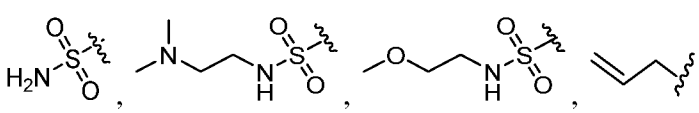
denote attachment points to the rest of the molecule. In some embodiments, Z is

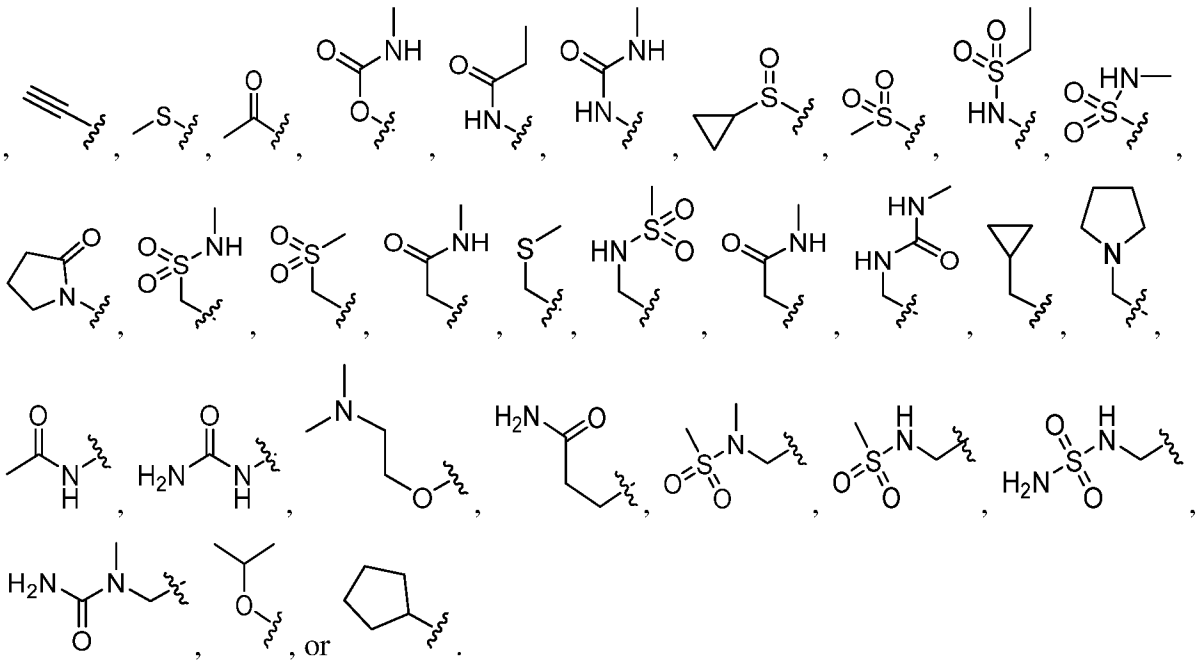


[0068] In some embodiments of a compound of Formula (J) or any related formula where applicable, R^7 is hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, -C(O)R^{10}, each of which (except hydrogen) is optionally substituted by halogen, oxo, -OR^{13}, -N$R^{13}R^{14}$, -C(O)R^{13}, -CN, -(C_1-C_3 alkylene)OR^{13}, -(C_1-C_3 alkylene)N$R^{13}R^{14}$, -(C_1-C_3 alkylene)C(O)R^{13}, C_3-C_8 cycloalkyl, or C_1-C_6 alkyl optionally substituted by oxo, -OH or halogen. In some embodiments of a compound of Formula (I), R^7 is hydrogen, methyl, ethyl, isopropyl, cyclopropyl, -C(O)CH_2NHCH_3, or –CH_2CH_2OH.

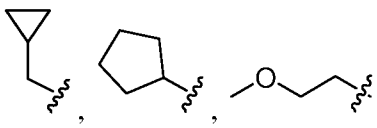
[0069] In some embodiments of a compound of Formula (J), or any related formula where applicable, p is 0. In some embodiments, p is 0 or 1. In some embodiments, p is 0, 1, or 2.

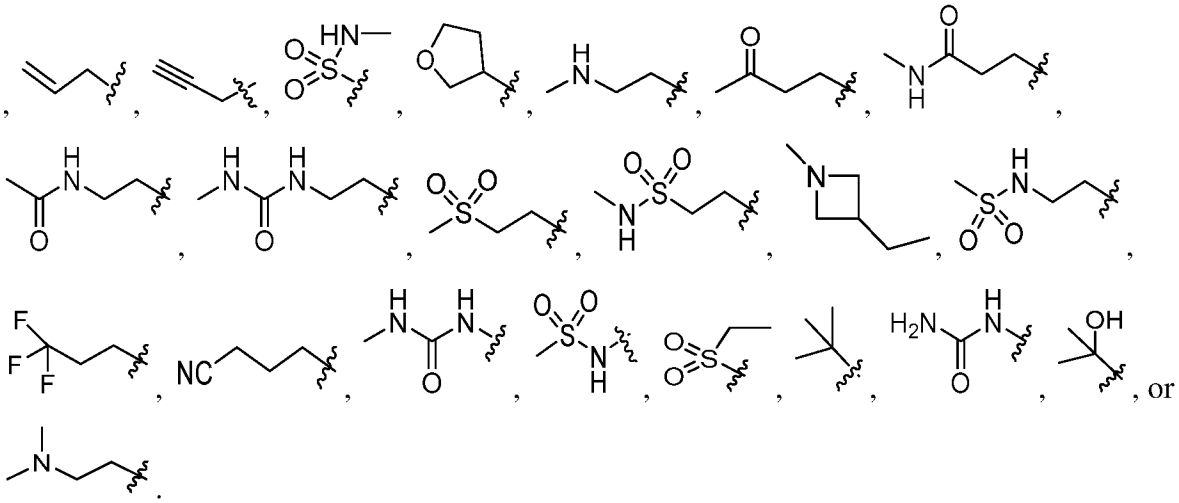
[0070] In some embodiments of a compound of Formula (J), or any related formula where applicable, each R^5 is independently C_1-C_6 alkyl, halogen, oxo, -CN, -OR^{10}, -N$R^{11}R^{12}$, -C(O)R^{10}, -C(O)N$R^{11}R^{12}$, C_3-C_6 cycloalkyl, 3- to 12-membered heterocyclyl, -(C_1-C_3 alkylene)OR^{10}, -(C_1-C_3 alkylene)N$R^{11}R^{12}$, -(C_1-C_3 alkylene)C(O)R^{10}, -(C_1-C_3 alkylene)(C_3-C_6 cycloalkyl), -(C_1-C_3 alkylene)(3- to 12-membered heterocyclyl), each of which is optionally substituted by halogen, oxo, -OR^{13}, -N$R^{13}R^{14}$, -C(O)R^{13}, -CN, -(C_1-C_3 alkylene)OR^{13}, -(C_1-C_3 alkylene)N$R^{13}R^{14}$, -(C_1-C_3 alkylene)C(O)R^{13}, C_3-C_8 cycloalkyl, or C_1-C_6 alkyl optionally substituted by oxo, -OH or halogen. In some embodiments, each R^5 is independently –CN, halogen, methoxy, oxo, trifluoromethoxy, -$NH(CH_3)$, -$N(CH_3)_2$, -$(CH_2)NH(CH_3)$, -$(CH_2)NH_2$, -$(CH_2)N(CH_3)_2$, -C(O)NH_2, -C(O)$N(CH_3)_2$, methyl, ethyl, isopropyl, cyclopropyl, -CH_2OH, -CH_2OCH_3, -$NH(CH_2)_2N(CH_2CH_3)_2$, -$O(CH_2)_2N(CH_2CH_3)_2$, or trifluoromethyl. In some embodiments, each R^5 is independently –CN, halogen, methoxy, oxo, trifluoromethoxy, -$NH(CH_3)$, -$N(CH_3)_2$, -$(CH_2)NH(CH_3)$, -$(CH_2)NH_2$, -$(CH_2)N(CH_3)_2$, -C(O)NH_2, -C(O)$N(CH_3)_2$, methyl, ethyl, isopropyl, n-propyl, cyclopropyl, -CH_2OH, -CH_2OCH_3, -$NH(CH_2)_2N(CH_2CH_3)_2$, -$O(CH_2)_2N(CH_2CH_3)_2$, trifluoromethyl,



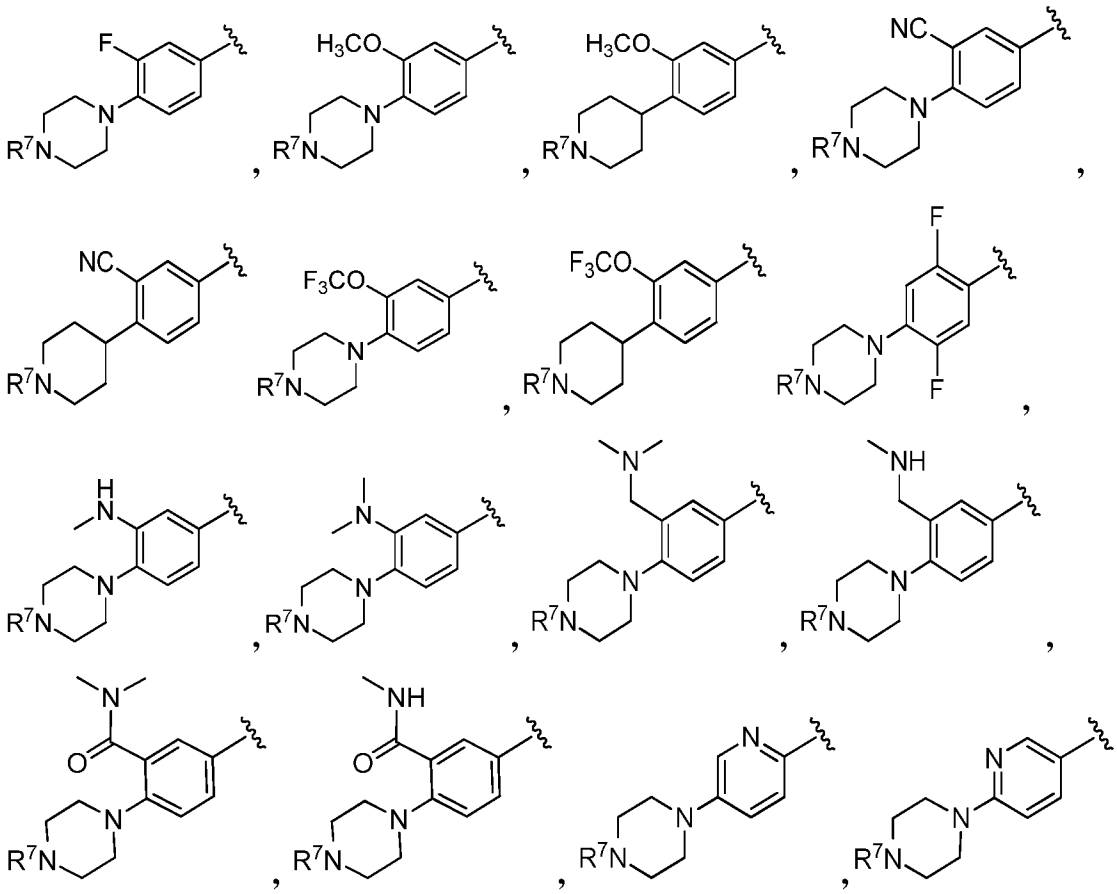


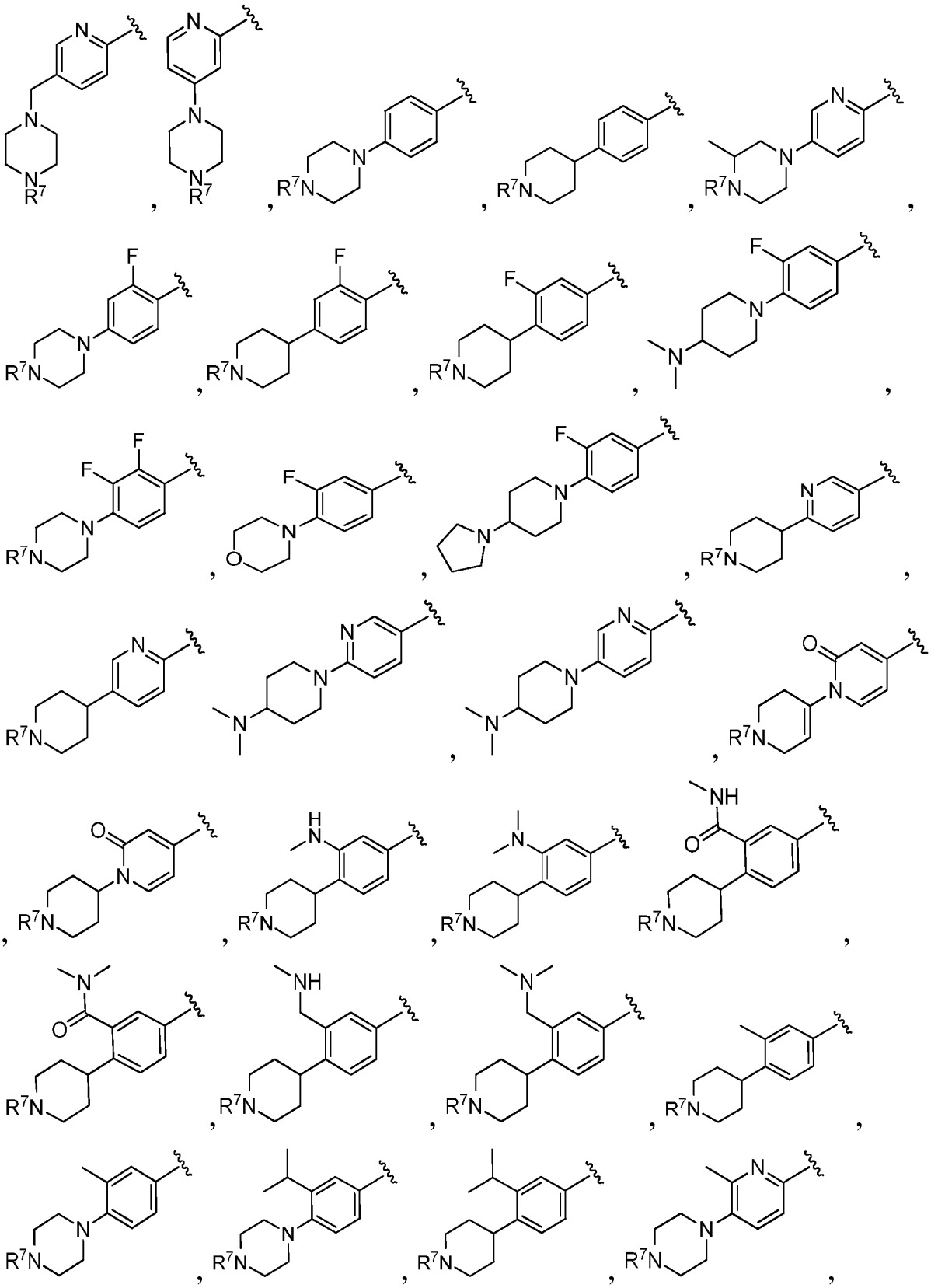
[0071] In some embodiments of a compound of Formula (J), or any related formula where applicable, q is 0. In some embodiments, q is 0 or 1. In some embodiments, q is 0, 1, or 2.

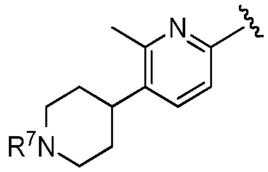
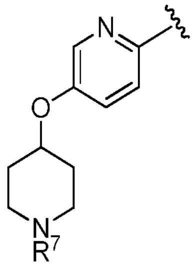
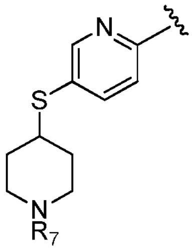
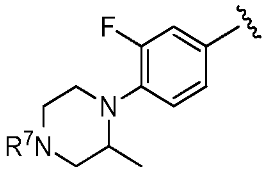
[0072] In some embodiments of a compound of Formula (J), or any related formula where applicable, each R^6 is independently C_1-C_6 alkyl, halogen, oxo, -CN, -$NR^{11}R^{12}$, -$C(O)R^{10}$, C_3-C_6 cycloalkyl, 3- to 12-membered heterocyclyl, -(C_1-C_3 alkylene)OR^{10}, -(C_1-C_3 alkylene)$NR^{11}R^{12}$, each of which is optionally substituted by halogen, oxo, -OR^{13}, -$NR^{13}R^{14}$, -$C(O)R^{13}$, -CN, -(C_1-C_3 alkylene)OR^{13}, -(C_1-C_3 alkylene)$NR^{13}R^{14}$, -(C_1-C_3 alkylene)$C(O)R^{13}$, C_3-C_8 cycloalkyl, or C_1-C_6 alkyl optionally substituted by oxo, -OH or halogen; or two R^6 groups when bound to the same carbon atom, are taken together with the carbon to which they are attached to form a C_3-C_6 cycloalkyl. In some embodiments, each R^6 is independently ethyl, methyl, isopropyl, pyrrolidinyl, -$N(CH_3)_2$, -CH_2OH, oxo, -$C(O)CH_2NHCH_3$, -CH_2CH_2OH, difluoroethyl, -$CH_2N(CH_3)_2$, -OH, or -$C(O)CH_2OH$. In some embodiments, each R^6 is independently ethyl, methyl, isopropyl, pyrrolidinyl, cyclopropyl, methoxy, -$N(CH_3)_2$, -$NHCH_3$, -CH_2OH, oxo, -$C(O)CH_2NHCH_3$, -CH_2CH_2OH, difluoroethyl, -$CH_2N(CH_3)_2$, -CH_2NH_2, -OH, -$C(O)CH_2OH$, -$C(O)CH_2N(CH_3)_2$, -$C(O)N(CH_3)_2$, -$C(O)NHCH_3$, -$C(O)NH_2$, -$NHC(O)CH_3$, -$C(O)CH_3$, -$S(O)_2CH_3$, 

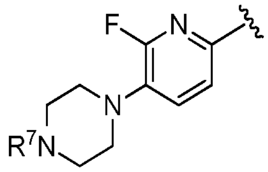
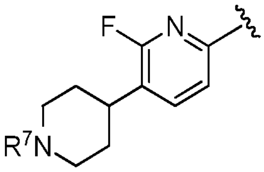
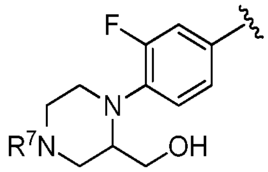
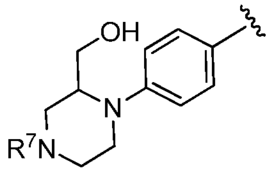


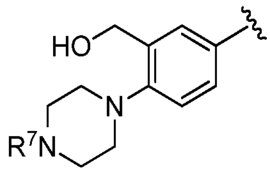
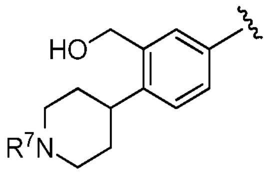
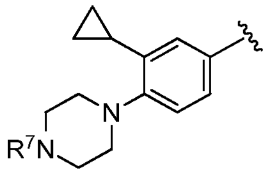
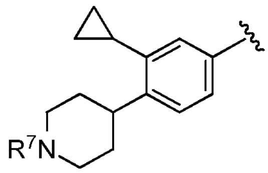
[0073] In some embodiments of a compound of Formula (J) or any related formula where applicable, Z is selected from the group consisting of:

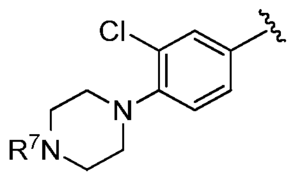
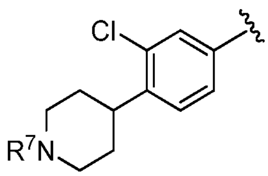
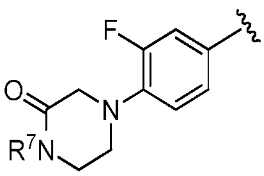
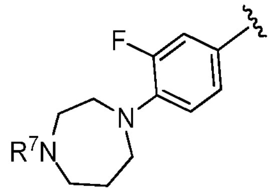


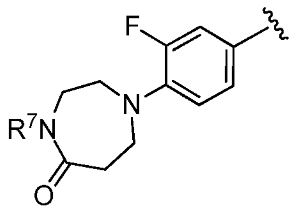
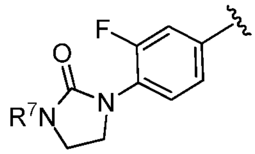
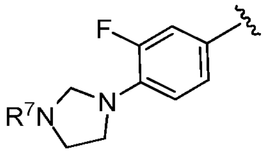
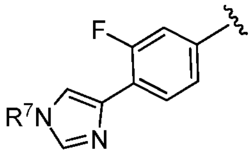


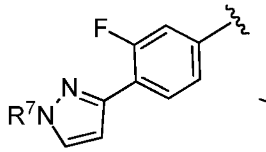
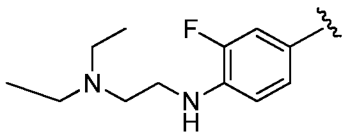
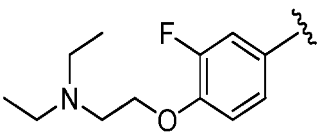
 ,  ,  ,  ,

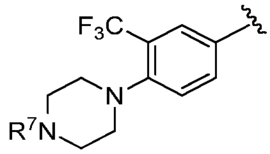
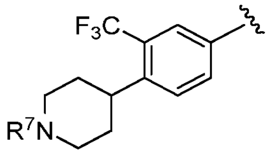
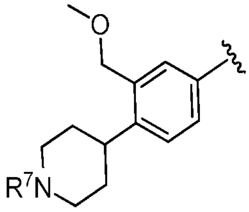
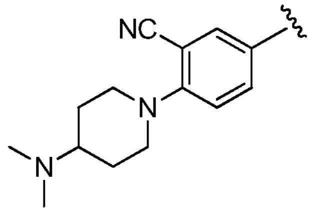
 ,    ,

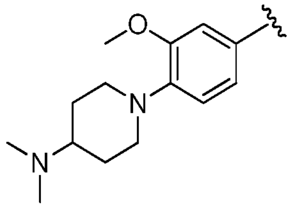
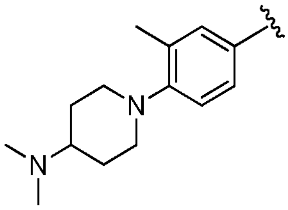
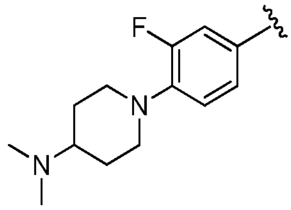
 ,  ,  ,  ,

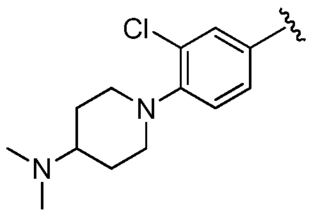
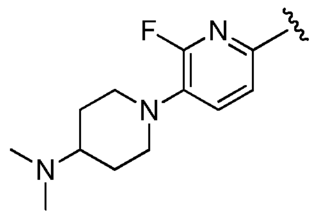
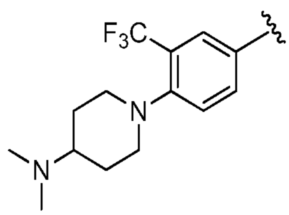
 ,  ,  ,  ,

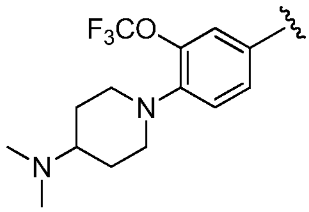
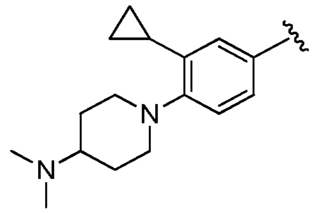
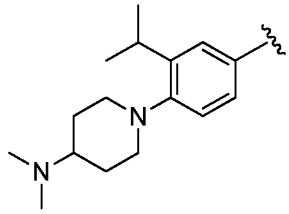
 ,  ,  ,  ,

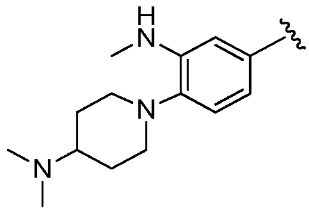
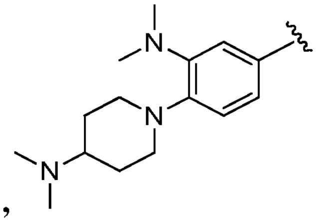
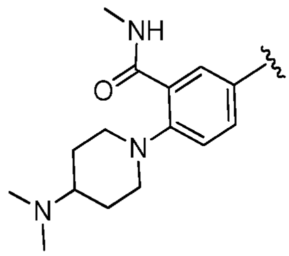
  ,  ,

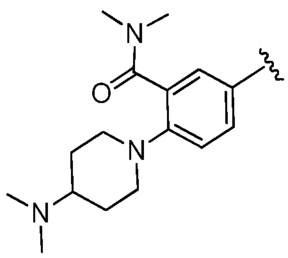
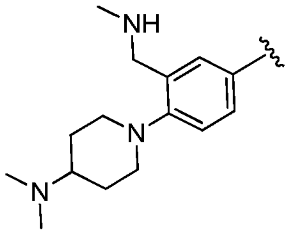
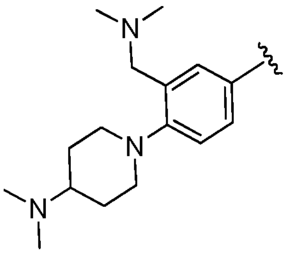
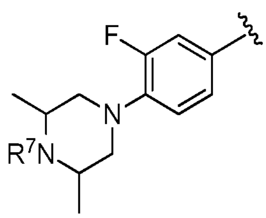
 ,  ,  ,  ,

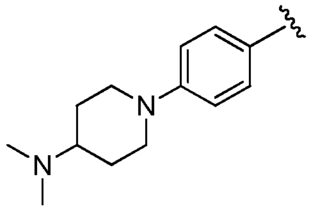
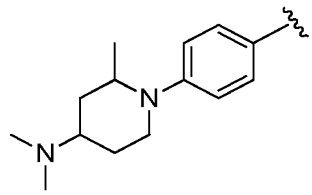
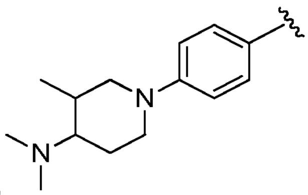
 ,  , 

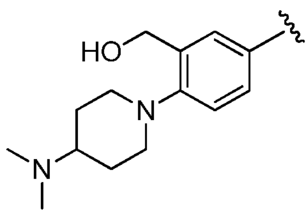
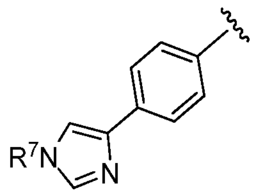
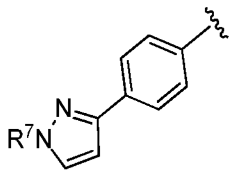
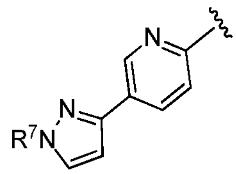
 ,  , 

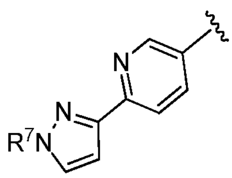
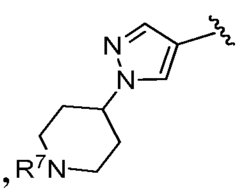
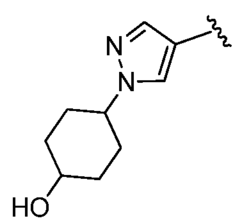
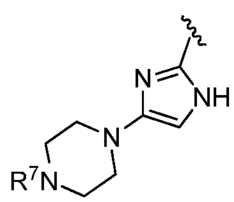
 ,  ,  ,

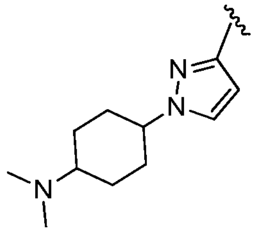
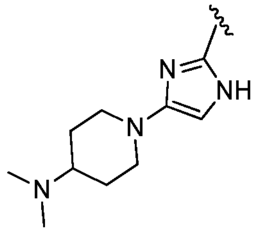
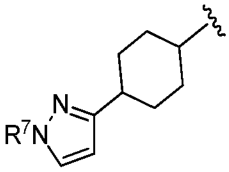
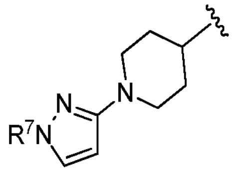
 ,  ,  ,

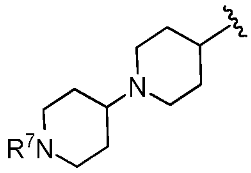
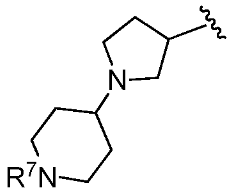
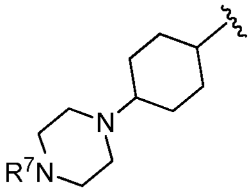
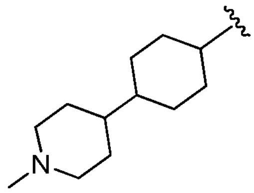
 ,  ,   ,

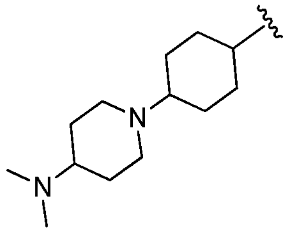
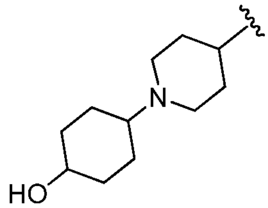
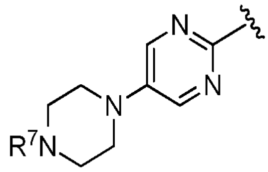
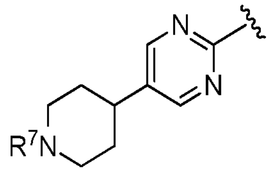
 ,  ,  ,

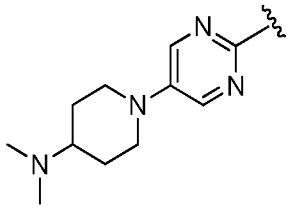
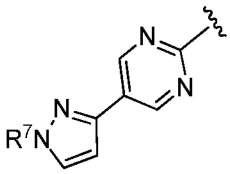
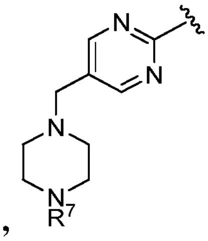
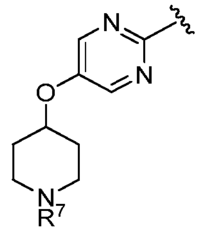
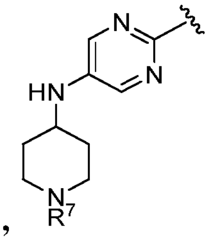
 ,  ,  ,  ,

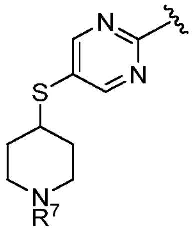
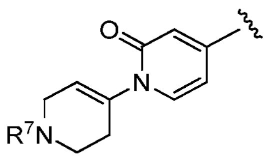
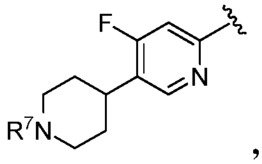
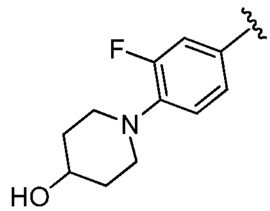
 ,  ,  ,  ,

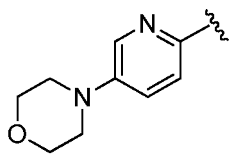
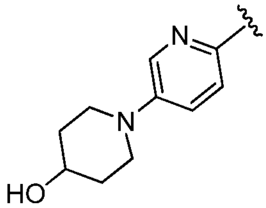
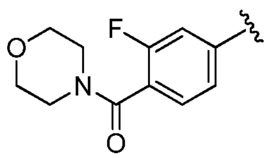
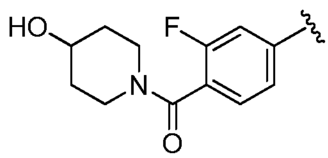
 ,  ,  ,  ,

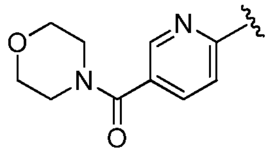
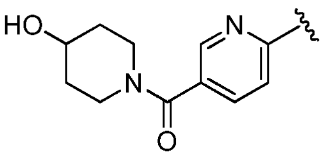
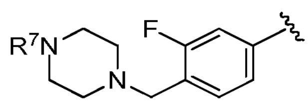
 ,  ,  ,  ,

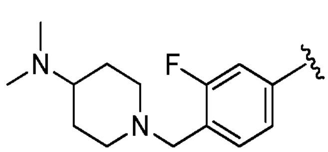
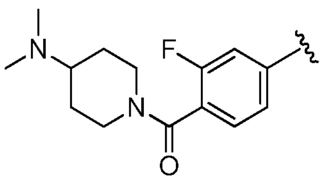
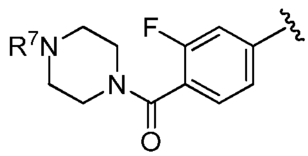
 ,  ,  ,  ,

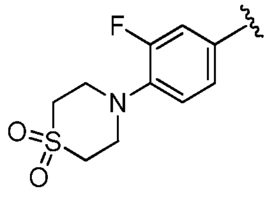
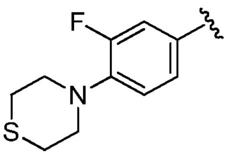
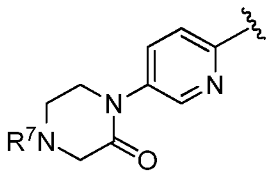
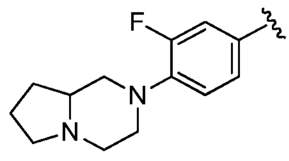
 ,  ,  ,  ,  ,

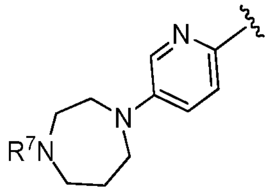
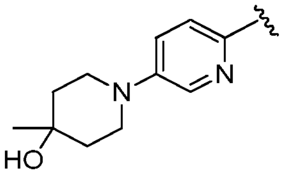
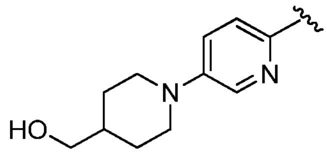
 ,  ,  ,  ,

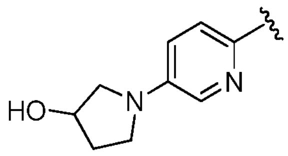
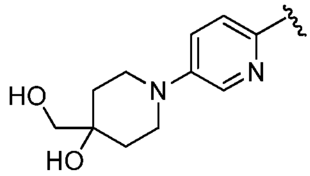
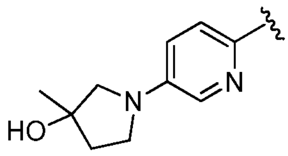
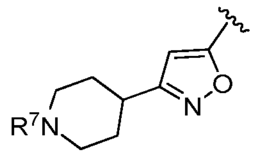
 ,  ,  ,  ,

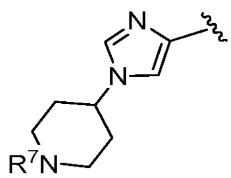
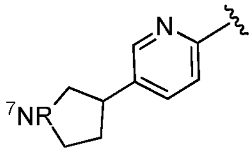
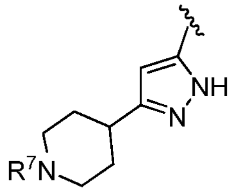
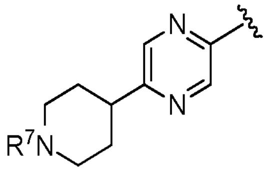
 ,  ,  ,

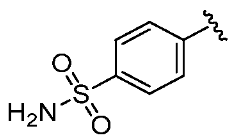
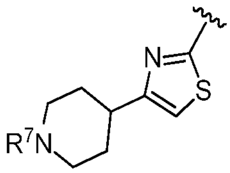
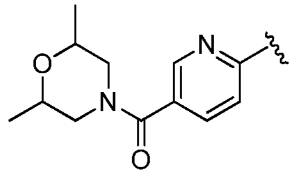
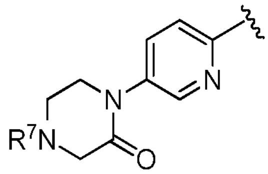
 ,  ,  ,

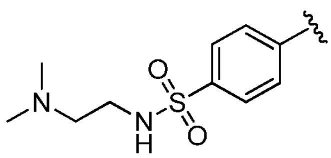
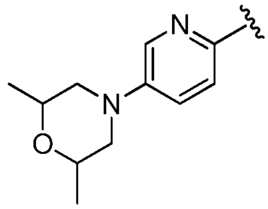
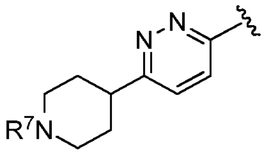
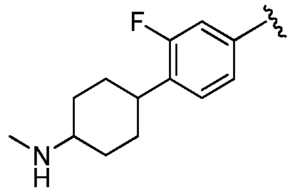
 ,  ,  ,  ,

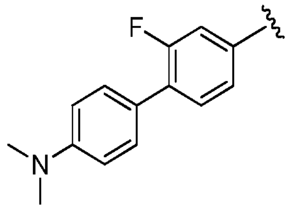
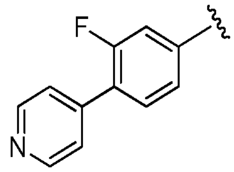
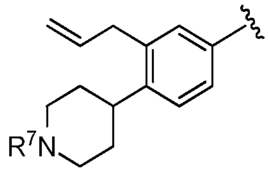
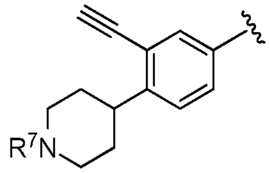
 ,  ,  ,

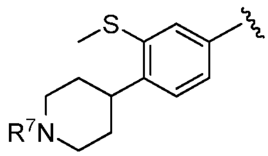
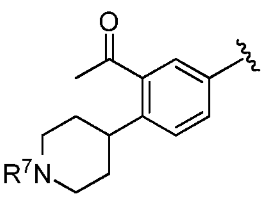
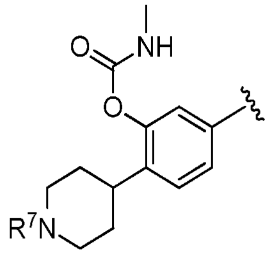
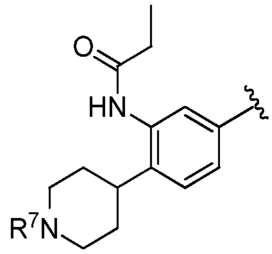
 ,  ,  ,  ,

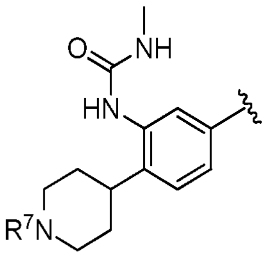
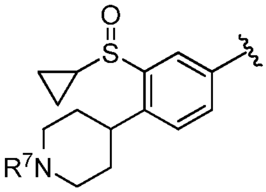
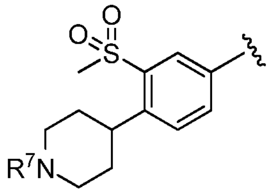
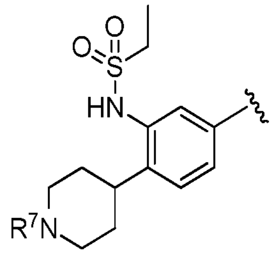
 ,  ,  ,  ,

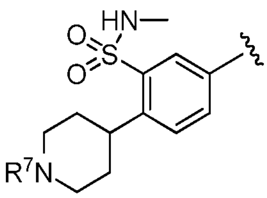
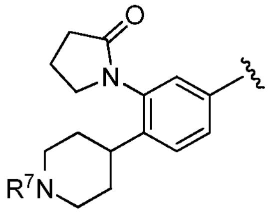
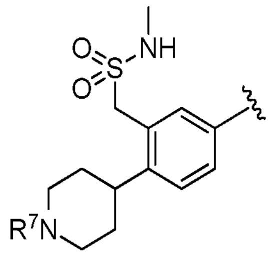
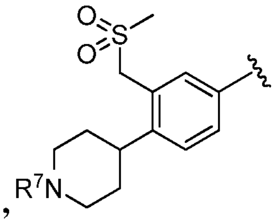
 ,  ,  ,  ,

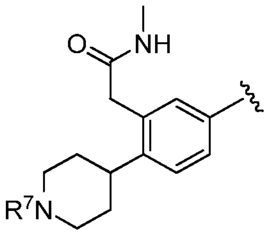
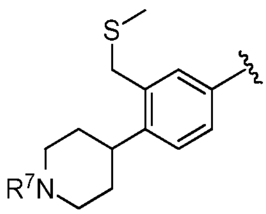
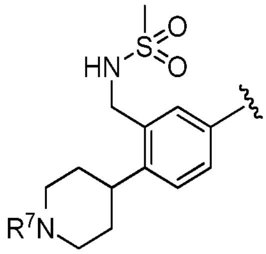
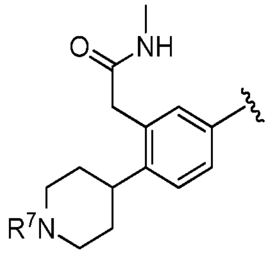
 ,  ,  , 

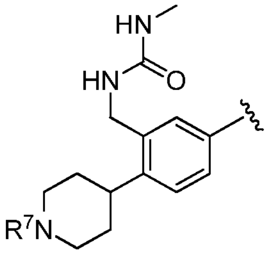
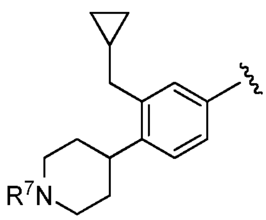
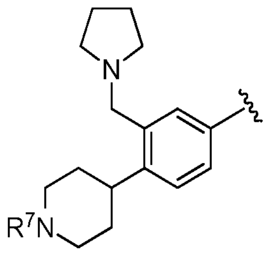
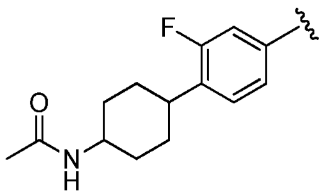
,  ,  ,  ,  ,

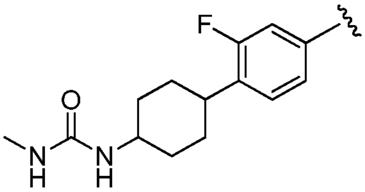
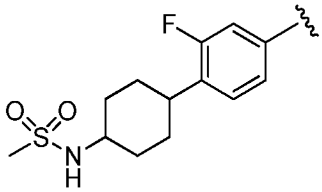
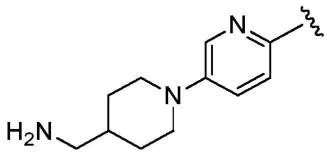
 ,  ,  ,  ,

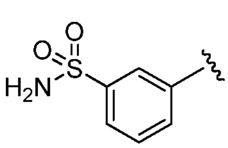
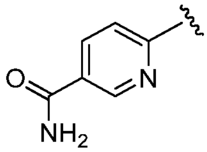
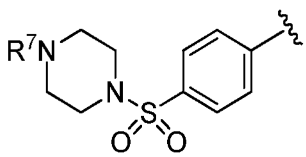
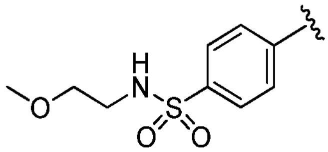
 ,  ,  ,  ,

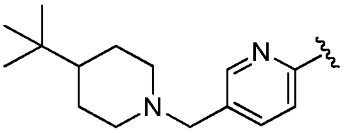
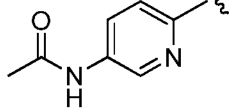
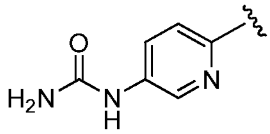
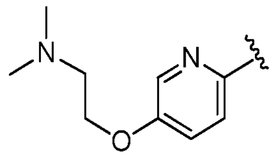
 ,  ,  ,  ,

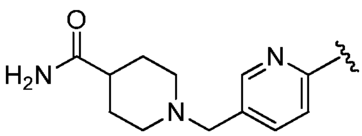
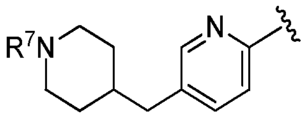
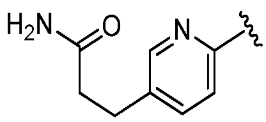
 ,  ,  ,  ,

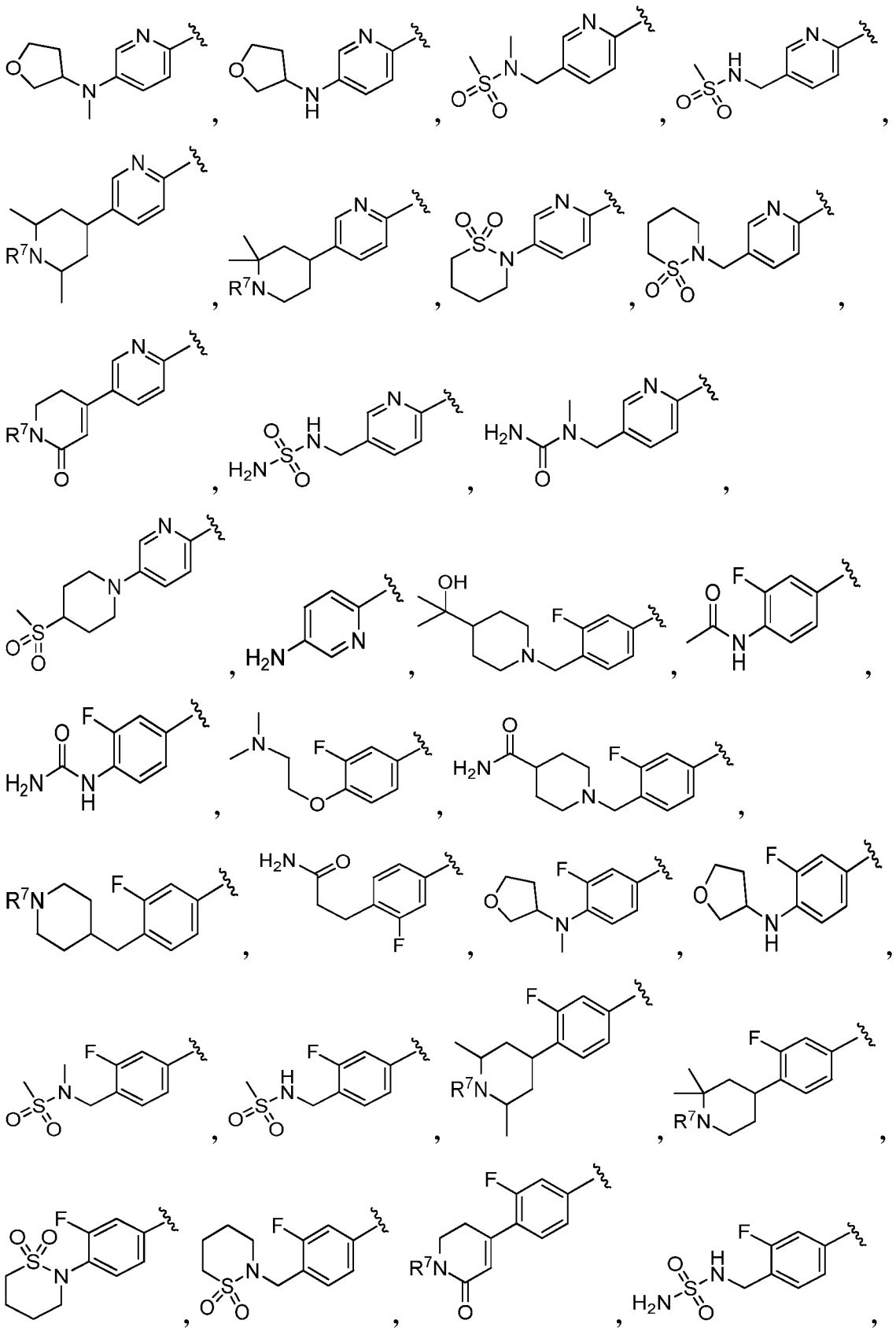
 ,  ,  ,  ,

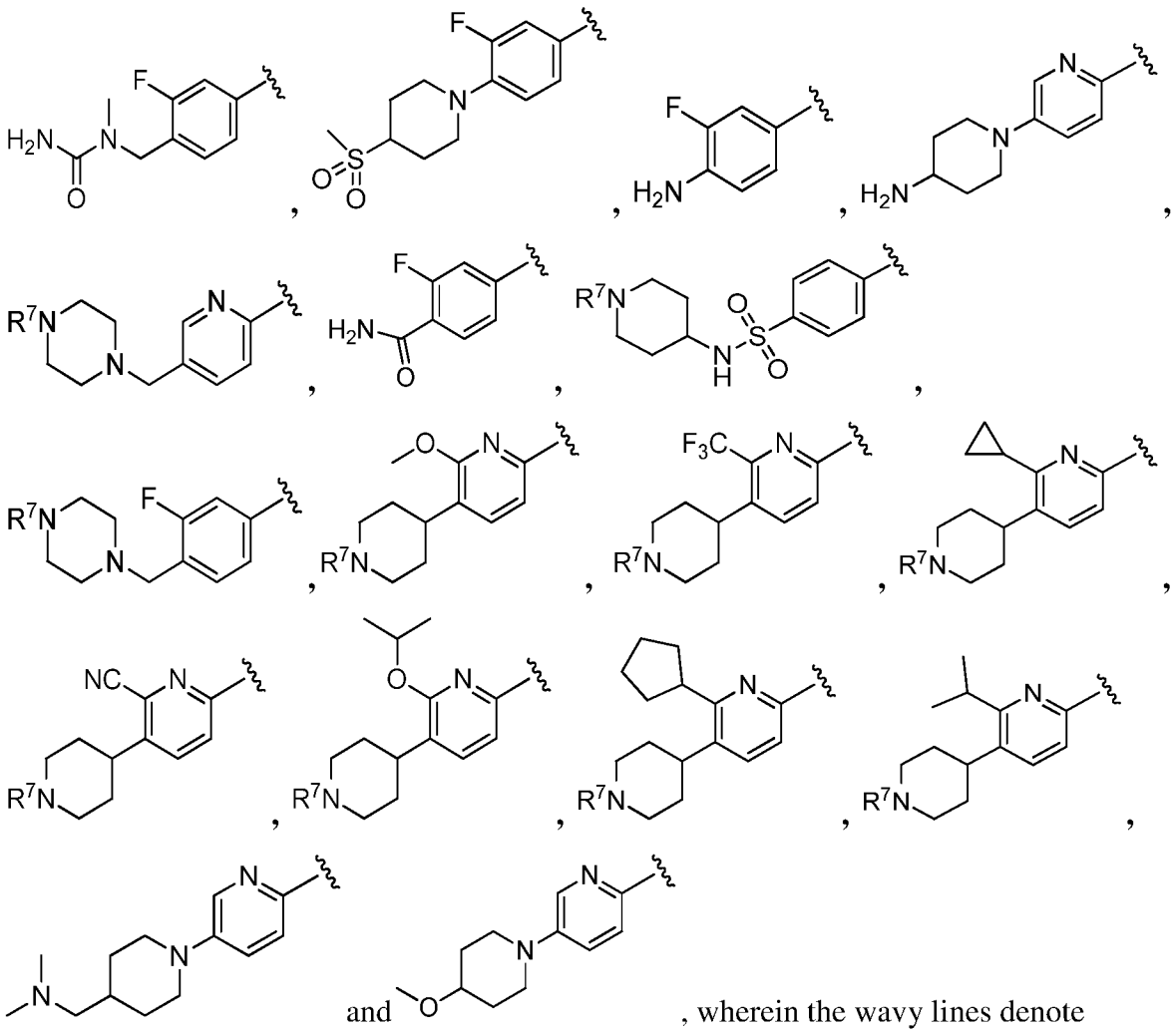
 ,  ,  ,

 ,  ,  ,  ,

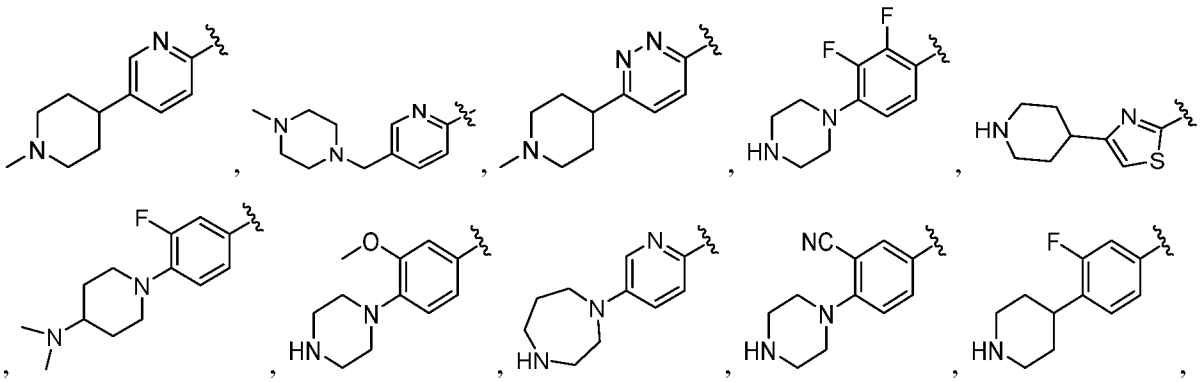
 ,  ,  ,  ,

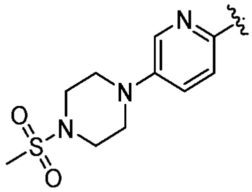
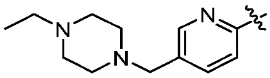
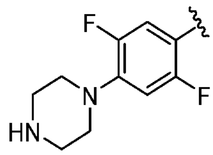
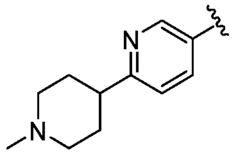
 ,  ,  ,

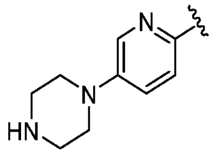
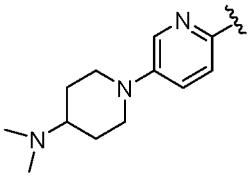




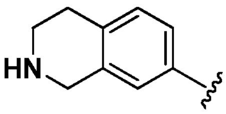
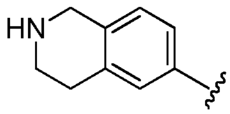
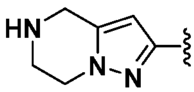
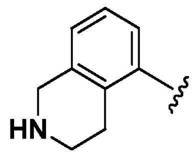
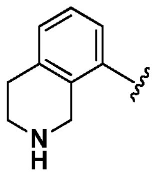
and , wherein the wavy lines denote attachment points to the rest of the molecule and R^7 is as described herein. In some embodiments, Z is

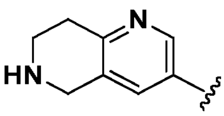
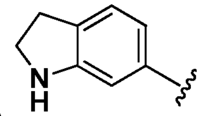
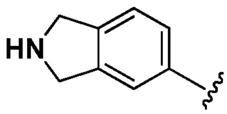
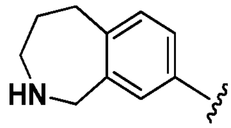
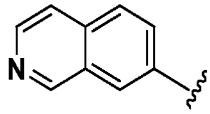


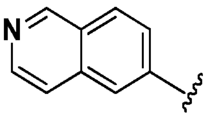
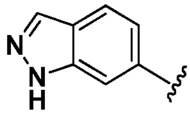
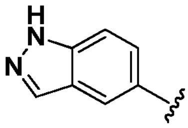
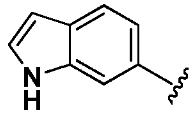
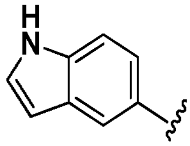
 ,  ,  ,  ,

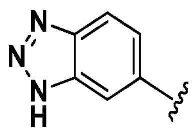
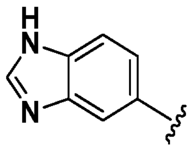
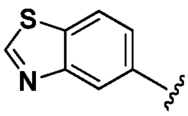
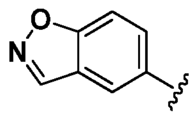
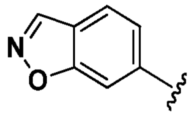
 , or  .

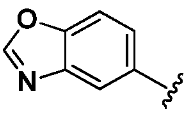
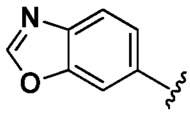
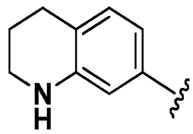
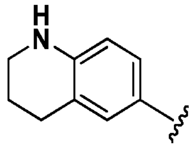
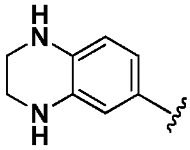
[0074] In some embodiments of a compound of Formula (J) or any related formula where applicable, Z is selected from the group consisting of:

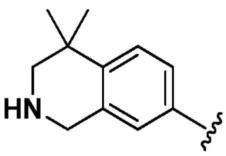
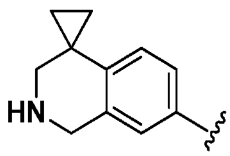
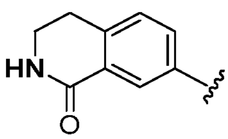
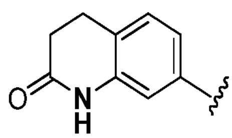
 ,  ,  ,  ,  ,

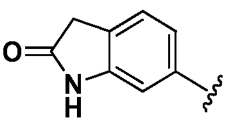
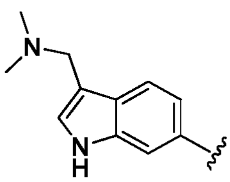
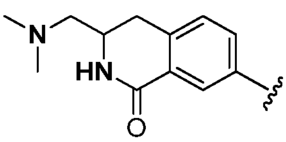
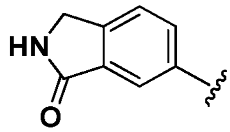
 ,  ,  ,  ,  ,

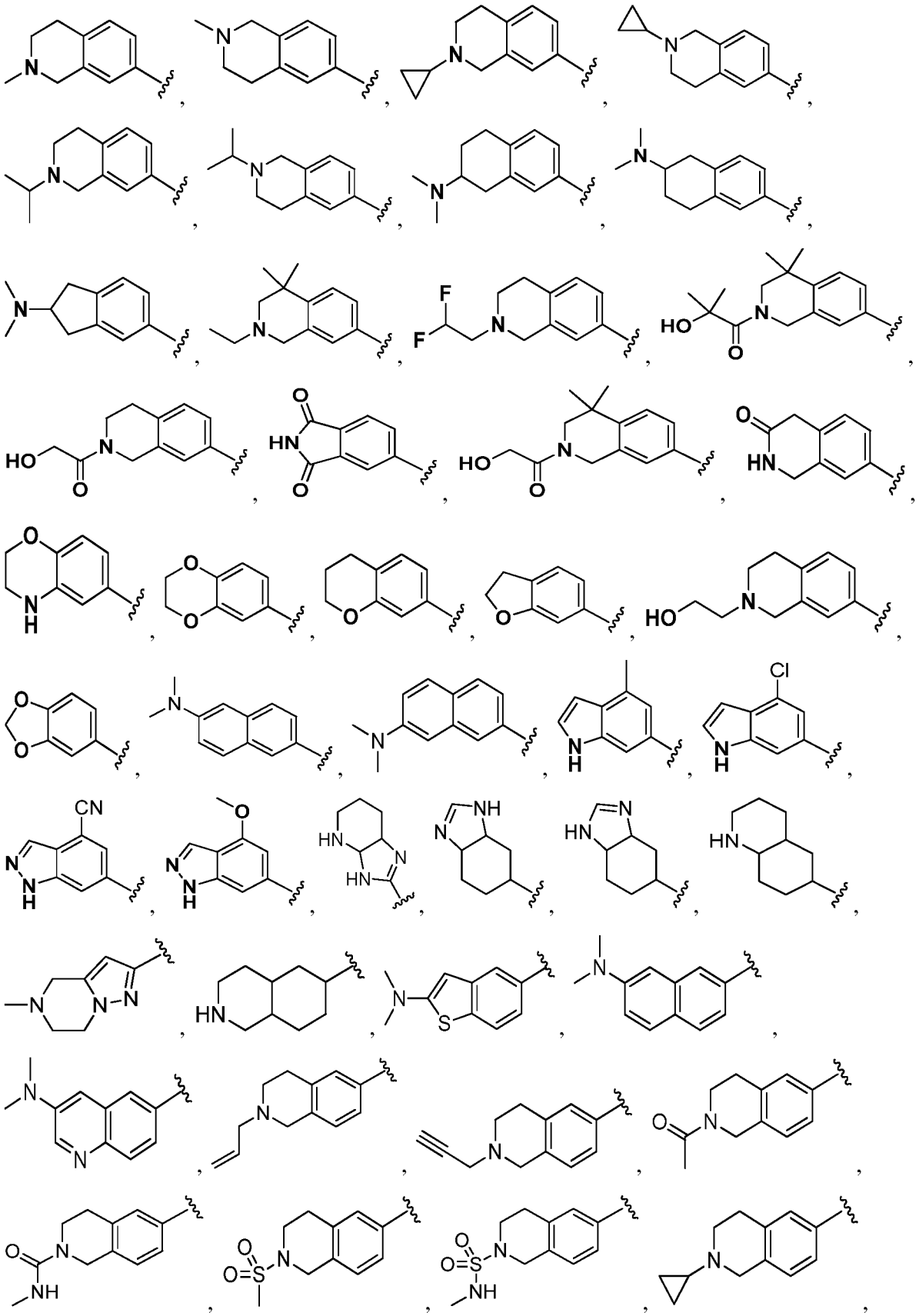
 ,  ,  ,  ,  ,

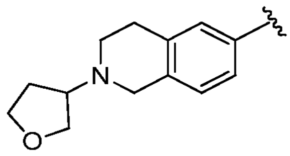
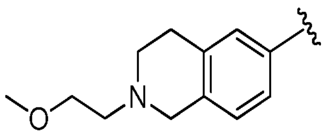
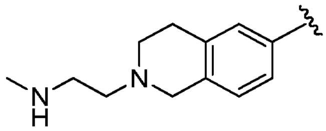
 ,  ,  ,  ,  ,

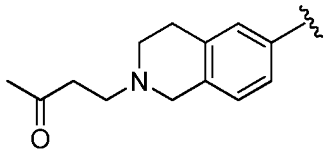
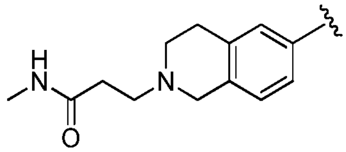
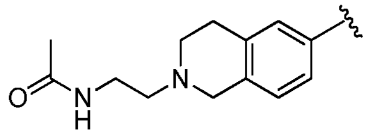
 ,  ,  ,  ,  ,

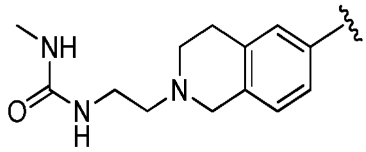
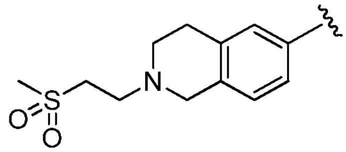
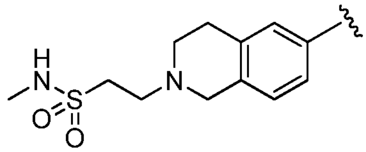
 ,  ,  ,  ,

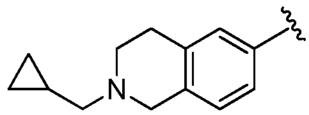
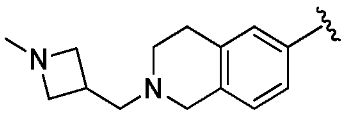
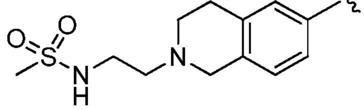
 ,  ,  ,  ,

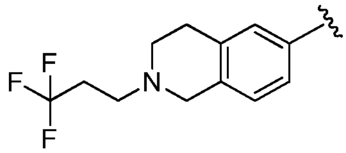
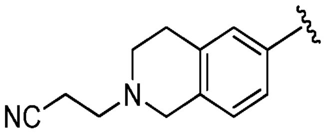
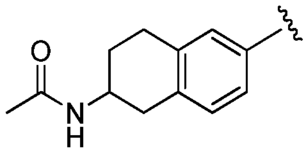


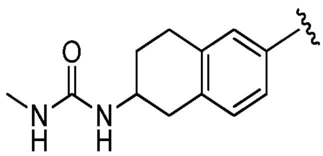
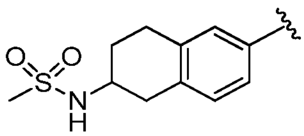
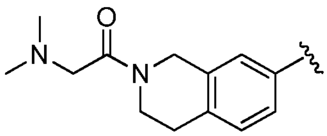
 ,  ,  ,

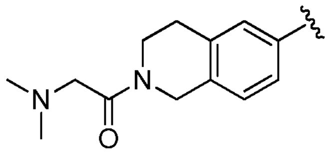
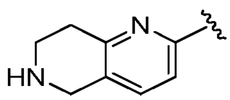
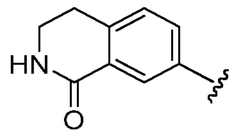
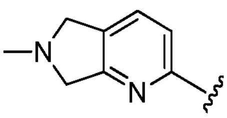
 ,  ,  ,

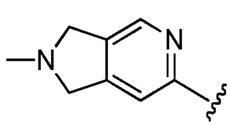
 ,  ,  ,

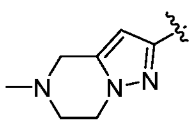
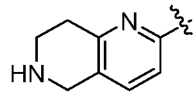
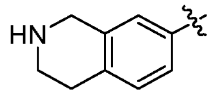
 ,  ,  ,

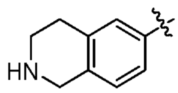
 ,  ,  ,

 ,  ,  ,

 ,  ,  ,  , and

 , wherein the wavy lines denote attachment points to the parent molecule.

In some embodiments, Z is  ,  ,  , or

 .

[0075] Specific values listed below are values for a compound of Formula (J) or any related formula where applicable. It is to be understood that two or more values may combined. Thus, it is to be understood that any variable for a compound of Formula (J) as well as all related formulae may be combined with any other variable for a compound of

Formula (J) as well as all related formulae the same as if each and every combination of variables were specifically and individually listed. For example, it is understood that any specific value of R^1 detailed herein for a compound of Formula (J) as well as all related formulae may be combined with any other specific value for one or more of the variables Z, X^1, X^2, X^3, R^2, R^3, R^4, *l*, m, and n the same as if each and every combination were specifically and individually listed.

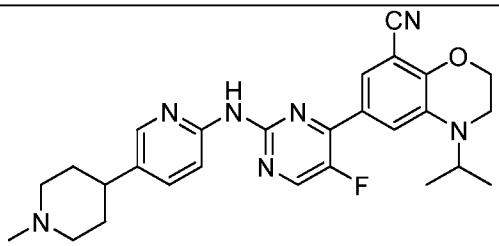
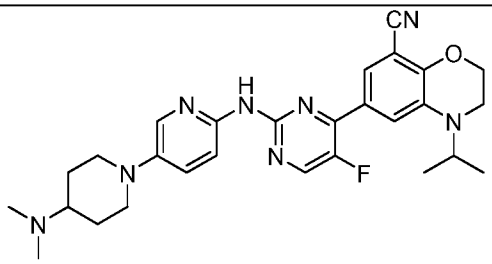
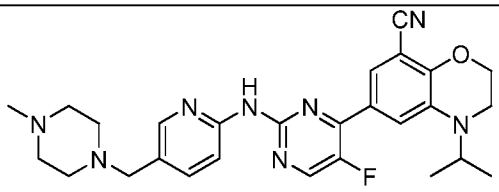
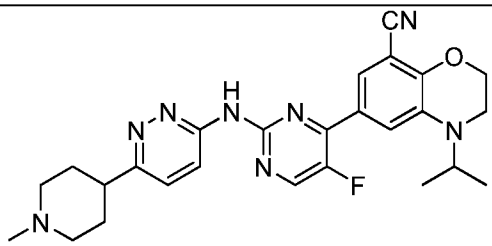
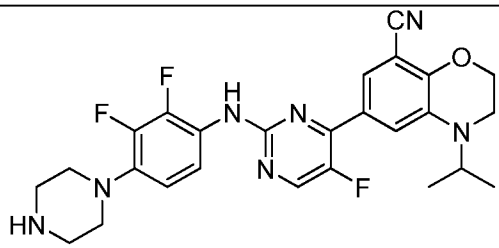
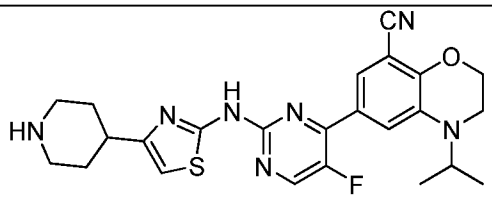
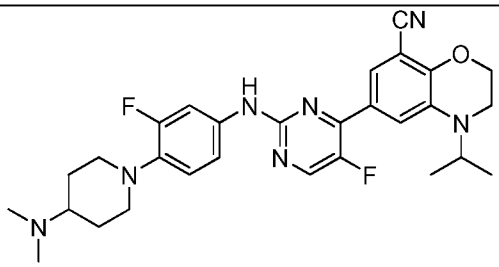
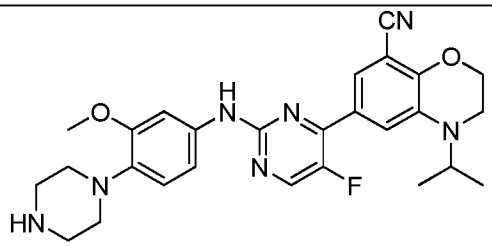
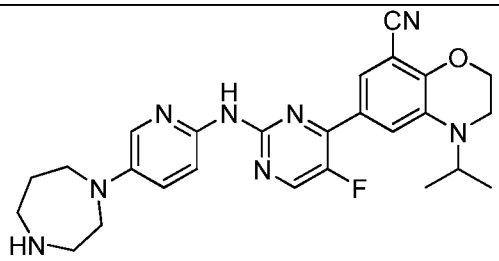
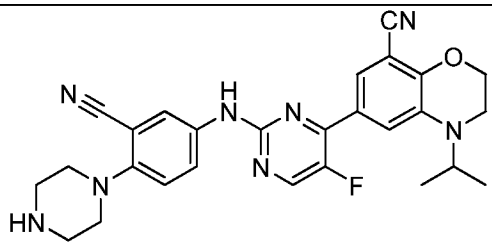
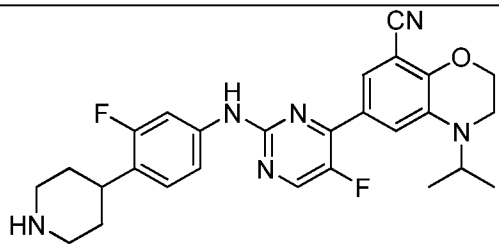
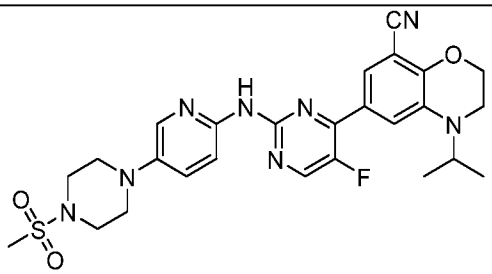
[0076] Also provided are salts of compounds referred to herein, such as pharmaceutically acceptable salts. The invention also includes any or all of the stereochemical forms, including any enantiomeric or diastereomeric forms, and any tautomers or other forms of the compounds described. It is understood that individual enantiomers and diastereomers are provided herein and their corresponding structures can be readily determined.

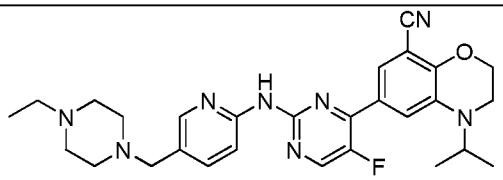
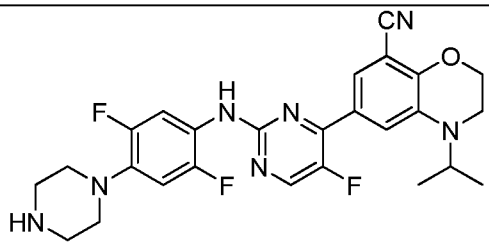
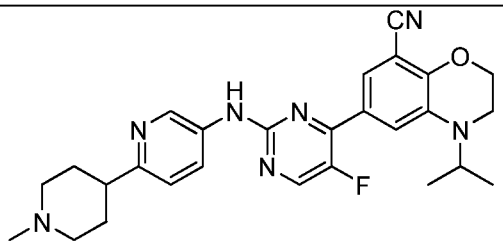
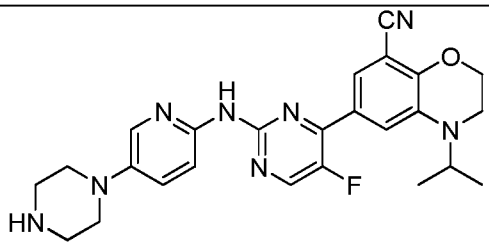
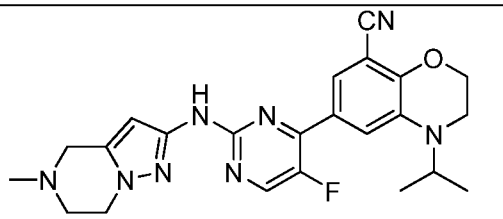
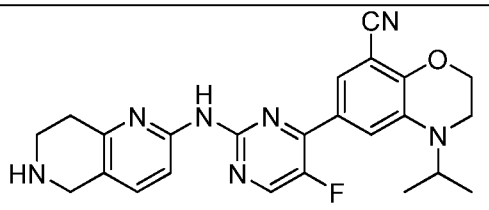
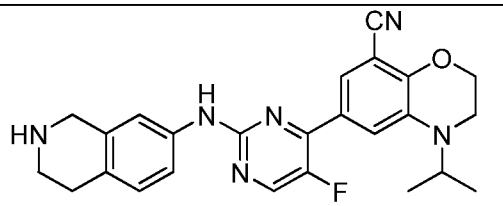
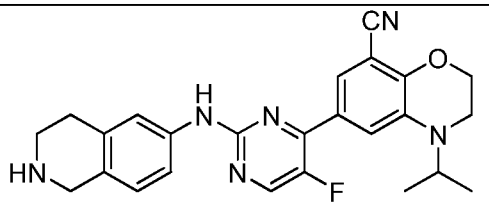
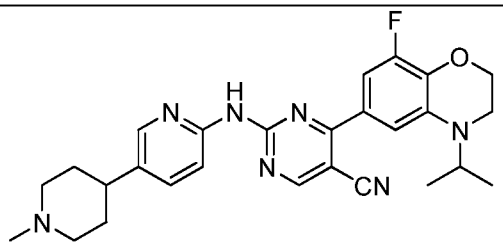
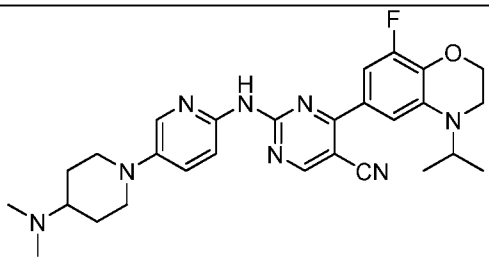
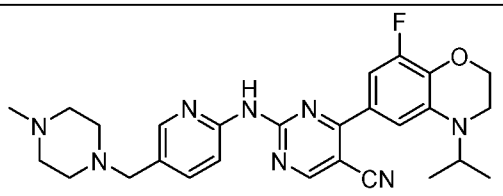
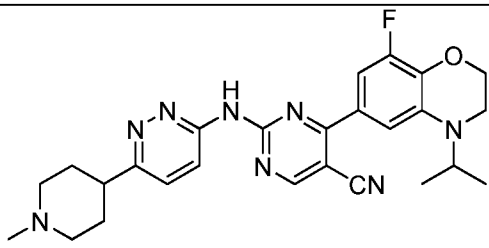
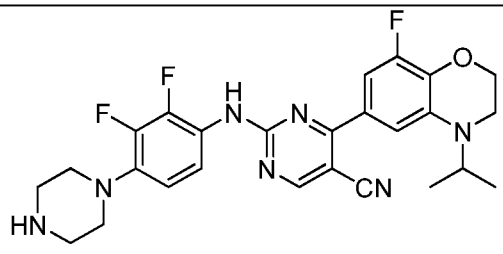
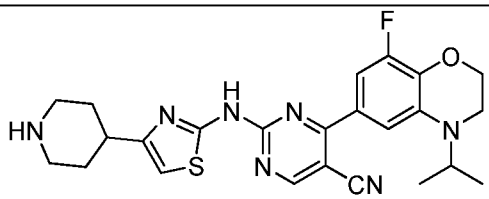
[0077] A compound as detailed herein may in one aspect be in a purified form and compositions comprising a compound in purified forms are detailed herein. Compositions comprising a compound as detailed herein or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, are provided, such as compositions of substantially pure compounds. In some embodiments, a composition containing a compound as detailed herein or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, is in substantially pure form. Unless otherwise stated, "substantially pure" intends a composition that contains no more than 35% impurity, wherein the impurity denotes a compound other than the compound comprising the majority of the composition or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing. In some embodiments, a composition of substantially pure compound or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, is provided wherein the composition contains no more than 25%, 20%, 15%, 10%, or 5% impurity. In some embodiments, a composition of substantially pure compound or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, is provided wherein the composition contains or no more than 3%, 2%, 1% or 0.5% impurity.

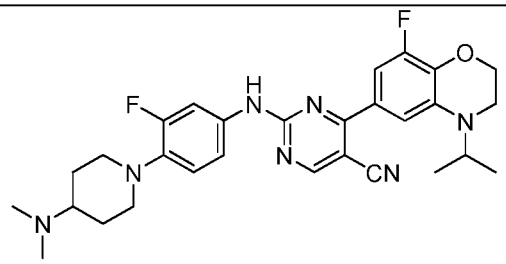
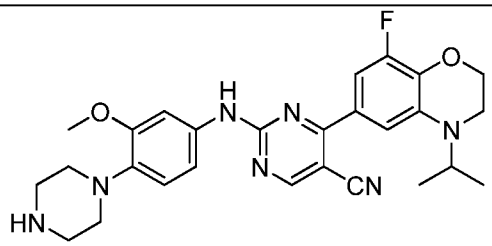
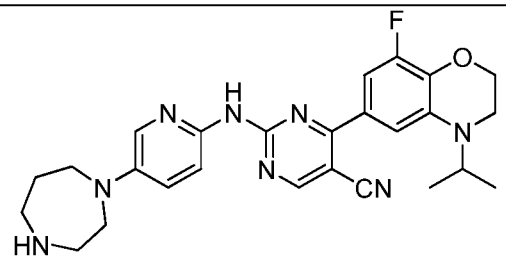
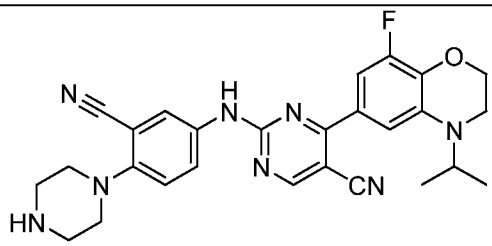
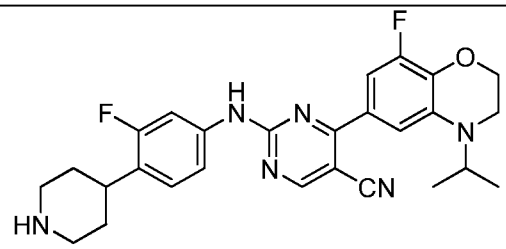
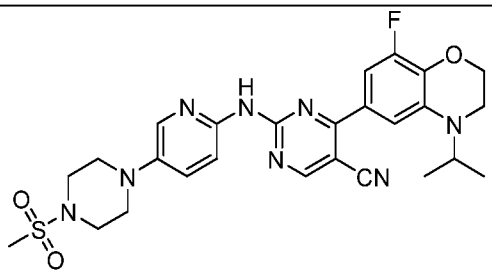
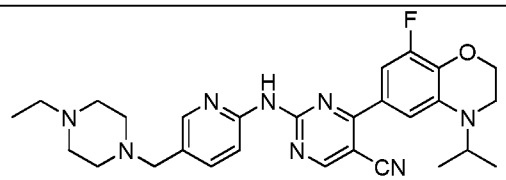
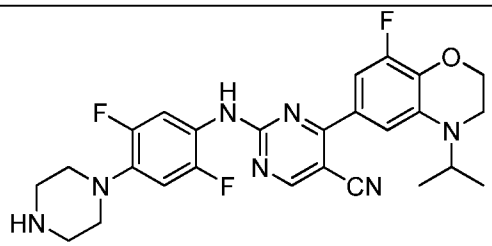
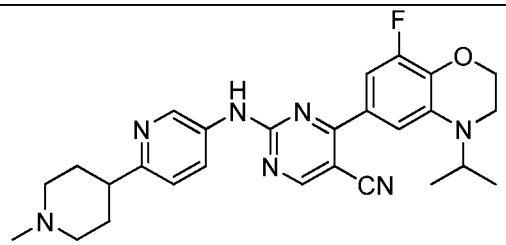
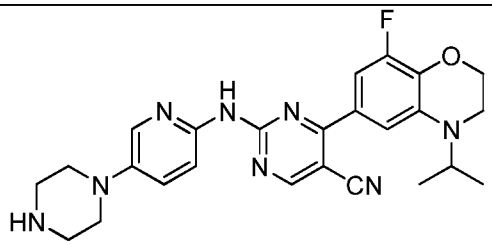
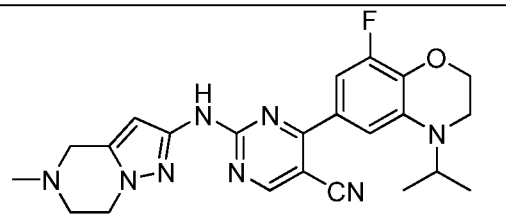
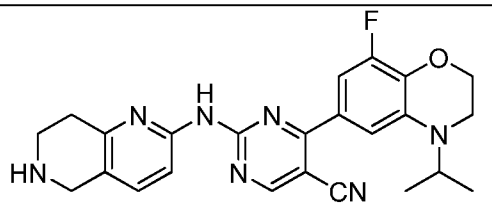
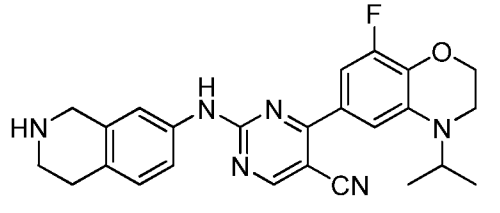
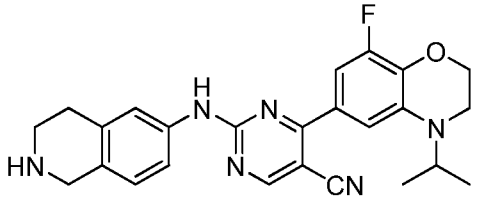
[0078] Representative compounds are provided below.

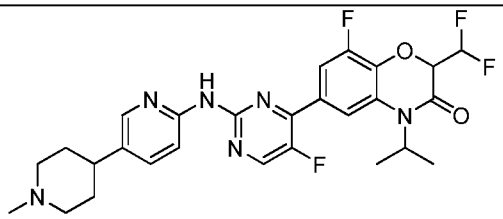
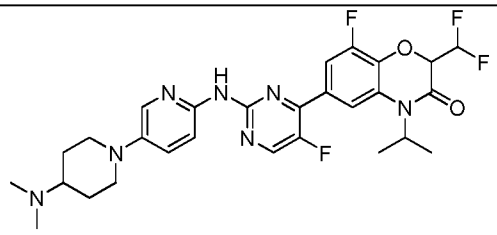
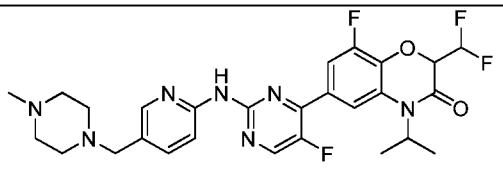
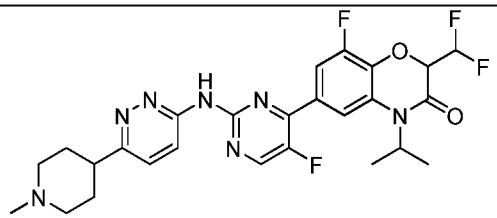
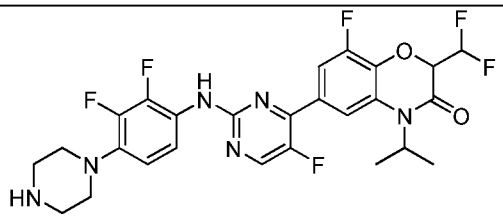
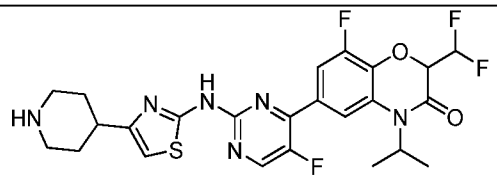
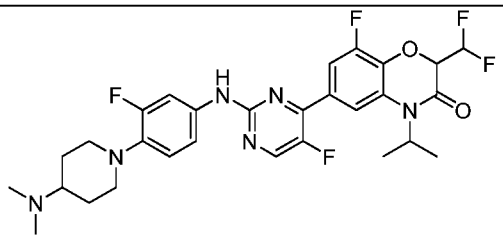
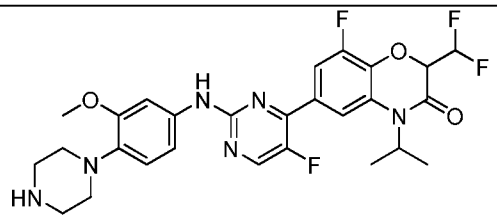
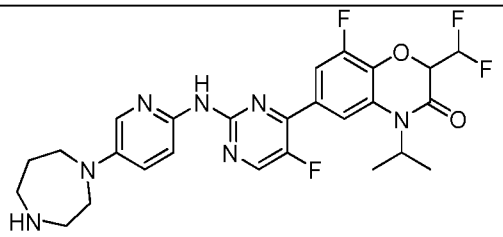
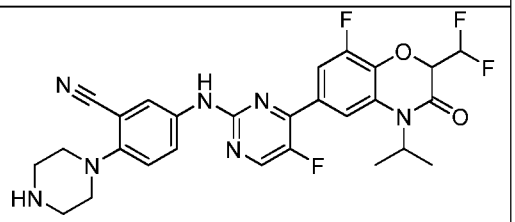
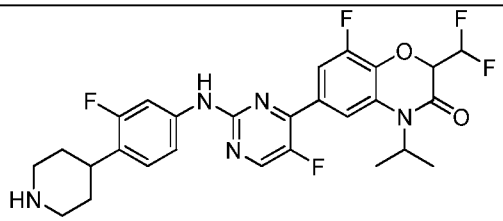
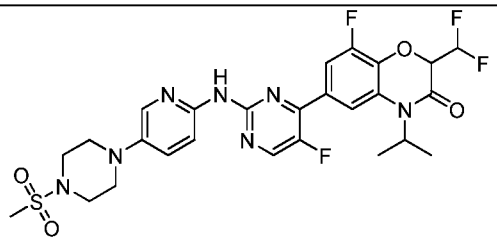
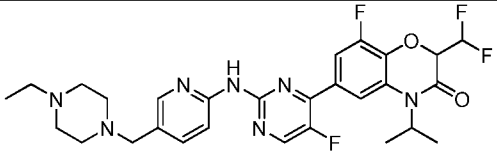
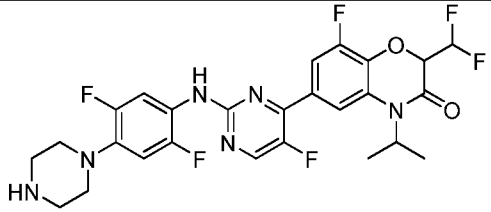
TABLE 1

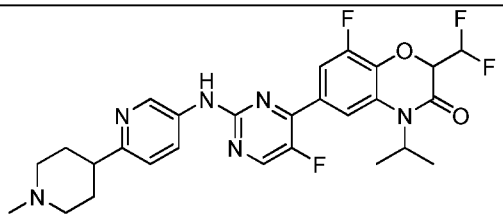
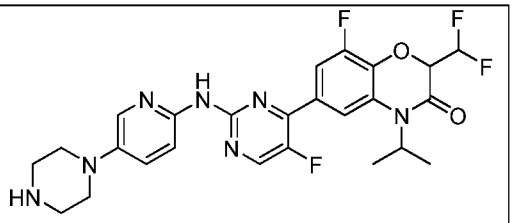
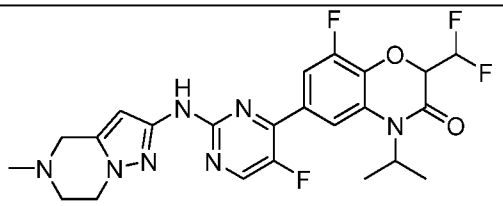
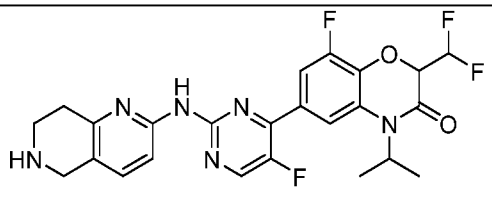
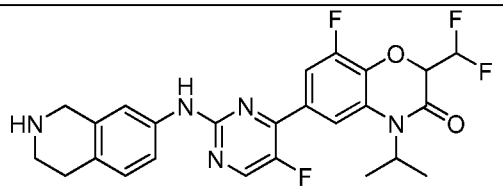
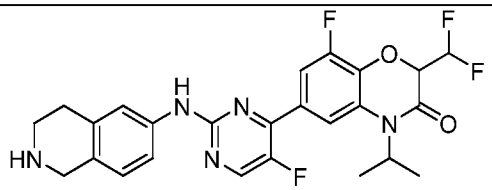
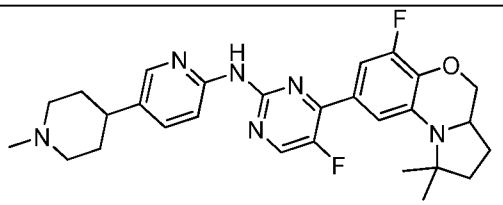
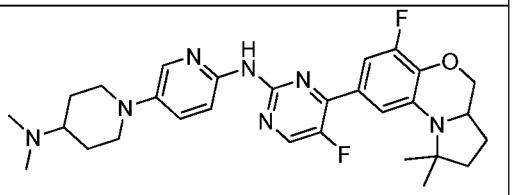
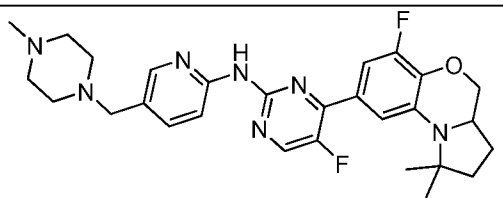
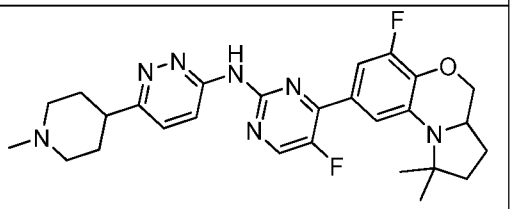
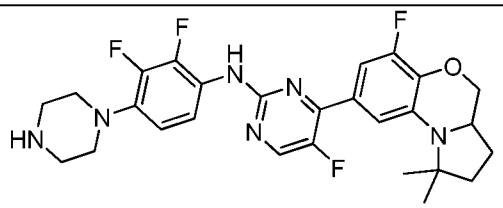
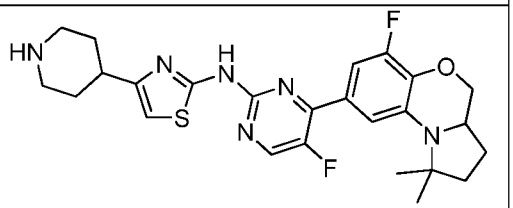
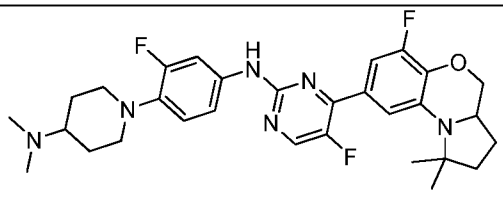
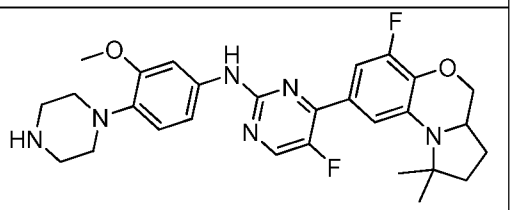
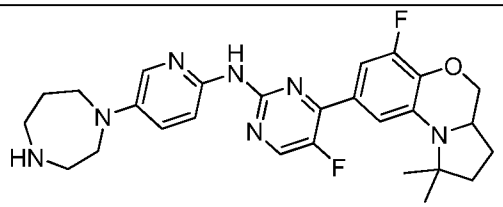
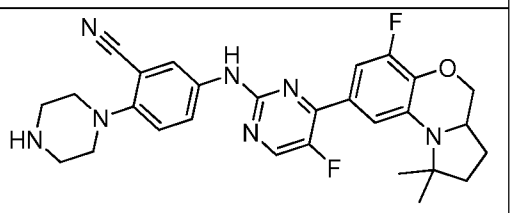
No.	Structure	No.	Structure

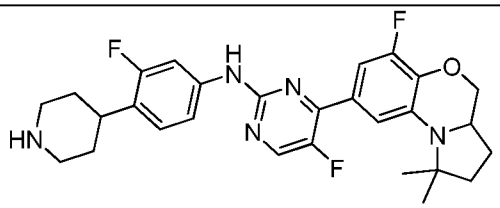
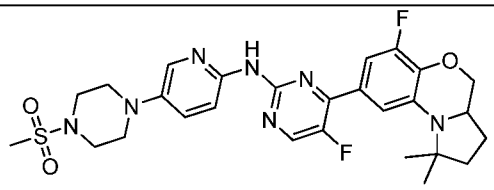
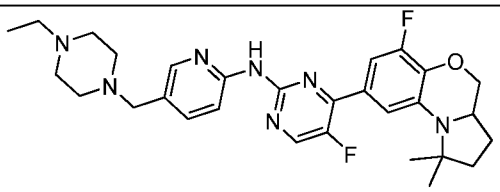
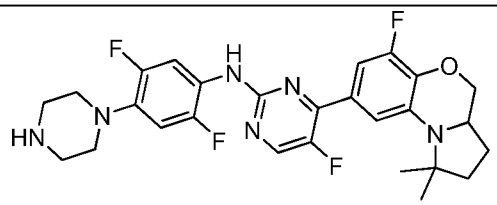
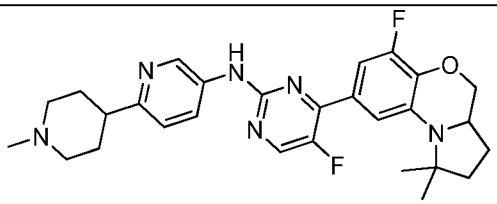
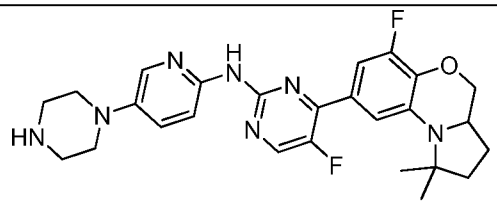
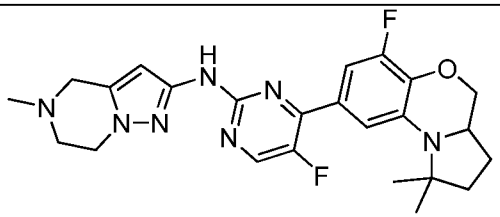
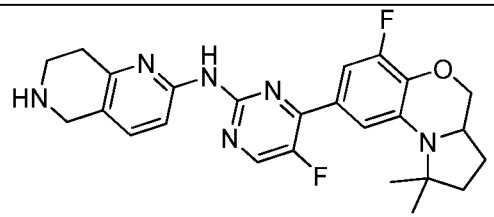
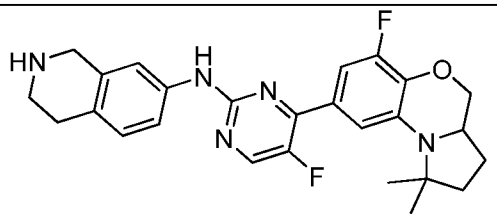
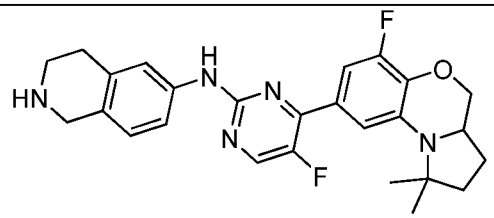
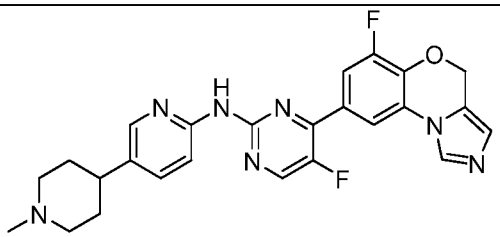
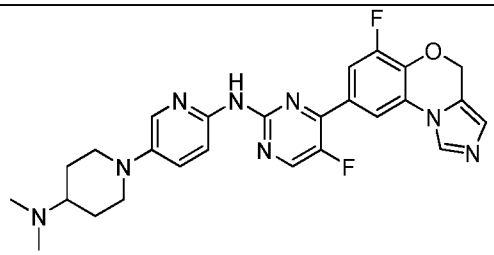
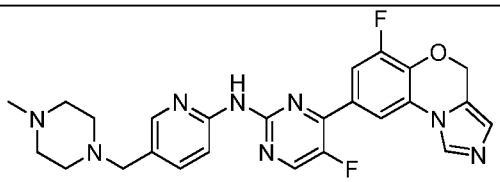
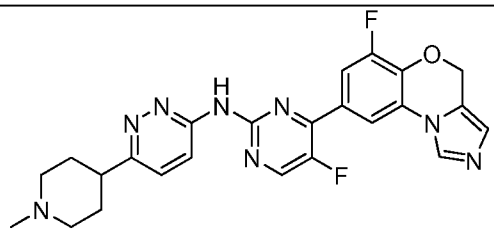
1		2	
3		4	
5		6	
7		8	
9		10	
11		12	

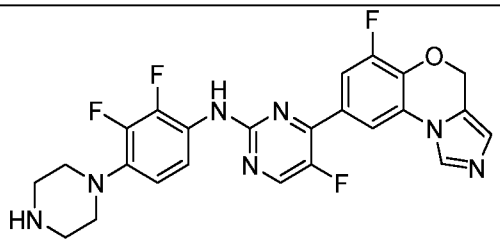
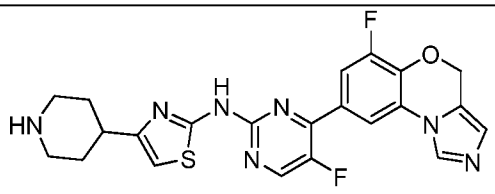
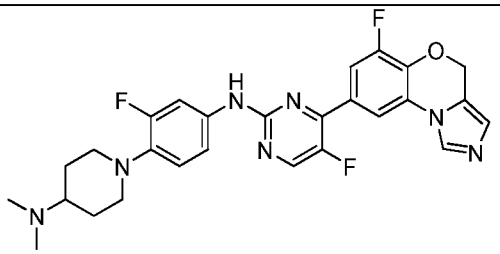
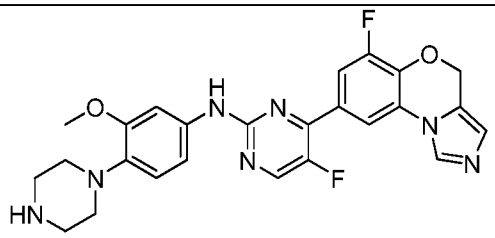
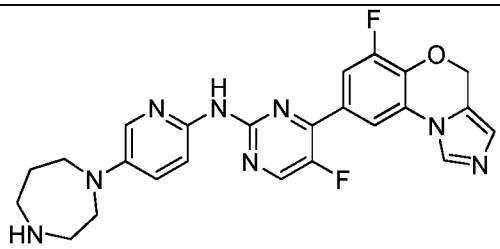
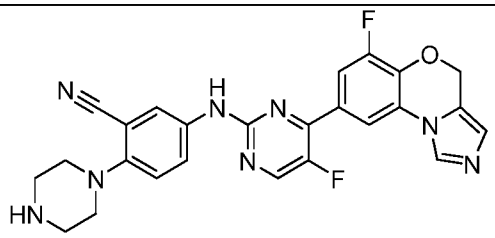
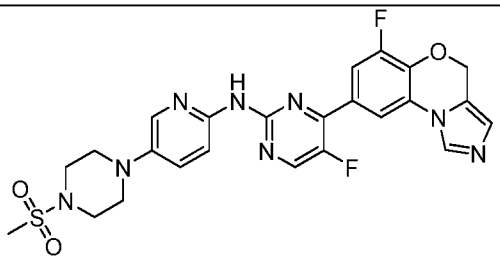
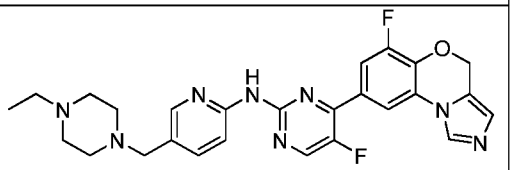
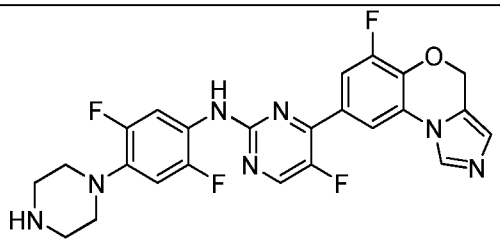
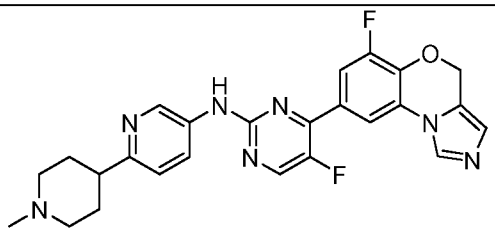
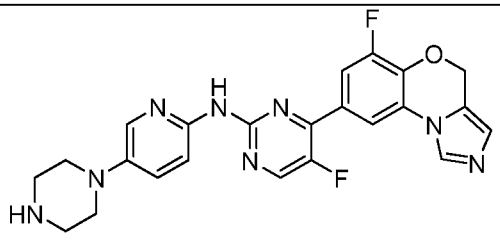
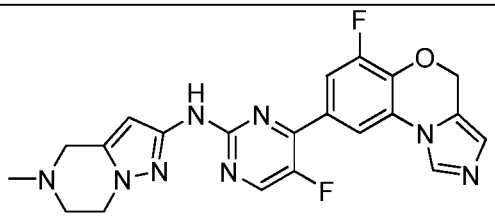
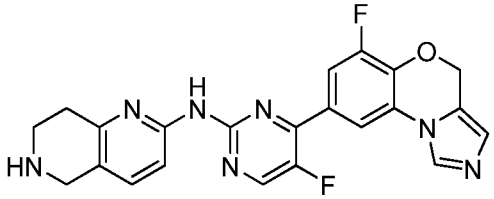
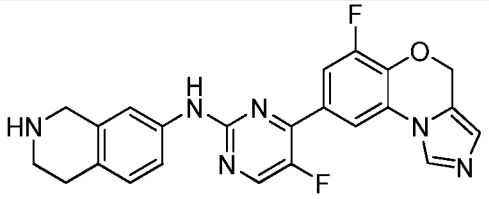
13		14	
15		16	
17		18	
19		20	
21		22	
23		24	
25		26	

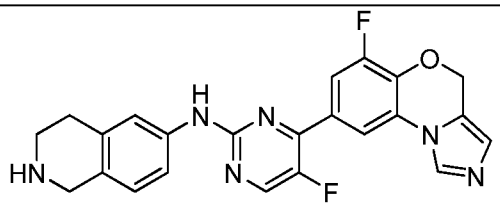
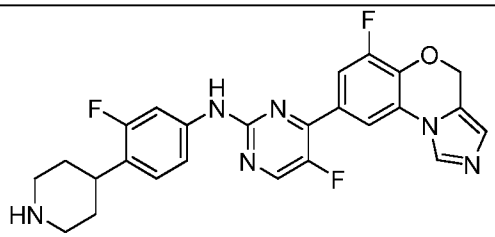
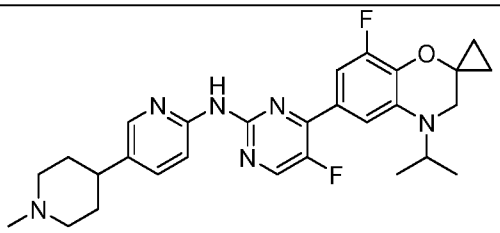
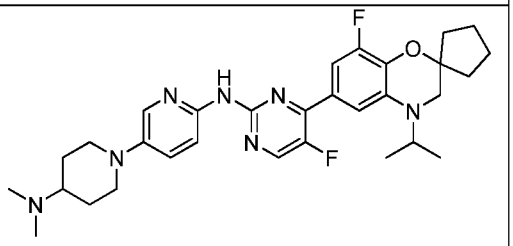
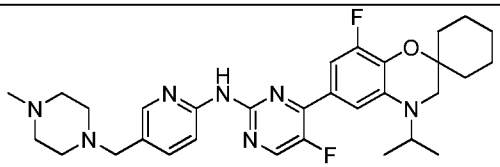
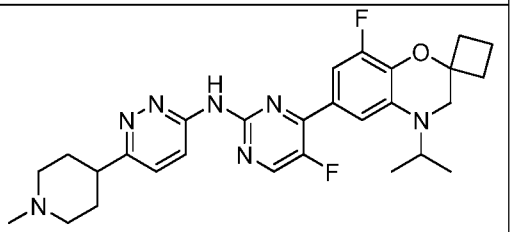
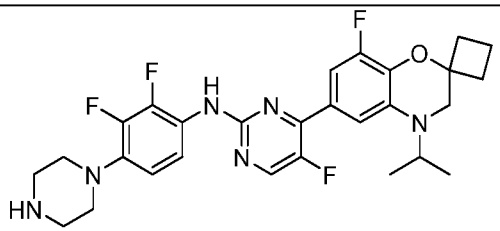
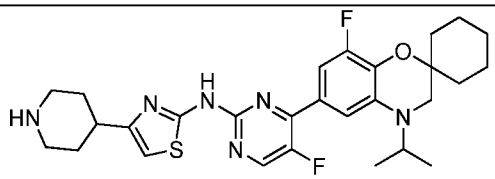
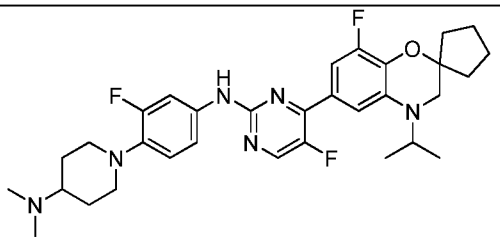
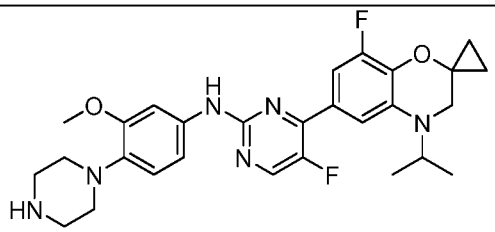
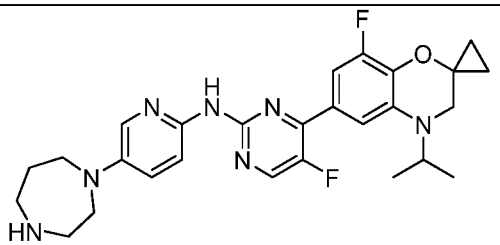
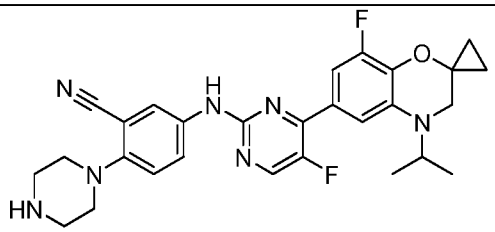
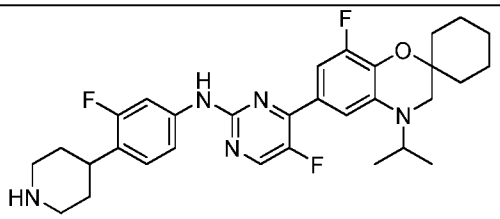
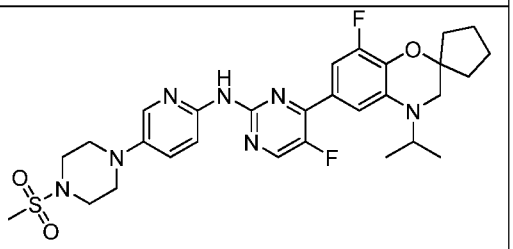
27		28	
29		30	
31		32	
33		34	
35		36	
37		38	
39		40	

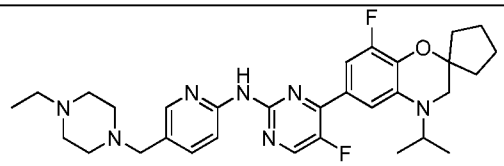
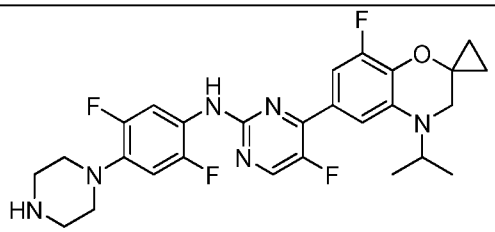
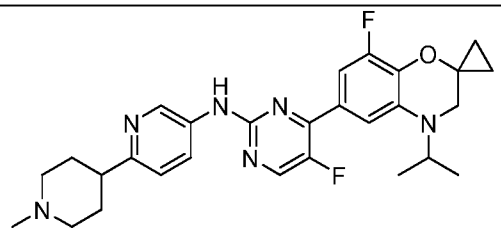
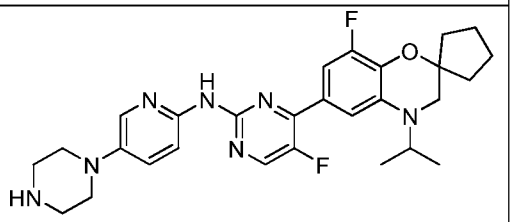
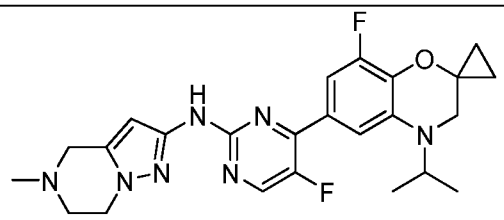
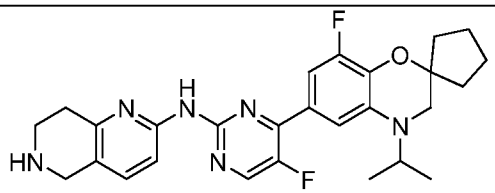
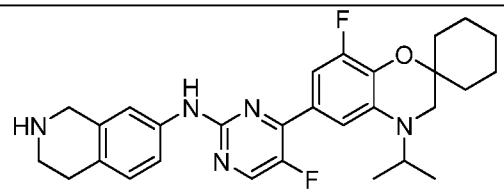
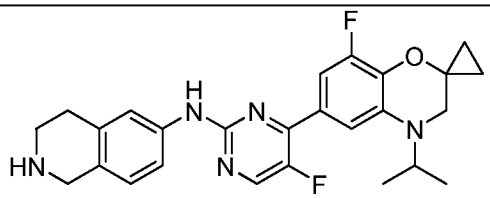
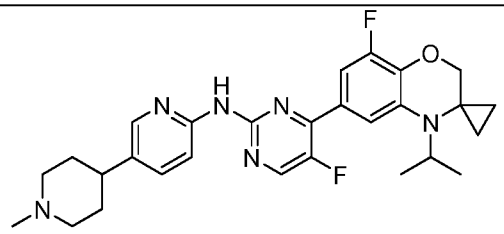
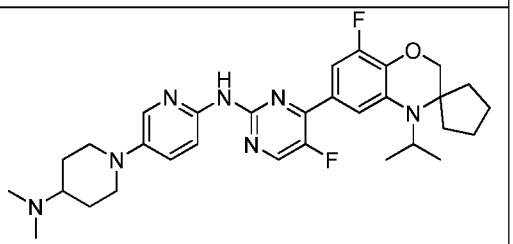
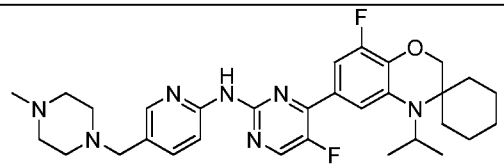
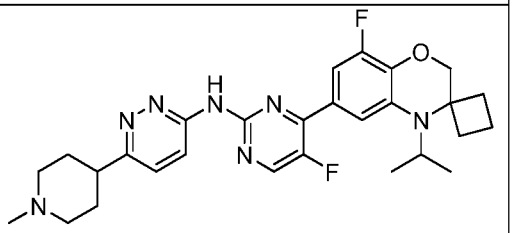
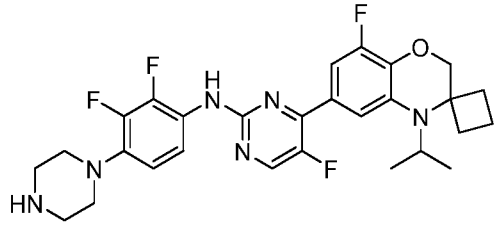
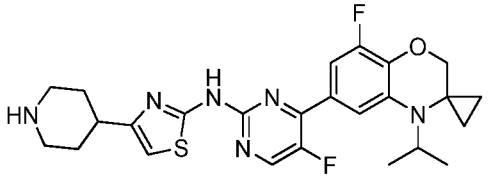
41		42	
43		44	
45		46	
47		48	
49		50	
51		52	
53		54	

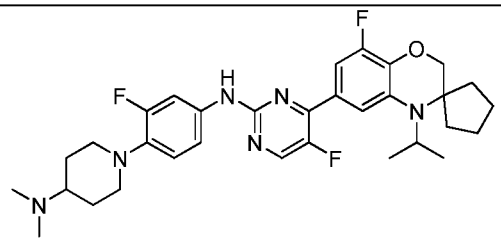
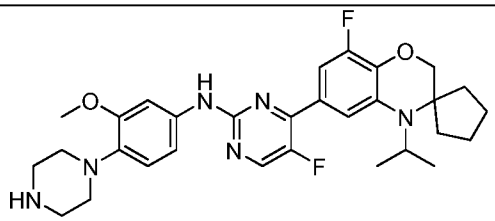
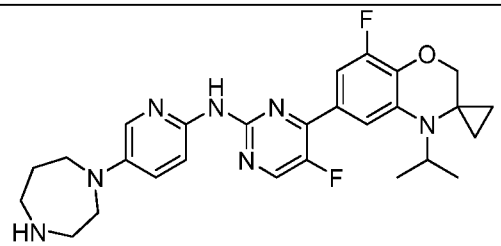
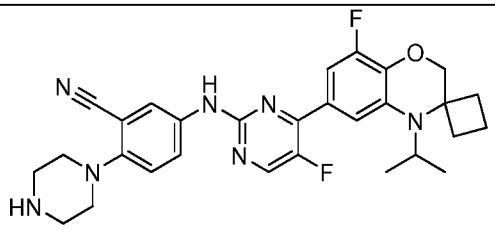
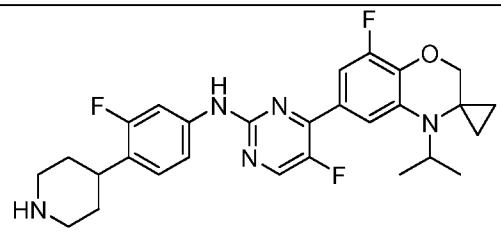
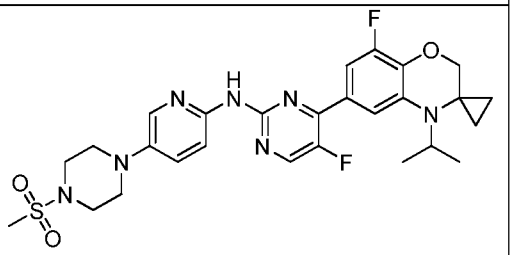
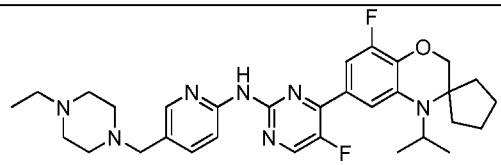
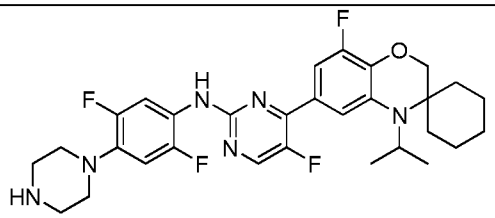
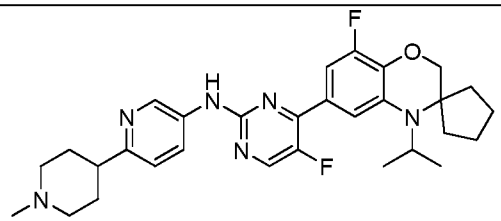
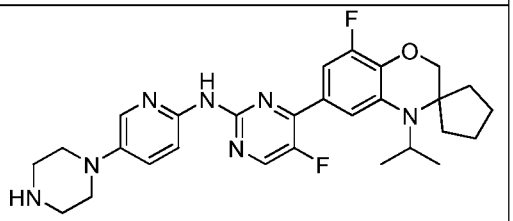
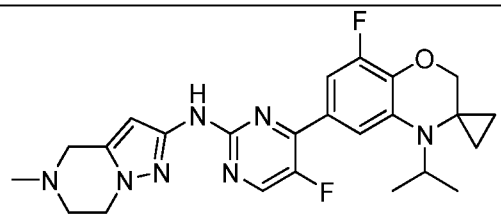
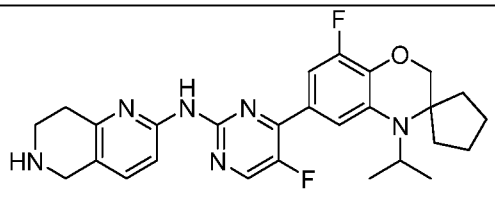
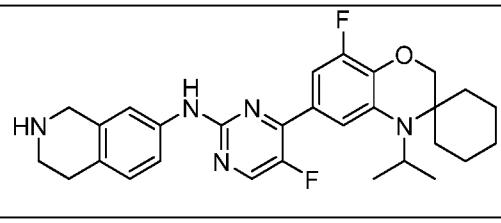
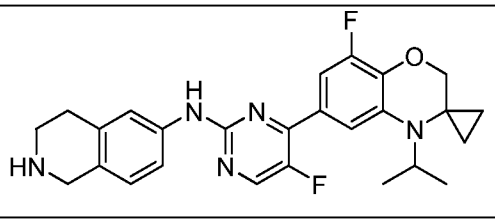
55		56	
57		58	
59		60	
61		62	
63		64	
65		66	
67		68	
69		70	

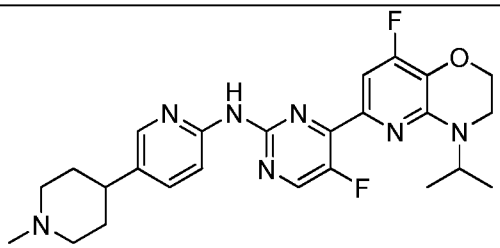
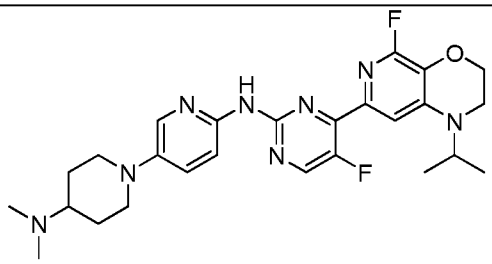
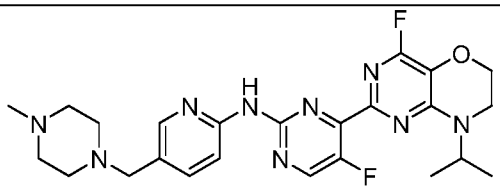
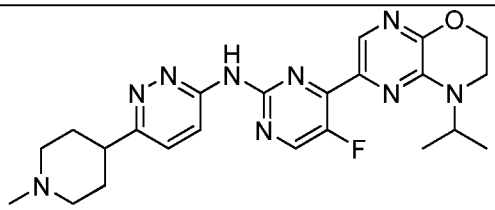
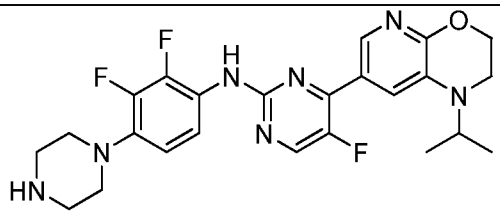
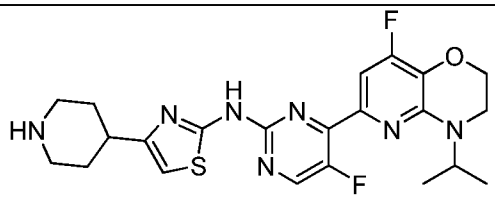
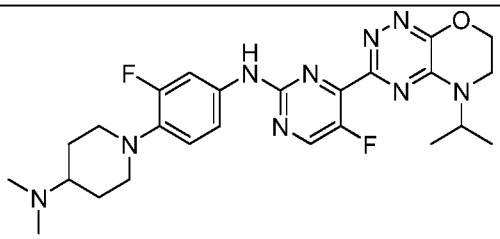
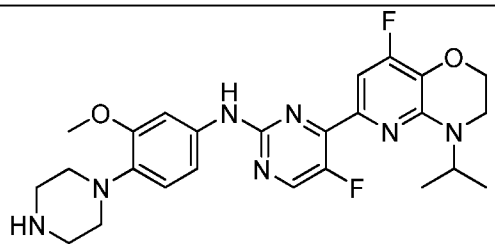
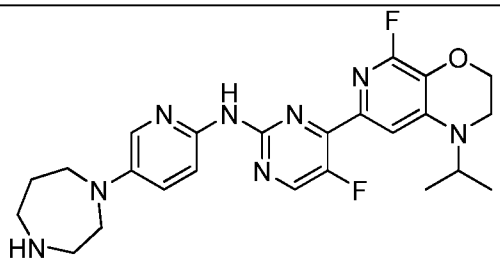
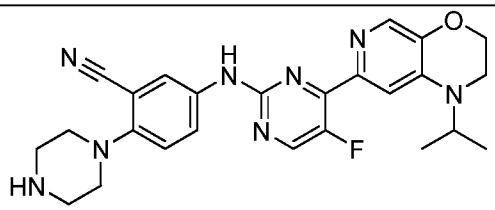
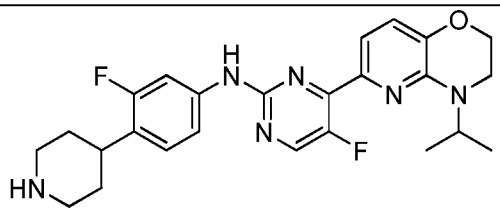
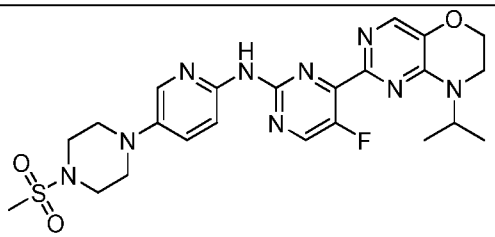
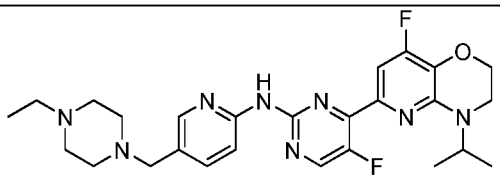
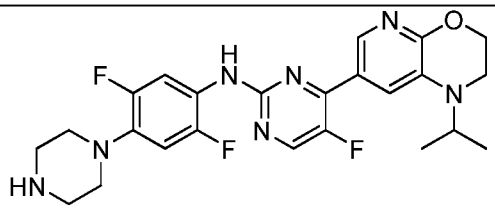
71		72	
73		74	
75		76	
77		78	
79		80	
81		82	
83		84	

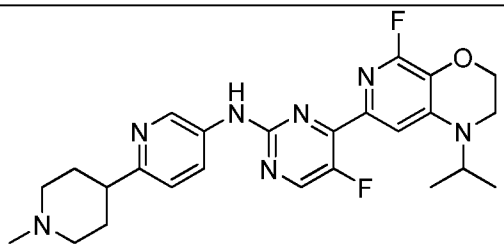
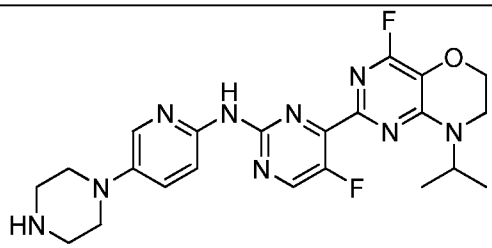
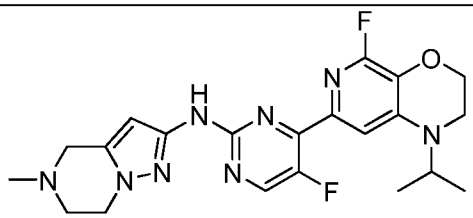
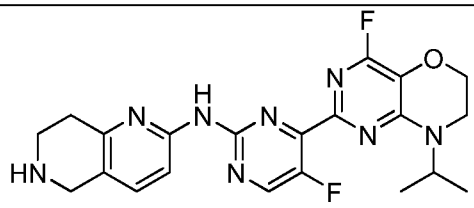
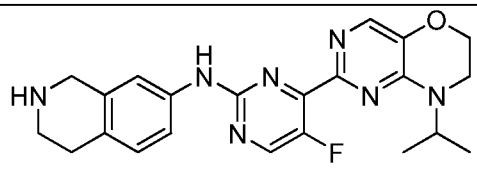
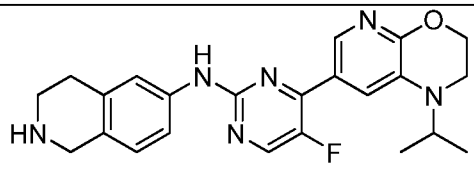
85		86	
87		88	
89		90	
91		92	
93		94	
95		96	
97		98	

99		100	
101		102	
103		104	
105		106	
107		108	
109		110	
111		112	

113		114	
115		116	
117		118	
119		120	
121		122	
123		124	
125		126	

127		128	
129		130	
131		132	
133		134	
135		136	
137		138	
139		140	

141		142	
143		144	
145		146	
147		148	
149		150	
151		152	
153		154	

155		156	
157		158	
159		160	

[0079] In some embodiments, provided herein are compounds described in Table 1, or a tautomer thereof, or a salt of any of the foregoing, and uses thereof.

[0080] The embodiments and variations described herein are suitable for compounds of any formulae detailed herein, where applicable.

[0081] Representative examples of compounds detailed herein, including intermediates and final compounds according to the present disclosure are depicted herein. It is understood that in one aspect, any of the compounds may be used in the methods detailed herein, including, where applicable, intermediate compounds that may be isolated and administered to an individual.

[0082] The compounds depicted herein may be present as salts even if salts are not depicted and it is understood that the present disclosure embraces all salts and solvates of the compounds depicted here, as well as the non-salt and non-solvate form of the compound, as is well understood by the skilled artisan. In some embodiments, the salts of the compounds provided herein are pharmaceutically acceptable salts. Where one or more tertiary amine moiety is present in the compound, the N-oxides are also provided and described.

[0083] Where tautomeric forms may be present for any of the compounds described herein, each and every tautomeric form is intended even though only one or some of the tautomeric forms may be explicitly depicted. The tautomeric forms specifically depicted may

or may not be the predominant forms in solution or when used according to the methods described herein.

[0084] The present disclosure also includes any or all of the stereochemical forms, including any enantiomeric or diastereomeric forms of the compounds described. The structure or name is intended to embrace all possible stereoisomers of a compound depicted. All forms of the compounds are also embraced by the invention, such as crystalline or non-crystalline forms of the compounds. Compositions comprising a compound of the invention are also intended, such as a composition of substantially pure compound, including a specific stereochemical form thereof, or a composition comprising mixtures of compounds of the invention in any ratio, including two or more stereochemical forms, such as in a racemic or non-racemic mixture.

[0085] The invention also intends isotopically-labeled and/or isotopically-enriched forms of compounds described herein. The compounds herein may contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. In some embodiments, the compound is isotopically-labeled, such as an isotopically-labeled compound of the formula (I) or variations thereof described herein, where a fraction of one or more atoms are replaced by an isotope of the same element. Exemplary isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, chlorine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C ^{13}N, ^{15}O, ^{17}O, ^{32}P, ^{35}S, ^{18}F, ^{36}Cl. Certain isotope labeled compounds (e.g. ^{3}H and ^{14}C) are useful in compound or substrate tissue distribution studies. Incorporation of heavier isotopes such as deuterium (^{2}H) can afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased in vivo half-life, or reduced dosage requirements and, hence may be preferred in some instances.

[0086] Isotopically-labeled compounds of the present invention can generally be prepared by standard methods and techniques known to those skilled in the art or by procedures similar to those described in the accompanying Examples substituting appropriate isotopically-labeled reagents in place of the corresponding non-labeled reagent.

[0087] The disclosure also includes any or all metabolites of any of the compounds described. The metabolites may include any chemical species generated by a biotransformation of any of the compounds described, such as intermediates and products of

metabolism of the compound, such as would be generated *in vivo* following administration to a human.

[0088] Articles of manufacture comprising a compound described herein, or a salt or solvate thereof, in a suitable container are provided. The container may be a vial, jar, ampoule, preloaded syringe, i.v. bag, and the like.

[0089] Preferably, the compounds detailed herein are orally bioavailable. However, the compounds may also be formulated for parenteral (*e.g.*, intravenous) administration.

[0090] One or several compounds described herein can be used in the preparation of a medicament by combining the compound or compounds as an active ingredient with a pharmacologically acceptable carrier, which are known in the art. Depending on the therapeutic form of the medication, the carrier may be in various forms. In one variation, the manufacture of a medicament is for use in any of the methods disclosed herein, *e.g.*, for the treatment of cancer.

General synthetic methods

[0091] The compounds of the invention may be prepared by a number of processes as generally described below and more specifically in the Examples hereinafter (such as the schemes provided in the Examples below). In the following process descriptions, the symbols when used in the formulae depicted are to be understood to represent those groups described above in relation to the formulae herein.

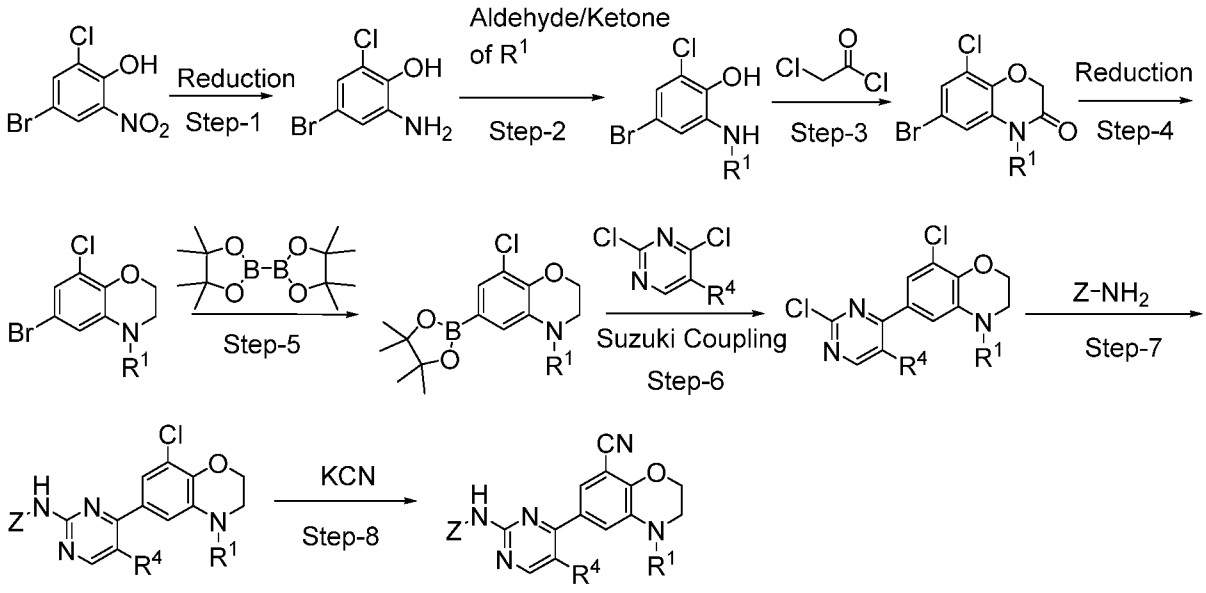
[0092] Where it is desired to obtain a particular enantiomer of a compound, this may be accomplished from a corresponding mixture of enantiomers using any suitable conventional procedure for separating or resolving enantiomers. Thus, for example, diastereomeric derivatives may be produced by reaction of a mixture of enantiomers, *e.g.,* a racemate, and an appropriate chiral compound. The diastereomers may then be separated by any convenient means, for example by crystallization and the desired enantiomer recovered. In another resolution process, a racemate may be separated using chiral High Performance Liquid Chromatography. Alternatively, if desired a particular enantiomer may be obtained by using an appropriate chiral intermediate in one of the processes described.

[0093] Chromatography, recrystallization and other conventional separation procedures may also be used with intermediates or final products where it is desired to obtain a particular isomer of a compound or to otherwise purify a product of a reaction.

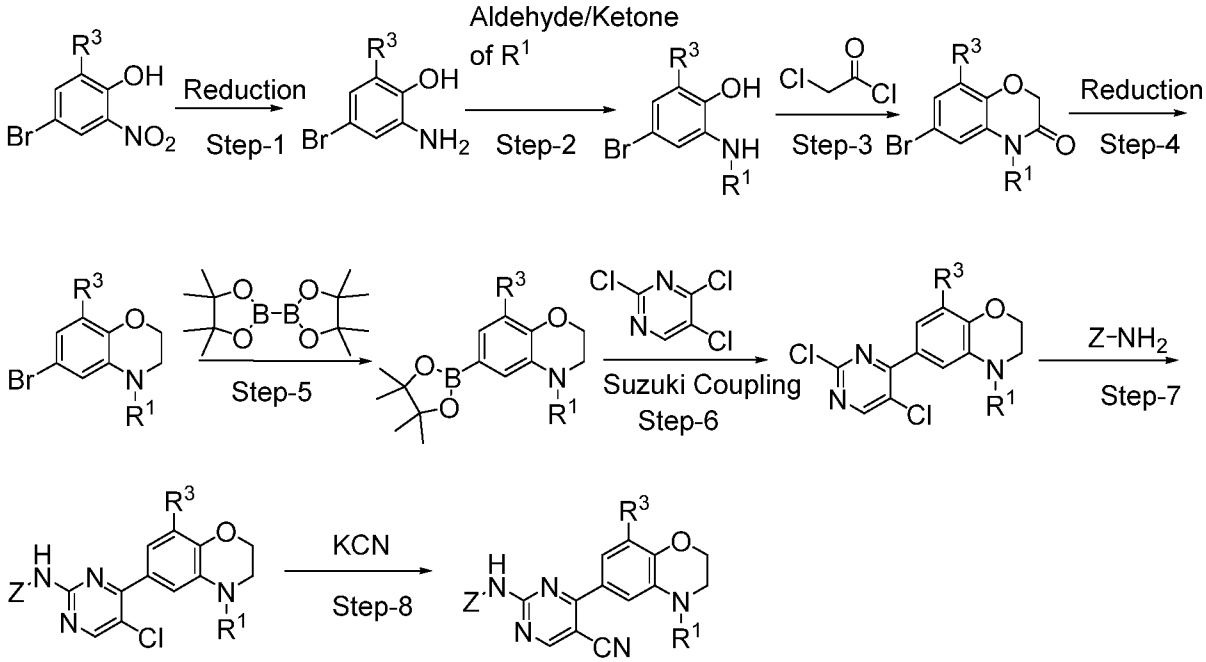
[0094] Solvates and/or polymorphs of a compound provided herein or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, are also contemplated. Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and are often formed during the process of crystallization. Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol.

[0095] In some embodiments, compounds disclosed herein may be synthesized according to the schemes shown below.

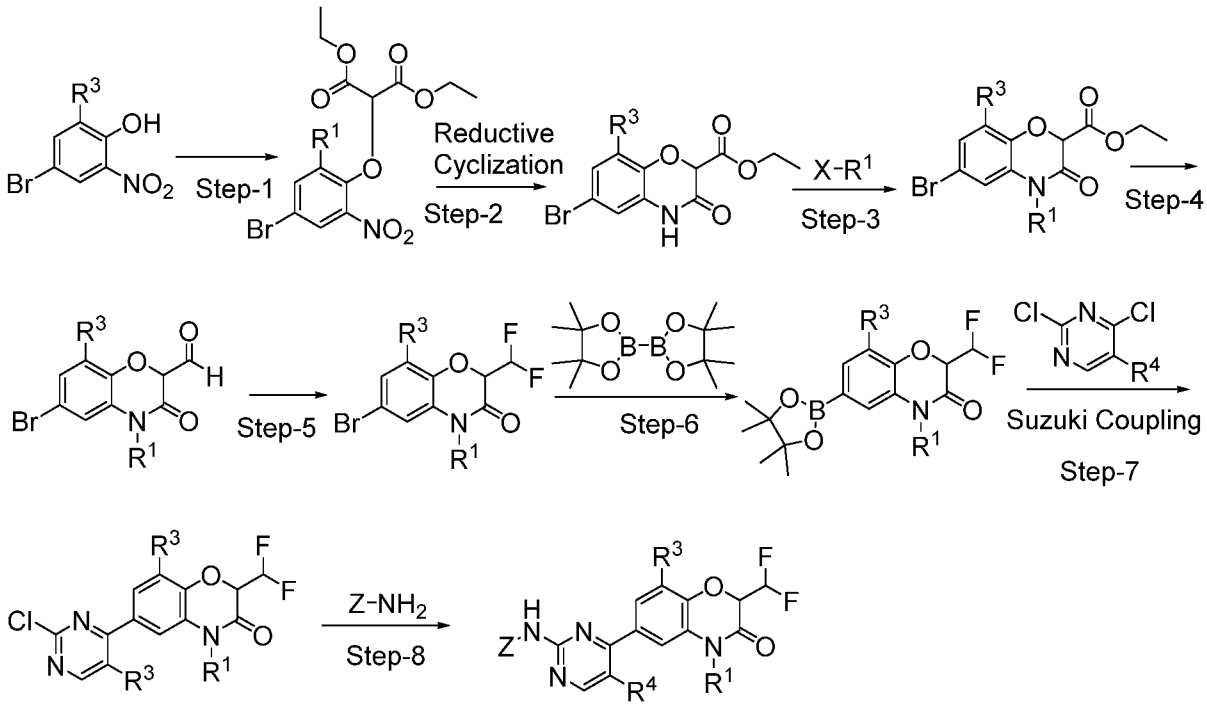
Scheme 1



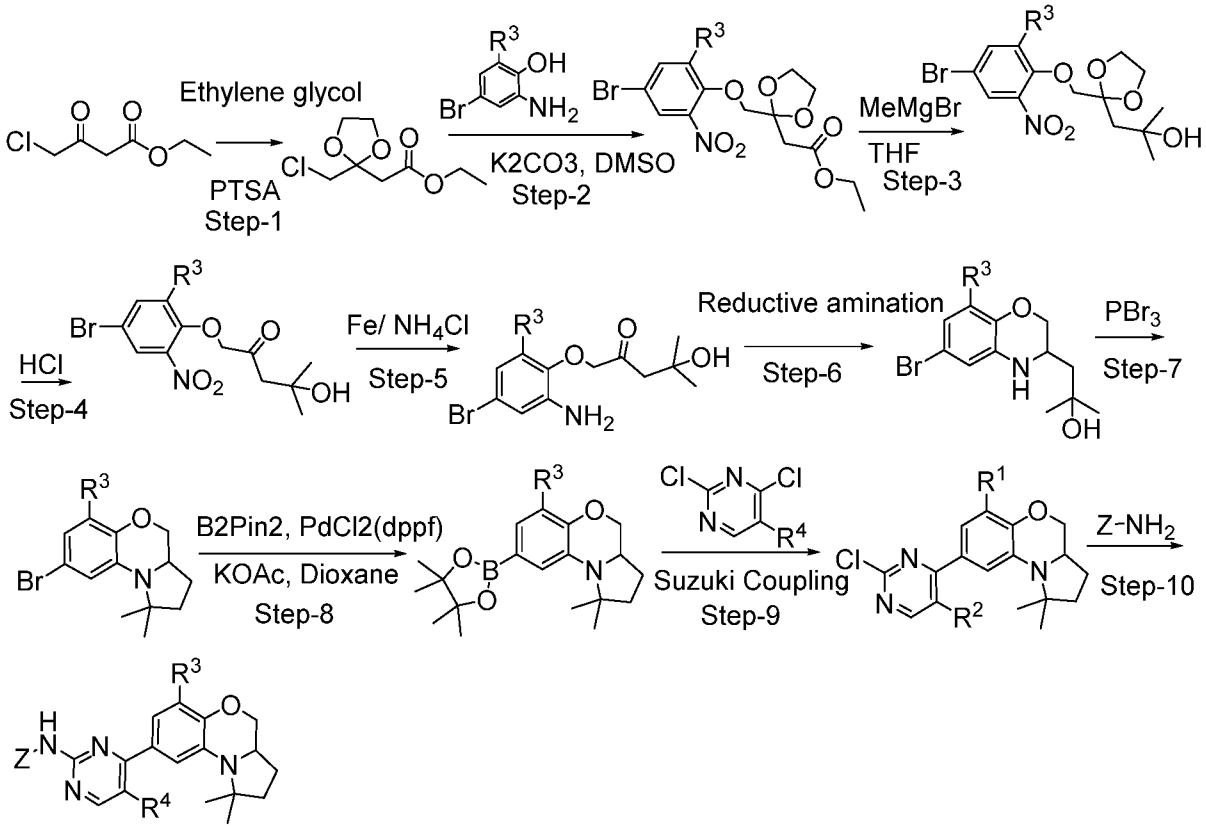
Scheme 2



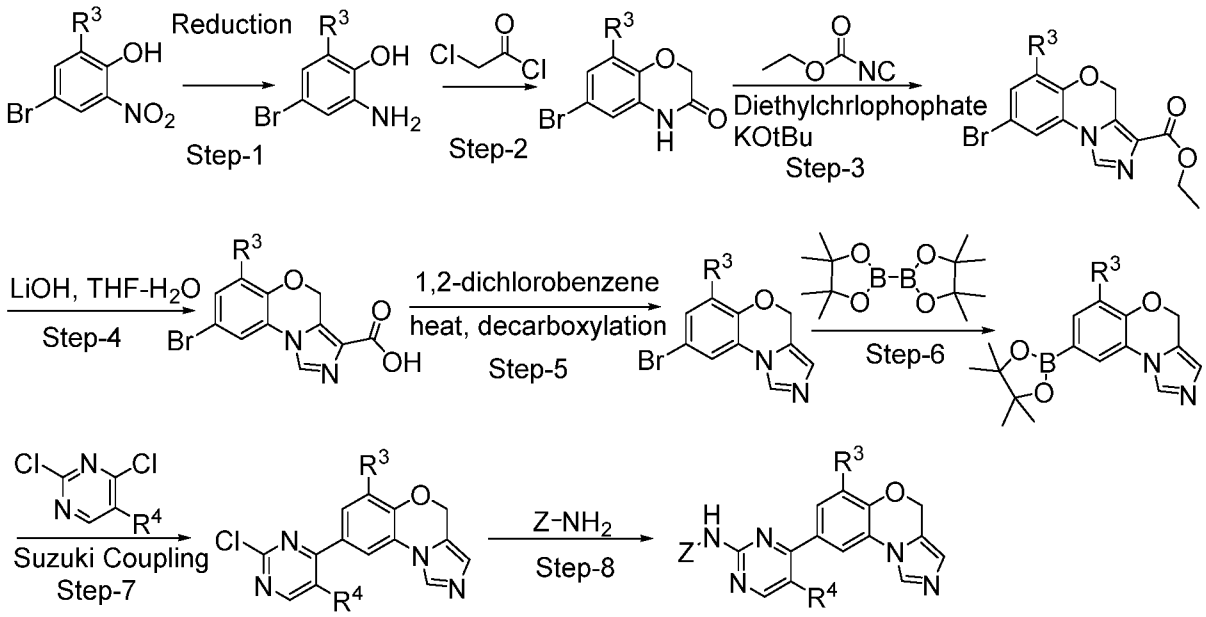
Scheme 3



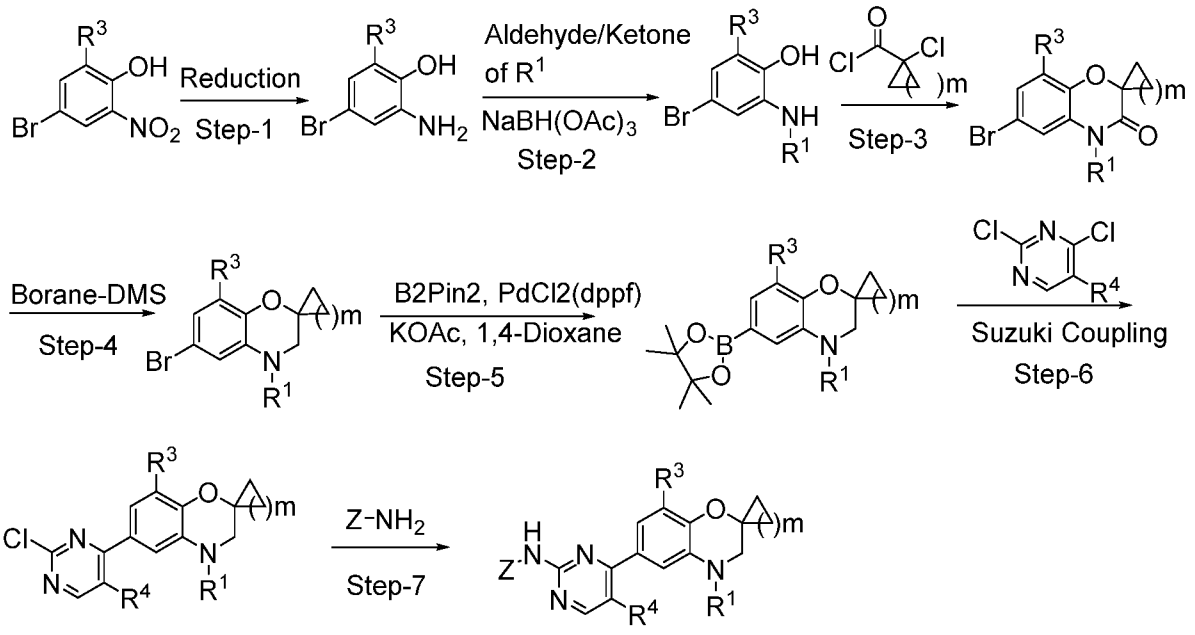
Scheme 4



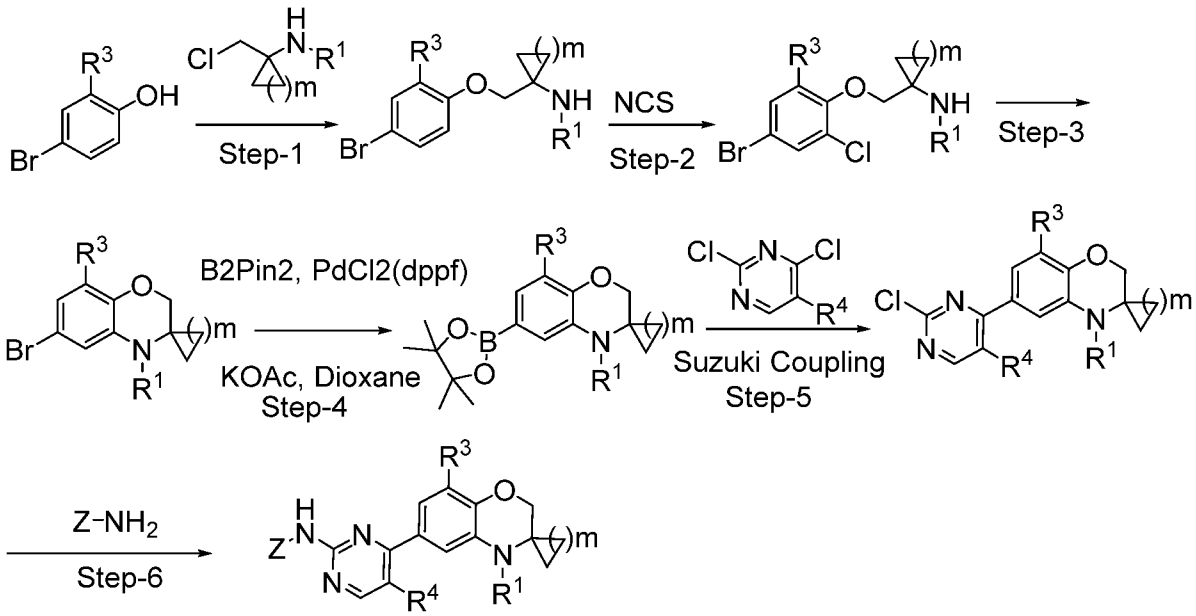
Scheme 5



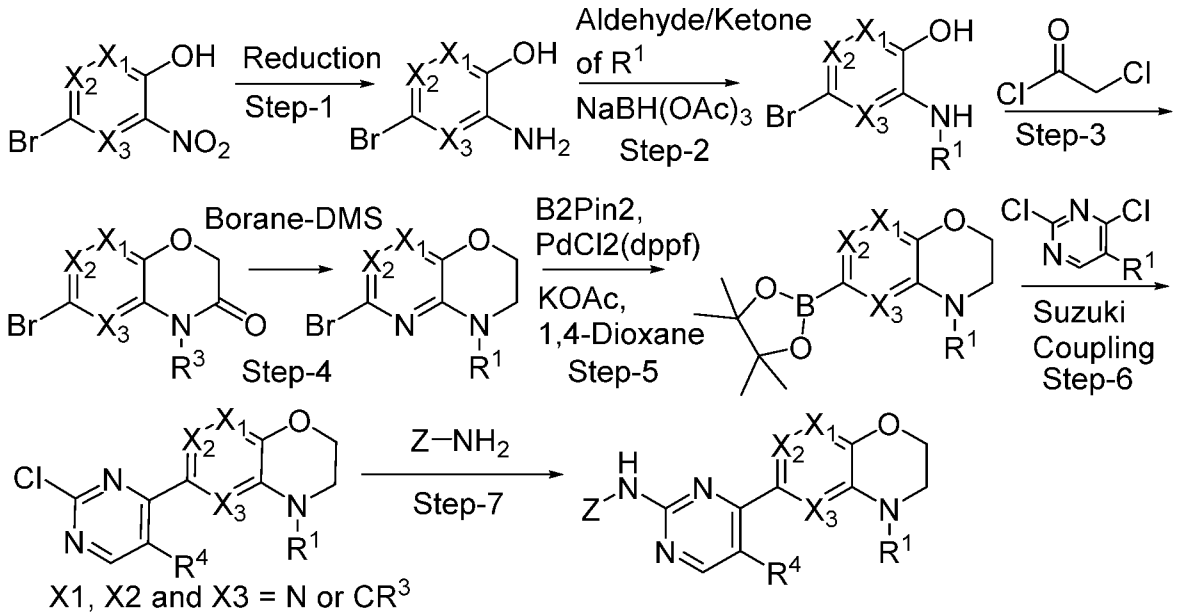
Scheme 6



Scheme 7



Scheme 8



Pharmaceutical Compositions and Formulations

[0096] Pharmaceutical compositions of any of the compounds detailed herein are embraced by this disclosure. Thus, the present disclosure includes pharmaceutical compositions comprising a compound as detailed herein or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and a pharmaceutically acceptable carrier or excipient. In one aspect, the pharmaceutically acceptable salt is an acid addition salt, such as a salt formed with an inorganic or organic acid. Pharmaceutical compositions may take a form suitable for oral, buccal, parenteral, nasal, topical or rectal administration or a form suitable for administration by inhalation.

[0097] A compound as detailed herein may in one aspect be in a purified form and compositions comprising a compound in purified forms are detailed herein. Compositions comprising a compound as detailed herein or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, are provided, such as compositions of substantially pure compounds. In some embodiments, a composition containing a compound as detailed herein or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, is in substantially pure form.

[0098] In one variation, the compounds herein are synthetic compounds prepared for administration to an individual. In another variation, compositions are provided containing a compound in substantially pure form. In another variation, the present disclosure embraces

pharmaceutical compositions comprising a compound detailed herein and a pharmaceutically acceptable carrier. In another variation, methods of administering a compound are provided. The purified forms, pharmaceutical compositions and methods of administering the compounds are suitable for any compound or form thereof detailed herein.

[0099] A compound detailed herein or salt thereof may be formulated for any available delivery route, including an oral, mucosal (*e.g.*, nasal, sublingual, vaginal, buccal or rectal), parenteral (*e.g.*, intramuscular, subcutaneous or intravenous), topical or transdermal delivery form. A compound or salt thereof may be formulated with suitable carriers to provide delivery forms that include, but are not limited to, tablets, caplets, capsules (such as hard gelatin capsules or soft elastic gelatin capsules), cachets, troches, lozenges, gums, dispersions, suppositories, ointments, cataplasms (poultices), pastes, powders, dressings, creams, solutions, patches, aerosols (*e.g.*, nasal spray or inhalers), gels, suspensions (*e.g.*, aqueous or non-aqueous liquid suspensions, oil-in-water emulsions or water-in-oil liquid emulsions), solutions and elixirs.

[0100] One or several compounds described herein or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, can be used in the preparation of a formulation, such as a pharmaceutical formulation, by combining the compound or compounds, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, as an active ingredient with a pharmaceutically acceptable carrier, such as those mentioned above. Depending on the therapeutic form of the system (*e.g.*, transdermal patch vs. oral tablet), the carrier may be in various forms. In addition, pharmaceutical formulations may contain preservatives, solubilizers, stabilizers, re-wetting agents, emulgators, sweeteners, dyes, adjusters, and salts for the adjustment of osmotic pressure, buffers, coating agents or antioxidants. Formulations comprising the compound may also contain other substances which have valuable therapeutic properties. Pharmaceutical formulations may be prepared by known pharmaceutical methods. Suitable formulations can be found, *e.g.*, in *Remington's Pharmaceutical Sciences*, Mack Publishing Company, Philadelphia, PA, 20th ed. (2000), which is incorporated herein by reference.

[0101] Compounds as described herein may be administered to individuals in a form of generally accepted oral compositions, such as tablets, coated tablets, and gel capsules in a hard or in soft shell, emulsions or suspensions. Examples of carriers, which may be used for the preparation of such compositions, are lactose, corn starch or its derivatives, talc, stearate

or its salts, *etc*. Acceptable carriers for gel capsules with soft shell are, for instance, plant oils, wax, fats, semisolid and liquid poly-ols, and so on. In addition, pharmaceutical formulations may contain preservatives, solubilizers, stabilizers, re-wetting agents, emulgators, sweeteners, dyes, adjusters, and salts for the adjustment of osmotic pressure, buffers, coating agents or antioxidants.

[0102] Any of the compounds described herein can be formulated in a tablet in any dosage form described, for example, a compound as described herein or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, can be formulated as a 10 mg tablet.

[0103] Compositions comprising a compound provided herein are also described. In one variation, the composition comprises a compound or salt thereof and a pharmaceutically acceptable carrier or excipient. In another variation, a composition of substantially pure compound is provided.

Methods of Use

[0104] Compounds and compositions detailed herein, such as a pharmaceutical composition containing a compound of any formula provided herein or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and a pharmaceutically acceptable carrier or excipient, may be used in methods of administration and treatment as provided herein. The compounds and compositions may also be used in *in vitro* methods, such as *in vitro* methods of administering a compound or composition to cells for screening purposes and/or for conducting quality control assays. In some embodiments of the methods detailed herein, the methods comprise administration of a compound detailed herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, as a monotherapy.

[0105] Provided herein is a method of treating a disease in an individual comprising administering an effective amount of a compound disclosed herein or a variation thereof, to the individual. Further provided herein is a method of treating a proliferative disease in an individual, comprising administering an effective amount of a compound disclosed herein to the individual. Also provided herein is a method of treating cancer in an individual comprising administering an effective amount of a compound disclosed herein to the individual. In some embodiments, the compound is administered to the individual according to a dosage and/or method of administration described herein.

[0106] In some embodiments, the cancer in the individual has one or more mutations or amplification or overexpression of the genes encoding cyclins or of the genes encoding the CDK or loss of endogenous INK4 inhibitors by gene deletion, mutation, or promoter hypermethylation, or other genetic events leading to overactivity of one or more of CDK1, CDK2, CDK4, CDK6 and CDK9. In some embodiments, the cancer in the individual has one or more mutations or amplification or overexpression of the genes encoding cyclins or of the genes encoding the CDK or loss of endogenous INK4 inhibitors by gene deletion, mutation, or promoter hypermethylation, or other genetic events leading to overactivity of CDK4/6 and one or more of CDK1, CDK2, and CDK9.

[0107] In some embodiments, there is provided a method of treating a cancer in an individual, comprising (a) selecting the individual for treatment based on (i) the presence of phosphorylation of the retinoblastoma (*Rb)* protein in the cancer, or (ii) presence of mutations or amplification or overexpression of CDK4 or CDK6 in the cancer, and administering an effective amount of a compound disclosed herein to the individual. In some embodiments, the cancer is assayed for the expression of phosphorylated Rb. In some embodiments, the cancer is assayed for the expression of CDK4 or CDK6. In some embodiments, the *CDK4* or *CDK6* gene of the cancer is sequenced to detect the one or more mutations or amplifications. In some embodiments, the *CDK4* or *CDK6* gene is sequenced by biopsying the cancer and sequencing the *CDK4* or *CDK6* gene from the biopsied cancer. In some embodiments, the *CDK4* or *CDK6* gene is sequenced by sequencing circulating-tumor DNA (ctDNA) from the individual.

[0108] In some embodiments, a compound disclosed herein is used to treat an individual having a proliferative disease, such as cancer as described herein. In some embodiments, the individual is at risk of developing a proliferative disease, such as cancer. In some of these embodiments, the individual is determined to be at risk of developing cancer based upon one or more risk factors. In some of these embodiments, the risk factor is a family history and/or gene associated with cancer.

[0109] A compound disclosed herein is believed to be effective for treating a variety of diseases and disorders. For example, in some embodiments, a compound disclosed herein may be used to treat a proliferative disease, such as cancer. In some embodiments the cancer is a solid tumor. In some embodiments the cancer is any of adult and pediatric oncology, myxoid and round cell carcinoma, locally advanced tumors, metastatic cancer, human soft

tissue sarcomas, including Ewing's sarcoma, cancer metastases, including lymphatic metastases, squamous cell carcinoma, particularly of the head and neck, esophageal squamous cell carcinoma, oral carcinoma, blood cell malignancies, including multiple myeloma, leukemias, including acute lymphocytic leukemia, acute nonlymphocytic leukemia, chronic lymphocytic leukemia, chronic myelocytic leukemia, and hairy cell leukemia, effusion lymphomas (body cavity based lymphomas), thymic lymphoma, cutaneous T cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, cancer of the adrenal cortex, ACTH-producing tumors, lung cancer, including small cell carcinoma and nonsmall cell cancers, breast cancer, including small cell carcinoma and ductal carcinoma, gastrointestinal cancers, including stomach cancer, colon cancer, colorectal cancer, polyps associated with colorectal neoplasia, pancreatic cancer, liver cancer, urological cancers, including bladder cancer, including primary superficial bladder tumors, invasive transitional cell carcinoma of the bladder, and muscle-invasive bladder cancer, prostate cancer, malignancies of the female genital tract, including ovarian carcinoma, primary peritoneal epithelial neoplasms, cervical carcinoma, uterine endometrial cancers, vaginal cancer, cancer of the vulva, uterine cancer and solid tumors in the ovarian follicle, malignancies of the male genital tract, including testicular cancer and penile cancer, kidney cancer, including renal cell carcinoma, brain cancer, including intrinsic brain tumors, neuroblastoma, astrocytic brain tumors, gliomas, metastatic tumor cell invasion in the central nervous system, bone cancers, including osteomas and osteosarcomas, skin cancers, including melanoma, tumor progression of human skin keratinocytes, squamous cell cancer, thyroid cancer, retinoblastoma, neuroblastoma, peritoneal effusion, malignant pleural effusion, mesothelioma, Wilms's tumors, gall bladder cancer, trophoblastic neoplasms, hemangiopericytoma, and Kaposi's sarcoma.

[0110] In some embodiments, the cancer is defined by a molecular characteristic. In some embodiments, the cancer is an estrogen receptor-posistive breast cancer. In some embodiments, the breast cancer is triple negative breast cancer. In some embodiments, the cancer is a KRAS-mutant non-small cell lung cancer. In some embodiments, the cancer is mantle cell lymphoma defined by a translocation involving CCND1 resulting in cyclin D1 overexpression.

[0111] In some embodiments, the compounds and compositions described herein cause G_1-S cell cycle arrest in a cell (such as a cancer cell). In some embodiments, the cancer cell is a cancer cell from any of the cancer types described herein. In some embodiments, arrested cells enter a state of apoptosis. In some embodiments, arrested cells enter a state of

senescence. In some embodiments, provided herein is a method of causing G_1-S checkpoint arrest in a cell comprising administering an effective amount of a compound disclosed herein to the cell. In some embodiments, the G_1-S cell cycle arrest occurs in about 40% or more, about 50% or more, about 60% or more, about 70% or more, about 80% or more, about 85% or more, about 90% or more, about 95% or more, about 96% or more, about 97% or more, about 98% or more, or about 99% or more of cells in a cell population. In some embodiments, the G_1-S cell cycle arrest occurs in up to about 99%, up to about 98%, up to about 97%, up to about 96%, up to about 95%, up to about 90%, up to about 85%, or up to about 80% of cells in the cell population.

[0112] In some embodiments, provided herein is a method of inducing senescence in a cell comprising administering an effective amount of a compound disclosed herein to the cell. In some embodiments, senescence is induced in about 40% or more, about 50% or more, about 60% or more, about 70% or more, about 80% or more, about 85% or more, about 90% or more, about 95% or more, about 96% or more, about 97% or more, about 98% or more, or about 99% or more of cells in a cell population. In some embodiments, senescence is induced in up to about 99%, up to about 98%, up to about 97%, up to about 96%, up to about 95%, up to about 90%, up to about 85%, or up to about 80% of cells in the cell population.

[0113] In some embodiments, provided herein is a method of inducing apoptosis in a cell comprising administering an effective amount of a compound disclosed herein to the cell. In some embodiments, apoptosis is induced in about 40% or more, about 50% or more, about 60% or more, about 70% or more, about 80% or more, about 85% or more, about 90% or more, about 95% or more, about 96% or more, about 97% or more, about 98% or more, or about 99% or more of cells in a cell population. In some embodiments, apoptosis is induced in up to about 99%, up to about 98%, up to about 97%, up to about 96%, up to about 95%, up to about 90%, up to about 85%, or up to about 80% of cells in the cell population.

[0114] In some embodiments, provided herein is a method of inhibiting CDK4 or CDK6 in a cell comprising administering an effective amount of a compound disclosed herein to the cell. In some embodiments, CDK4 or CDK6 is inhibited by about 10% or more, about 20% or more, about 30% or more, about 40% or more, about 50% or more, about 60% or more, about 70% or more, about 75% or more, about 80% or more, about 90% or more, about 95% or more, about 96% or more, about 97% or more, about 98% or more, or about 99% or more. In some embodiments, CDK4 or CDK6is inhibited up to about 99%, up to about 98%, up to

about 97%, up to about 96%, up to about 95%, up to about 90%, up to about 85%, up to about 80%, up to about 70%, or up to about 60%. In some embodiments, the activity of CDK4 or CDK6 is measured according to a kinase assay.

[0115] In some embodiments, provided herein is a method of inhibiting one or more of CDK1, CDK2, CDK4, CDK6, and CDK9 in a cell comprising administering an effective amount of a compound disclosed herein to the cell. In some embodiments, one or more of CDK1, CDK2, CDK4, CDK6, and CDK9 is inhibited by about 10% or more, about 20% or more, about 30% or more, about 40% or more, about 50% or more, about 60% or more, about 70% or more, about 75% or more, about 80% or more, about 90% or more, about 95% or more, about 96% or more, about 97% or more, about 98% or more, or about 99% or more. In some embodiments, one or more of CDK1, CDK2, CDK4, CDK6, and CDK9 is inhibited up to about 99%, up to about 98%, up to about 97%, up to about 96%, up to about 95%, up to about 90%, up to about 85%, up to about 80%, up to about 70%, or up to about 60%. In some embodiments, the activity of one or more of CDK1, CDK2, CDK4, CDK6, and CDK9 is measured according to a kinase assay.

[0116] In some embodiments, provided herein is a method of inhibiting CDK4 or CDK6 comprising contacting CDK4 or CDK6 with an effective amount of a compound disclosed herein or a variation thereof. In some embodiments, a compound disclosed herein binds to CDK4 or CDK6 with an IC_{50} of less than 1 μM, less than 900 nM, less than 800 nM, less than 700 nM, less than 600 nM, less than 500 nM, less than 400 nM, less than 300 nM, less than 200 nM, less than 100 nM, less than 50 nM, less than 10 nM, less than 5 nM, less than 1 nM, or less than 0.5 nM. In some embodiments, a compound disclosed herein binds to CDK4 or CDK6 with an IC_{50} between 0.1 nM and 1 nM, between 1 nM and 5 nM, between 5 nM and 10 nM, between 10 nM and 50 nM, between 50 nM and 100 nM, beween 100 nM and 200 nM, between 200 nM and 300 nM, between 300 nM and 400 nM, betwee 400 nM and 500 nM, between 500 nM and 600 nM, between 600 nM and 700 nM, between 700 nM and 800 nM, between 800 nM and 900 nM, or between 900 nM and 1 μM. In some embodiments, the IC_{50} is measured according to a kinase assay. In some embodiments, the IC_{50} is measured according to a cell proliferation assay.

[0117] In some embodiments, provided herein is a method of inhibiting one or more of CDK1, CDK2, CDK4, CDK6, and CDK9 comprising contacting one or more of CDK1, CDK2, CDK4, CDK6, and CDK9 with an effective amount of a compound disclosed herein

or a variation thereof. In some embodiments, a compound disclosed herein binds to one or more of CDK1, CDK2, CDK4, CDK6, and CDK9 with an IC_{50} of less than 1 μM, less than 900 nM, less than 800 nM, less than 700 nM, less than 600 nM, less than 500 nM, less than 400 nM, less than 300 nM, less than 200 nM, less than 100 nM, less than 50 nM, less than 10 nM, less than 5 nM, less than 1 nM, or less than 0.5 nM. In some embodiments a compound disclosed herein binds to one or more of CDK1, CDK2, CDK4, CDK6, and CDK9 with an IC_{50} between 0.1 nM and 1 nM, between 1 nM and 5 nM, between 5 nM and 10 nM, between 10 nM and 50 nM, between 50 nM and 100 nM, beween 100 nM and 200 nM, between 200 nM and 300 nM, between 300 nM and 400 nM, betwee 400 nM and 500 nM, between 500 nM and 600 nM, between 600 nM and 700 nM, between 700 nM and 800 nM, between 800 nM and 900 nM, or between 900 nM and 1 μM. In some embodiments, the IC_{50} is measured according to a kinase assay. In some embodiments, the IC_{50} is measured according to a cell proliferation assay.

[0118] In some embodiments, provided herein is a method of modulating CDK4/6 in an individual, comprising administering to the individual a compound disclosed herein or a variation thereof. In some embodiments, provided herein is a method of modulating CDK4 and CDK 6 in an individual, comprising administering to the individual a compound disclosed herein or a variation thereof. In some embodiments, provided herein is a method of modulating CDK4/6 and one or more of CDK1, CDK2, and CDK9 in an individual, comprising administering to the a compound disclosed herein or a variation thereof. In some embodiments, provided herein is a method of modulating CDK4 and CDK 6 and one or more of CDK1, CDK2, and CDK9 in an individual, comprising administering to the individual a compound disclosed herein or a variation thereof. In some embodiments, a compound disclosed herein binds to one or more of CDK4/6 with an IC_{50} of less than 1 μM, less than 900 nM, less than 800 nM, less than 700 nM, less than 600 nM, less than 500 nM, less than 400 nM, less than 300 nM, less than 200 nM, less than 100 nM, less than 50 nM, less than 10 nM, less than 5 nM, less than 1 nM, or less than 0.5 nM. In some embodiments, a compound disclosed herein binds to one or more of CDK4 and CDK6 with an IC_{50} of less than 1 μM, less than 900 nM, less than 800 nM, less than 700 nM, less than 600 nM, less than 500 nM, less than 400 nM, less than 300 nM, less than 200 nM, less than 100 nM, less than 50 nM, less than 10 nM, less than 5 nM, less than 1 nM, or less than 0.5 nM. In some embodiments, a compound disclosed herein binds to one or more of CDK1, CDK2, CDK4, CDK6, and CDK9 with an IC_{50} between 0.1 nM and 1 nM, between 1 nM and 5 nM, between 5 nM and 10 nM,

between 10 nM and 50 nM, between 50 nM and 100 nM, beween 100 nM and 200 nM, between 200 nM and 300 nM, between 300 nM and 400 nM, betwee 400 nM and 500 nM, between 500 nM and 600 nM, between 600 nM and 700 nM, between 700 nM and 800 nM, between 800 nM and 900 nM, or between 900 nM and 1 μM. In some embodiments, the IC_{50} is measured according to a kinase assay. In some embodiments, the IC_{50} is measured according to a cell proliferation assay.

[0119] In one embodiment, a compound disclosed herein may enhance the antitumour immunity by increasing the functional capacity of tumour cells to present antigen or by reducing the immunosuppressive T_{Reg} population by suppressing their proliferation.

[0120] In some embodiments, provided herein is a method of inhibiting the proliferation of a cell, comprising contacting the cell with an effective amount of a compound disclosed herein or a variation thereof. In some embodiments, a compound disclosed herein is effective in inhibiting the proliferation of the cell with an EC_{50} of less than 5 μM, less than 2 μM, less than 1 μM, less than 900 nM, less than 800 nM, less than 700 nM, less than 600 nM, less than 500 nM, less than 400 nM, less than 300 nM, less than 200 nM, less than 100 nM, or less than 50 nM. In some embodiments, a compound disclosed herein is effective in inhibiting the proliferation of the cell with an EC_{50} between 10 nM and 20 nM, between 20 nM and 50 nM, between 50 nM and 100 nM, between 100 nM and 500 nM, between 500 nM and 1 μM, beween 1 μM and 2 μM, or between 2 μM and 5 μM. In some embodiments, the EC_{50} is measured according to a cell proliferation assay.

Combination Therapy

[0121] As provided herein, a compound disclosed herein may affect the immune system. Accordingly, a compound disclosed herein may be used in combination with other anti-cancer agents or immunotherapies. In some embodiments, provided herein is a method of treating a disease in an individual comprising administering an effective amount of a compound disclosed herein and an additional therapeutic agent to the individual. In some embodiments, the additional therapeutic agent is a cancer immunotherapy agent or an endocrine therapy agent or a chemotherapeutic agent. In some embodiments, the disease is a proliferative disease such as cancer.

[0122] In some embodiments, the additional therapeutic agent is a cancer immunotherapy agent. In some embodiments, the additional therapeutic agent is an immunostimulatory agent. In some embodiments, the additional therapeutic agent targets a checkpoint protein

(for example an immune checkpoint inhibitor). In some embodiments, the additional therapeutic agent is effective to stimulate, enhance or improve an immune response against a tumor.

[0123] In another aspect provided herein is a combination therapy for the treatment of a disease, such as cancer. In some embodiments, provided is a method of treating a disease in an individual comprising administering an effective amount of a compound disclosed herein in combination with a radiation therapy.

[0124] In some embodiments, there is provide a method of treating a disease in an individual comprising (a) administering an effective amount of a compound disclosed herein and (b) administering an effective amount of an endocrine therapy agent. In some embodiments, the endocrine therapy is antiestrogen therapy. In some embodiments, the endocrine therapy is a selective estrogen receptor degrader (SERD, such as fulvestrant). In some embodiments, the endocrine therapy is an aromatase inhibitor (such as letrozole). In some embodiments, the combination of a CDK4/6 inhibitor and endocrine therapy causes enhancement of G1-S cell-cycle arrest. In some embodiments, the combination of a CDK4/6 inhibitor and endocrine therapy causes enhanced entry into a senescent state. In some embodiments, a compound disclosed herein is administered prior to, after, or simultaneously co-administered with the endocrine therapy agent. In some embodiments, a compound disclosed herein is administered 1 or more hours (such as 2 or more hours, 4 or more hours, 8 or more hours, 12 or more hours, 24 or more hours, or 48 or more hours) prior to or after the endocrine therapy agent.

[0125] In some embodiments, there is provide a method of treating a disease in an individual comprising (a) administering an effective amount of a compound disclosed herein and (b) administering an effective amount of a second chemotherapeutic agent. In some embodiments, the chemotherapeutic agent is another kinase inhibitor. In some embodiments, a compound disclosed herein is administered prior to, after, or simultaneously co-administered with the second chemotherapeutic agent. In some embodiments, a compound disclosed herein is administered 1 or more hours (such as 2 or more hours, 4 or more hours, 8 or more hours, 12 or more hours, 24 or more hours, or 48 or more hours) prior to or after the second chemotherapeutic agent.

[0126] Examples of chemotherapeutic agents that can be used in combination with a compound disclosed herein include DNA-targeted agents, a DNA alkylating agent (such as

cyclophosphamide, mechlorethamine, chlorambucil, melphalan, dacarbazine, or nitrosoureas), a topoisomerase inhibitor (such as a Topoisomerase I inhibitor (e.g., irinotecan or topotecan) or a Topoisomerase II inhibitor (e.g., etoposide or teniposide)), an anthracycline (such as daunorubicin, doxorubicin, epirubicin, idarubicin, mitoxantrone, or valrubicin), a histone deacetylase inhibitor (such as vorinostat or romidepsin), a bromodomain inhibitor, other epigenetic inhibitors, a taxane (such as paclitaxel or docetaxel), a kinase inhibitor (such as bortezomib, erlotinib, gefitinib, imatinib, vemurafenib, vismodegib, ibrutinib), an anti-angiogenic inhibitor, a nucleotide analog or precursor analog (such as azacitidine, azathioprine, capecitabine, cytarabine, doxifluridine, 5-fluorouracil, gemcitabine, hydroxyurea, mercaptopurine, methotrexate, or tioguanine), or a platinum-based chemotherapeutic agent (such as cisplatin, carboplatin, or oxaliplatin), pemetrexed, or a combination thereof. In some embodiments, provided is a method of treating a disease in an individual comprising (a) administering an effective amount of a compound disclosed herein and (b) administering an effective amount of a kinase inhibitor (such as bortezomib, erlotinib, gefitinib, imatinib, vemurafenib, vismodegib, or ibrutinib). In some embodiments, a compound disclosed herein is administered prior to, after, or simultaneously co-administered with the kinase inhibitor. In some embodiments, a compound disclosed herein is administered 1 or more hours (such as 2 or more hours, 4 or more hours, 8 or more hours, 12 or more hours, 24 or more hours, or 48 or more hours) prior to or after the kinase inhibitor.

[0127] In some embodiments, provided is a method of treating a disease in an individual comprising (a) administering an effective amount of a compound disclosed herein and (b) administering an effective amount of a DNA damaging agent. In some embodiments, a compound disclosed herein is administered prior to, after, or simultaneously co-administered with the DNA damaging agent. In some embodiments, a compound disclosed herein is administered 1 or more hours (such as 2 or more hours, 4 or more hours, 8 or more hours, 12 or more hours, 24 or more hours, or 48 or more hours) prior to or after the DNA damaging agent.

[0128] In some embodiments, provided is a method of treating a disease in an individual comprising (a) administering an effective amount of a compound disclosed herein and (b) administering an effective amount of a DNA alkylating agent (such as cyclophosphamide, mechlorethamine, chlorambucil, melphalan, dacarbazine, or nitrosoureas). In some embodiments, a compound disclosed herein is administered prior to, after, or simultaneously co-administered with the DNA alkylating agent. In some embodiments, a compound

disclosed herein is administered 1 or more hours (such as 2 or more hours, 4 or more hours, 8 or more hours, 12 or more hours, 24 or more hours, or 48 or more hours) prior to or after the DNA alkylating agent.

[0129] In some embodiments, provided is a method of treating a disease in an individual comprising (a) administering an effective amount of a compound disclosed herein and (b) administering an effective amount of a topoisomerase inhibitor (such as a Topoisomerase I inhibitor (e.g., irinotecan or topotecan) or a Topoisomerase II inhibitor (e.g., etoposide or teniposide)). In some embodiments, a compound disclosed herein is administered prior to, after, or simultaneously co-administered with the topoisomerase inhibitor. In some embodiments, a compound disclosed herein is administered 1 or more hours (such as 2 or more hours, 4 or more hours, 8 or more hours, 12 or more hours, 24 or more hours, or 48 or more hours) prior to or after the topoisomerase inhibitor.

[0130] In some embodiments, provided is a method of treating a disease in an individual comprising (a) administering an effective amount of a compound disclosed herein and (b) administering an effective amount of an anthracycline (such as daunorubicin, doxorubicin, epirubicin, idarubicin, mitoxantrone, or valrubicin). In some embodiments, a compound disclosed herein is administered prior to, after, or simultaneously co-administered with the anthracycline. In some embodiments, a compound disclosed herein is administered 1 or more hours (such as 2 or more hours, 4 or more hours, 8 or more hours, 12 or more hours, 24 or more hours, or 48 or more hours) prior to or after the anthracycline.

[0131] In some embodiments, provided is a method of treating a disease in an individual comprising (a) administering an effective amount of a compound disclosed herein and (b) administering an effective amount of a histone deacetylase inhibitor (such as vorinostat or romidepsin). In some embodiments, a compound disclosed herein is administered prior to, after, or simultaneously co-administered with the histone deacetylase inhibitor. In some embodiments, a compound disclosed herein is administered 1 or more hours (such as 2 or more hours, 4 or more hours, 8 or more hours, 12 or more hours, 24 or more hours, or 48 or more hours) prior to or after the histone deacetylase inhibitor.

[0132] In some embodiments, provided is a method of treating a disease in an individual comprising (a) administering an effective amount of a compound disclosed herein and (b) administering an effective amount of a taxane (such as paclitaxel or docetaxel). In some embodiments, a compound disclosed herein is administered prior to, after, or simultaneously

co-administered with the taxane. In some embodiments, a compound disclosed herein is administered 1 or more hours (such as 2 or more hours, 4 or more hours, 8 or more hours, 12 or more hours, 24 or more hours, or 48 or more hours) prior to or after the taxane.

[0133] In some embodiments, provided is a method of treating a disease in an individual comprising (a) administering an effective amount of a compound disclosed herein and (b) administering an effective amount of a nucleotide analog or precursor analog (such as azacitidine, azathioprine, capecitabine, cytarabine, doxifluridine, 5-fluorouracil, gemcitabine, hydroxyurea, mercaptopurine, methotrexate, or tioguanine). In some embodiments, a compound disclosed herein is administered prior to, after, or simultaneously co-administered with the nucleotide analog or precursor analog. In some embodiments, a compound disclosed herein is administered 1 or more hours (such as 2 or more hours, 4 or more hours, 8 or more hours, 12 or more hours, 24 or more hours, or 48 or more hours) prior to or after the nucleotide analog or precursor analog.

[0134] In some embodiments, provided is a method of treating a disease in an individual comprising (a) administering an effective amount of a compound disclosed herein and (b) administering an effective amount of a platinum-based chemotherapeutic agent (such as cisplatin, carboplatin, or oxaliplatin). In some embodiments, a compound disclosed herein is administered prior to, after, or simultaneously co-administered with the platinum-based chemotherapeutic agent. In some embodiments, a compound disclosed herein is administered 1 or more hours (such as 2 or more hours, 4 or more hours, 8 or more hours, 12 or more hours, 24 or more hours, or 48 or more hours) prior to or after the platinum-based chemotherapeutic agent.

[0135] In some embodiments, provided is a method of treating a disease in an individual comprising (a) administering an effective amount of a compound disclosed herein and (b) administering an effective amount of pemetrexed. In some embodiments, Formula (J a compound disclosed herein is administered prior to, after, or simultaneously co-administered with the pemetrexed. In some embodiments, a compound disclosed herein is administered 1 or more hours (such as 2 or more hours, 4 or more hours, 8 or more hours, 12 or more hours, 24 or more hours, or 48 or more hours) prior to or after the pemetrexed.

[0136] In some embodiments, provided is a method of treating a disease in an individual comprising (a) administering an effective amount a compound disclosed herein and (b) administering an effective amount of a Bruton's tyrosine kinase (BTK) inhibitor. In some

embodiments, a compound disclosed herein is administered prior to, after, or simultaneously co-administered with the BTK inhibitor. In some embodiments, a compound disclosed herein is administered 1 or more hours (such as 2 or more hours, 4 or more hours, 8 or more hours, 12 or more hours, 24 or more hours, or 48 or more hours) prior to or after the BTK inhibitor.

[0137] In some embodiments, provided is a method of treating a disease in an individual comprising (a) administering an effective amount of a compound disclosed herein and (b) administering an effective amount of a PI3K or Akt inhibitor. In some embodiments, a compound disclosed herein is administered prior to, after, or simultaneously co-administered with the PI3K or Akt inhibitor. In some embodiments, a compound disclosed herein is administered 1 or more hours (such as 2 or more hours, 4 or more hours, 8 or more hours, 12 or more hours, 24 or more hours, or 48 or more hours) prior to or after the PI3K or Akt inhibitor.

[0138] In some embodiments, provided is a method of treating a disease in an individual comprising (a) administering an effective amount of a compound disclosed herein and (b) administering an effective amount of a DNA damage repair (DDR) pathway inhibitor. In some embodiments, a compound disclosed herein is administered prior to, after, or simultaneously co-administered with the DDR pathway inhibitor. In some embodiments, a compound disclosed herein is administered 1 or more hours (such as 2 or more hours, 4 or more hours, 8 or more hours, 12 or more hours, 24 or more hours, or 48 or more hours) prior to or after the DDR pathway inhibitor. Examples of inhibitors of the DDR pathway include poly(ADP-ribose) polymerase (PARP) inhibitors (such as olaparib, rucaparib, niraparib, or talazoparib), ataxia telangiectasia mutated (ATM) protein inhibitors, ataxia telangiectasia and Rad3-related (ATR) protein inhibitors, checkpoint kinase 1 (Chk1) inhibitors, or combinations thereof.

[0139] In some embodiments, provided is a method of treating a disease in an individual comprising (a) administering an effective amount of a compound disclosed herein and (b) administering an effective amount of a PARP inhibitor (such as olaparib, rucaparib, niraparib, or talazoparib). In some embodiments, a compound disclosed herein is administered prior to, after, or simultaneously co-administered with the PARP inhibitor. In some embodiments, a compound disclosed herein is administered 1 or more hours (such as 2 or more hours, 4 or more hours, 8 or more hours, 12 or more hours, 24 or more hours, or 48 or more hours) prior to or after the PARP inhibitor.

[0140] In some embodiments, provided is a method of treating a disease in an individual comprising (a) administering an effective amount of a compound disclosed herein and (b) administering an effective amount of an ATM protein inhibitor. In some embodiments, a compound disclosed herein is administered prior to, after, or simultaneously co-administered with the ATM protein inhibitor. In some embodiments, a compound disclosed herein is administered 1 or more hours (such as 2 or more hours, 4 or more hours, 8 or more hours, 12 or more hours, 24 or more hours, or 48 or more hours) prior to or after the ATM protein inhibitor.

[0141] In some embodiments, provided is a method of treating a disease in an individual comprising (a) administering an effective amount of a compound disclosed herein and (b) administering an effective amount of an ATR protein inhibitor. In some embodiments, a compound disclosed herein is administered prior to, after, or simultaneously co-administered with the ATR protein inhibitor. In some embodiments, a compound disclosed herein is administered 1 or more hours (such as 2 or more hours, 4 or more hours, 8 or more hours, 12 or more hours, 24 or more hours, or 48 or more hours) prior to or after the ATR protein inhibitor.

[0142] In some embodiments, provided is a method of treating a disease in an individual comprising (a) administering an effective amount of a compound disclosed herein and (b) administering an effective amount of an Chk1 inhibitor. In some embodiments, a compound disclosed herein is administered prior to, after, or simultaneously co-administered with the Chk1 inhibitor. In some embodiments, a compound disclosed herein is administered 1 or more hours (such as 2 or more hours, 4 or more hours, 8 or more hours, 12 or more hours, 24 or more hours, or 48 or more hours) prior to or after the Chk1 inhibitor.

[0143] In some embodiments, provided is a method of treating a disease in an individual comprising (a) administering an effective amount of a compound disclosed herein and (b) administering an effective amount of a further CDK4/6 inhibitor. In some embodiments, a compound disclosed herein is administered prior to, after, or simultaneously co-administered with the further CDK4/6 inhibitor. In some embodiments, a compound disclosed herein is administered 1 or more hours (such as 2 or more hours, 4 or more hours, 8 or more hours, 12 or more hours, 24 or more hours, or 48 or more hours) prior to or after the further CDK4/6 inhibitor.

[0144] In another aspect, provided herein is a combination therapy in which a compound disclosed herein is coadministered (which may be separately or simultaneously) with one or more additional agents that are effective in stimulating immune responses to thereby further enhance, stimulate or upregulate immune responses in a subject. For example, provided is a method for stimulating an immune response in a subject comprising administering to the subject a compound disclosed herein and one or more immunostimulatory antibodies, such as an anti-PD-1 antibody, an anti-PD-L1 antibody and/or an anti-CTLA-4 antibody, such that an immune response is stimulated in the subject, for example to inhibit tumor growth. In one embodiment, the subject is administered a compound disclosed herein and an anti-PD-1 antibody. In another embodiment, the subject is administered a compound disclosed herein and an anti-PD-L1 antibody. In yet another embodiment, the subject is administered a compound disclosed herein and an anti-CTLA-4 antibody. In another embodiment, the immunostimulatory antibody (e.g., anti-PD-1, anti-PD-L1 and/or anti-CTLA-4 antibody) is a human antibody. Alternatively, the immunostimulatory antibody can be, for example, a chimeric or humanized antibody (e.g., prepared from a mouse anti-PD-1, anti-PD-L1 and/or anti-CTLA-4 antibody).

[0145] In one embodiment, the present disclosure provides a method for treating a proliferative disease (e.g., cancer), comprising administering a compound disclosed herein and an anti-PD-1 antibody to a subject. In further embodiments, a compound disclosed herein is administered at a subtherapeutic dose, the anti-PD-1 antibody is administered at a subtherapeutic dose, or both are administered at a subtherapeutic dose. In another embodiment, the present disclosure provides a method for altering an adverse event associated with treatment of a hyperproliferative disease with an immunostimulatory agent, comprising a compound disclosed herein and a subtherapeutic dose of anti-PD-1 antibody to a subject. In certain embodiments, the subject is human. In certain embodiments, the anti-PD-1 antibody is a human sequence monoclonal antibody.

[0146] In one embodiment, the present invention provides a method for treating a hyperproliferative disease (e.g., cancer), comprising administering a compound disclosed herein and an anti-PD-L1 antibody to a subject. In further embodiments, a compound disclosed herein is administered at a subtherapeutic dose, the anti-PD-L1 antibody is administered at a subtherapeutic dose, or both are administered at a subtherapeutic dose. In another embodiment, the present invention provides a method for altering an adverse event associated with treatment of a hyperproliferative disease with an immunostimulatory agent,

comprising administering a compound disclosed herein and a subtherapeutic dose of anti-PD-L1 antibody to a subject. In certain embodiments, the subject is human. In certain embodiments, the anti-PD-L1 antibody is a human sequence monoclonal antibody.

[0147] In certain embodiments, the combination of therapeutic agents discussed herein can be administered concurrently as a single composition in a pharmaceutically acceptable carrier, or concurrently as separate compositions each in a pharmaceutically acceptable carrier. In another embodiment, the combination of therapeutic agents can be administered sequentially. For example, an anti-CTLA-4 antibody and a compound disclosed herein can be administered sequentially, such as anti-CTLA-4 antibody being administered first and a compound disclosed herein second, or a compound disclosed herein being administered first and anti-CTLA-4 antibody second. Additionally or alternatively, an anti-PD-1 antibody and a compound disclosed herein can be administered sequentially, such as anti-PD-1 antibody being administered first and a compound disclosed herein second, or a compound disclosed herein being administered first and anti-PD-1 antibody second. Additionally or alternatively, an anti-PD-L1 antibody and a compound disclosed herein can be administered sequentially, such as anti-PD-L1 antibody being administered first and a compound disclosed herein second, a compound disclosed herein being administered first and anti-PD-L1 antibody second.

[0148] Furthermore, if more than one dose of the combination therapy is administered sequentially, the order of the sequential administration can be reversed or kept in the same order at each time point of administration, sequential administrations can be combined with concurrent administrations, or any combination thereof.

[0149] Optionally, the combination of a compound disclosed herein can be further combined with an immunogenic agent, such as cancerous cells, purified tumor antigens (including recombinant proteins, peptides, and carbohydrate molecules), cells, and cells transfected with genes encoding immune stimulating cytokines.

[0150] A compound disclosed herein can also be further combined with standard cancer treatments. For example, a compound disclosed herein can be effectively combined with chemotherapeutic regimens. In these instances, it is possible to reduce the dose of other chemotherapeutic reagent administered with the combination of the instant disclosure. Other combination therapies with a compound disclosed herein include radiation, surgery, or hormone deprivation. Angiogenesis inhibitors can also be combined with a compound

disclosed herein. Inhibition of angiogenesis leads to tumor cell death, which can be a source of tumor antigen fed into host antigen presentation pathways.

[0151] In another example, a compound disclosed herein can be used in conjunction with anti-neoplastic antibodies. By way of example and not wishing to be bound by theory, treatment with an anti-cancer antibody or an anti-cancer antibody conjugated to a toxin can lead to cancer cell death (e.g., tumor cells) which would potentiate an immune response mediated by CTLA-4, PD-1, PD-L1 or a compound disclosed herein. In an exemplary embodiment, a treatment of a hyperproliferative disease (e.g., a cancer tumor) can include an anti-cancer antibody in combination with a compound disclosed herein and anti-CTLA-4 and/or anti-PD-1 and/or anti-PD-L1 antibodies, concurrently or sequentially or any combination thereof, which can potentiate anti-tumor immune responses by the host. Other antibodies that can be used to activate host immune responsiveness can be further used in combination with a compound disclosed herein.

[0152] In some embodiments, a compound disclosed herein can be combined with an anti-CD73 therapy, such as an anti-CD73 antibody.

Dosing and Method of Administration

[0153] The dose of a compound administered to an individual (such as a human) may vary with the particular compound or salt thereof, the method of administration, and the particular disease, such as type and stage of cancer, being treated. In some embodiments, the amount of the compound or salt thereof is a therapeutically effective amount.

[0154] The effective amount of the compound may in one aspect be a dose of between about 0.01 and about 100 mg/kg. Effective amounts or doses of the compounds of the invention may be ascertained by routine methods, such as modeling, dose escalation, or clinical trials, taking into account routine factors, e.g., the mode or route of administration or drug delivery, the pharmacokinetics of the agent, the severity and course of the disease to be treated, the subject's health status, condition, and weight. An exemplary dose is in the range of about from about 0.7 mg to 7 g daily, or about 7 mg to 350 mg daily, or about 350 mg to 1.75 g daily, or about 1.75 to 7 g daily.

[0155] Any of the methods provided herein may in one aspect comprise administering to an individual a pharmaceutical composition that contains an effective amount of a compound

provided herein or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and a pharmaceutically acceptable excipient.

[0156] A compound or composition of the invention may be administered to an individual in accordance with an effective dosing regimen for a desired period of time or duration, such as at least about one month, at least about 2 months, at least about 3 months, at least about 6 months, or at least about 12 months or longer, which in some variations may be for the duration of the individual's life. In one variation, the compound is administered on a daily or intermittent schedule. The compound can be administered to an individual continuously (for example, at least once daily) over a period of time. The dosing frequency can also be less than once daily, *e.g.*, about a once weekly dosing. The dosing frequency can be more than once daily, *e.g.*, twice or three times daily. The dosing frequency can also be intermittent, including a 'drug holiday' (*e.g.*, once daily dosing for 7 days followed by no doses for 7 days, repeated for any 14 day time period, such as about 2 months, about 4 months, about 6 months or more). Any of the dosing frequencies can employ any of the compounds described herein together with any of the dosages described herein.

[0157] The compounds provided herein or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, may be administered to an individual via various routes, including, e.g., intravenous, intramuscular, subcutaneous, oral and transdermal. A compound provided herein can be administered frequently at low doses, known as 'metronomic therapy,' or as part of a maintenance therapy using compound alone or in combination with one or more additional drugs. Metronomic therapy or maintenance therapy can comprise administration of a compound provided herein in cycles. Metronomic therapy or maintenance therapy can comprise intra-tumoral administration of a compound provided herein.

[0158] In one aspect, the invention provides a method of treating cancer in an individual by parenterally administering to the individual (e.g., a human) an effective amount of a compound or salt thereof. In some embodiments, the route of administration is intravenous, intra-arterial, intramuscular, or subcutaneous. In some embodiments, the route of administration is oral. In still other embodiments, the route of administration is transdermal.

[0159] The invention also provides compositions (including pharmaceutical compositions) as described herein for the use in treating, preventing, and/or delaying the onset and/or development of cancer and other methods described herein. In certain

embodiments, the composition comprises a pharmaceutical formulation which is present in a unit dosage form.

[0160] Also provided are articles of manufacture comprising a compound of the disclosure or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, composition, and unit dosages described herein in suitable packaging for use in the methods described herein. Suitable packaging is known in the art and includes, for example, vials, vessels, ampules, bottles, jars, flexible packaging and the like. An article of manufacture may further be sterilized and/or sealed.

Kits

[0161] The present disclosure further provides kits for carrying out the methods of the invention, which comprises one or more compounds described herein or a composition comprising a compound described herein. The kits may employ any of the compounds disclosed herein. In one variation, the kit employs a compound described herein or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing. The kits may be used for any one or more of the uses described herein, and, accordingly, may contain instructions for the treatment of cancer.

[0162] Kits generally comprise suitable packaging. The kits may comprise one or more containers comprising any compound described herein. Each component (if there is more than one component) can be packaged in separate containers or some components can be combined in one container where cross-reactivity and shelf life permit.

[0163] The kits may be in unit dosage forms, bulk packages (*e.g.*, multi-dose packages) or sub-unit doses. For example, kits may be provided that contain sufficient dosages of a compound as disclosed herein and/or a second pharmaceutically active compound useful for a disease detailed herein to provide effective treatment of an individual for an extended period, such as any of a week, 2 weeks, 3 weeks, 4 weeks, 6 weeks, 8 weeks, 3 months, 4 months, 5 months, 7 months, 8 months, 9 months, or more. Kits may also include multiple unit doses of the compounds and instructions for use and be packaged in quantities sufficient for storage and use in pharmacies (*e.g.*, hospital pharmacies and compounding pharmacies).

[0164] The kits may optionally include a set of instructions, generally written instructions, although electronic storage media (*e.g.*, magnetic diskette or optical disk) containing instructions are also acceptable, relating to the use of component(s) of the methods

of the present invention. The instructions included with the kit generally include information as to the components and their administration to an individual.

[0165] The invention can be further understood by reference to the following examples, which are provided by way of illustration and are not meant to be limiting.

Biological Examples

Example B1. In Vitro Kinase Inhibition IC_{50} Determination

[0166] IC_{50} values of compounds against CDK4 and CDK6 are determined by luminescence using retinoblastoma as substrate. Kinase assays are performed in kinase buffer (#PV6135, Invitrogen, Life Technologies Grand Island, NY) where total reaction volume is 30 µL/well in 96-well half area white plates (#3693, Costar). One microliter of 25×test compounds at specific concentrations (e.g., final concentration range: 0.1 nM – 200 nM) is mixed with 10 µL of 2.5×kinase (5 nM, CDK4 #PR8064A and CDK6 #PR8422B, Invitrogen) solution and 14 µL of 4× mixed solution with retinoblastoma (1 µM, #12-439, EMD Millipore, Hayward, CA) and ATP (25 µM, #V7038, Promega, Madison, WI). The plates are covered and incubated for 2H at room temperature. At the end of incubation, 25 µL of stop solution - ADP Glo reagent (#V7002, Promega) is added. After incubation for 45 min at room temperature, 50 µL of detection reagent (##V7002, Promega) is added. Readings are taken at 15 min and 45 min incubation after detection reagent is added in a Synergy Neo Plate reader (BioTek, Winooski, VT) at single excitation of 340 nm and Dual emission at 495 nm and 520 nm respectively. The following equations are used in the CDK4 and CDK6 assay data analysis. Percent inhibition (100 –% activity) is fitted to the "four-parameter logistic model" in XLfit for determination of IC_{50} values.

Equation 1: Percent conversion of enzyme = 100- {(RLU $_{\text{No Drug-No enzyme}}$*100)/ RLU $_{\text{No drug+Enzyme}}$}

Equation 2: Percent conversion at each data point = 100- {(RLU $_{\text{Average(Drug+enzyme)}}$*100)/ RLU $_{\text{No drug+Enzyme}}$}

Equation 3: Percent Inhibition=100*(%Conversion $_{\text{each data point}}$/% Conversion $_{\text{Enzyme}}$)

[0167] IC_{50} values of compounds against CDK1 (cyclin B) are determined by Z'-LYTE™. These screening assays are performed at Invitrogen Life Technologies (Grand Island, NY) on a low volume NBS, black 384-well plate (#4514, Corning). 0.1 µL of 100 ×

test compound in 100% DMSO (at specific solutions) is mixed with 2.4 µL of Kinase Buffer (50 mM HEPES pH 7.5, 0.01% BRIJ-35, 10 mM $MgCl_2$, 1 mM EGTA), 5 µL of 2× Kinase (3.5 - 46.4 ng CDK1/cyclin B)/Peptide (2 µM Ser/Thr 18), and 2.5 µL of 4×ATP solution (34 µM). The plates are shaken for 30 seconds, and incubated for 60 minutes at room temperature. Development Reagent Solution (5 µL of 1:1024 dilution) is added to the plates followed with another 30-second plate shake, and the plates are further incubated at room temperature for one hour. The plates are read on fluorescence plate reader with Dual emission at 445 nm and 520 nm.

[0168] IC_{50} values of compounds against CDK2 (cyclin A) are determined by Z′-LYTE™. These screening assays are performed at Invitrogen Life Technologies (Grand Island, NY) on a low volume NBS, black 384-well plate (#4514, Corning). 0.1 µL of 100 × test compound in 100% DMSO (at specific solutions) is mixed with 2.4 µL of Kinase Buffer (50 mM HEPES pH 7.5, 0.01% BRIJ-35, 10 mM $MgCl_2$, 1 mM EGTA), 5 µL of 2× Kinase (1.22 - 10.3 ng CDK2/cyclin A)/Peptide (2 µM Ser/Thr 12), and 2.5 µL of 4×ATP solution (31 µM). The plates are shaken for 30 seconds, and incubated for 60 minutes at room temperature. Development Reagent Solution (5 µL of 1:1024 dilution) is added to the plates followed with another 30-second plate shake and the plates are further incubated at room temperature for one hour. The plates are read on fluorescence plate reader with Dual emission at 445 nm and 520 nm.

[0169] IC_{50} values of compounds against CDK5 (p25) are determined by Z′-LYTE™. These screening assays are performed at Invitrogen Life Technologies (Grand Island, NY) on a low volume NBS, black 384-well plate (#4514, Corning). 0.1 µL of 100 × test compound in 100% DMSO (at specific solutions) is mixed with 2.4 µL of Kinase Buffer (50 mM HEPES pH 7.5, 0.01% BRIJ-35, 10 mM $MgCl_2$, 1 mM EGTA), 5 µL of 2× Kinase (0.18 - 2 ng CDK5/p25)/Peptide (2 µM Ser/Thr 12), and 2.5 µL of 4×ATP solution (17 µM). The plates are shaken for 30 seconds, and incubated for 60 minutes at room temperature. Development Reagent Solution (5 µL of 1:4096 dilution) is added to the plates followed with another 30-second plate shake and the plates are further incubated at room temperature for one hour. The plates are read on fluorescence plate reader with Dual emission at 445 nm and 520 nm.

[0170] The following equations are used for Z′-LYTE™ Screening Assay Data Analysis. Percent inhibition (100 –% activity) was fitted to the “four-parameter logistic model” in XLfit for determination of IC_{50} values.

	Equation
Correction for Background Fluorescence	$\mathbf{FI}_{\text{Sample}} - \mathbf{FI}_{\text{TCFI Ctl}}$
Emission Ratio (using values corrected for background fluorescence)	$\frac{\textbf{Coumarin Emission (445 nm)}}{\textbf{Fluorescein Emission (520 nm)}}$
% Phosphorylation (% Phos)	$\left\{1 - \frac{(\textbf{Emission Ratio} \times \mathbf{F}_{100\%}) - \mathbf{C}_{100\%}}{(\mathbf{C}_{0\%} - \mathbf{C}_{100\%}) + [\textbf{Emission Ratio} \times (\mathbf{F}_{100\%} - \mathbf{F}_{0\%})]}\right\} * \mathbf{100}$
% Inhibition	$\left\{1 - \frac{\%\,\mathbf{Phos}_{\text{Sample}}}{\%\,\mathbf{Phos}_{\text{0\% Inhibition Ctl}}}\right\} * \mathbf{100}$
Z' (using Emission Ratio Values)	$1 - \frac{\mathbf{3} * \mathbf{Stdev}_{\text{0\% Phos Ctl}} + \mathbf{3} * \mathbf{Stdev}_{\text{0\% Inhibition}}}{\mathbf{Mean}_{\text{0\% Phos Ctl}} - \mathbf{Mean}_{\text{0\% Inhibition}}}$
Difference Between Data Points (single point only)	$\lvert\ \%\mathbf{Inhibition}_{\text{Point 1}} - \%\mathbf{Inhibition}_{\text{Point 2}}\ \rvert$
Development Reaction Interference (DRI) (no ATP control	$\frac{\mathbf{Emission\ Ratio}_{\text{DRI Ctl}}}{\mathbf{Emission\ Ratio}_{\text{0\% Phos Ctl}}}$
Test Compound Fluorescence Interference (TCFI) (check both Coumarin and Fluorescein emissions)	$\frac{\mathbf{FI}_{\text{TCFI Ctl}}}{\mathbf{FI}_{\text{0\% Inhibitor Ctl}}}$

FI = Fluorescence Intensity; $\mathbf{C}_{100\%}$ = Average Coumarin emission signal of the 100% Phos. Control; $\mathbf{C}_{0\%}$ = Average Coumarin emission signal of the 0% Phos. Control; $\mathbf{F}_{100\%}$ = Average Fluorescein emission signal of the 100% Phos. Control; $\mathbf{F}_{0\%}$ = Average Fluorescein emission signal of the 0% Phos. Control; **DRI** = Development Reaction Interference; **TCFI** = Test Compound Fluorescence Interference

[0171] IC_{50} values of compounds against CDK7 (cyclin H) are determined by Adapta™ Assay at Invitrogen Life Technologies (Grand Island, NY) where total reaction volume is 10 µL/well in low volume, white 384-well plate (#4512, Corning). 0.100 µL of 100 × test compound in 100% DMSO (at specific solutions) is mixed with 2.4 µL of HEPES (30 mM), 2.5 µL of 4× ATP solution (153 µM) and 5 µL of 2× Substrate/Kinase mixture (the 2× CDK7/cyclin H/MNAT1 / CDK7/9tide mixture is prepared in 50 mM HEPES pH 7.5, 0.01% BRIJ-35, 10 mM $MgCl_2$, 1 mM EGTA). The final 10 µL Kinase Reaction consists of 5 - 38.75 ng CDK7/cyclin H/MNAT1 and 200 µM CDK7/9tide in 32.5 mM HEPES pH 7.5, 0.005% BRIJ-35, 5 mM $MgCl_2$, 0.5 mM EGTA. The plates are shaken for 30 seconds, centrifuged for 1 min at 1000×g, and incubated for 60 minutes at room temperature. 5 µL of Detection Mix (prepared in TR-FRET Dilution Buffer; the Detection mix consists of EDTA (30 mM), Eu-anti-ADP antibody (6 nM) and ADP tracer, and contains the EC_{60} concentration of tracer for 5-150 µM ATP) is added to the plates followed with another 30-second plate shake and centrifugation for 1 min at 1000×g, and the plates are further incubated at room

temperature for one hour. The plates are read on fluorescence plate reader with Dual emission at 615 nm and 665 nm.

[0172] The following equations are used for Adapta™ Assay Data Analysis. The ATP/ADP standard curve is fit to model number 205 (sigmoidal dose-response model) in XLfit. The dose response curve is also curve fit to model number 205.

	Equation
Emission Ratio	$\frac{\textbf{AF647 Emission (665 nm)}}{\textbf{Europium Emission (615 nm)}}$
% Conversion	$\left\{\frac{\textbf{EC}_{50\ SC}}{\left(\frac{\textbf{Top}_{SC}-\textbf{Bottom}_{SC}}{\textbf{Emission Ratio}_{Sample}-\textbf{Bottom}_{SC}}\right)-1\ \hat{}\ \left(\frac{1}{\textbf{Hillslope}_{SC}}\right)}\right\}*100$
% Inhibition	$\left\{1-\frac{\%\ \textbf{Conversion}_{Sample}}{\%\ \textbf{Conversion}_{0\%\ Inhibition\ Ctrl}}\right\}*100$
Difference Between Data Points (single point only)	$\lvert\ \%\ \textbf{Inhibition}_{Point\ 1}-\%\ \textbf{Inhibition}_{Point\ 2}\ \rvert$
Test Compound Interference	For each emission wavelength, fluorescence interference is flagged for a compound well that is more than 20% outside the range of the controls.
Z' (using Emission Ratio values)	$1-\frac{3*\textbf{Stdev}_{0\%\ Conv\ Ctrl}+3*\textbf{Stdev}_{0\%\ Inhibition}}{\lvert\textbf{Mean}_{0\%\ Conv\ Ctrl}-\textbf{Mean}_{0\%\ Inhibition}\rvert}$

* SC = Standard Curve

[0173] IC_{50} values of compounds against CDK2 (cyclin E1) are determined by LanthaScreen™ Eu Kinase Binding Assay at Invitrogen Life Technologies (Grand Island, NY) where total reaction volume is 16 µL/well in low volume, white 384-well plates (#784207, Greiner). 0.16 µL of 100 × test compound in 100% DMSO (at specific solutions) is mixed with 3.84 µL of Kinase Buffer (50 mM HEPES pH 7.5, 0.01% BRIJ-35, 10 mM $MgCl_2$, 1 mM EGTA), 8.0 µL of 2× Kinase (2.5 nM)/Antibody (Eu-anti-GST, 2 nM) Mixture and 4.0 µL of 4 × Tracer (Tracer 236, 100 nM). The plates are shaken for 30 seconds, and incubated for 60 minutes at room temperature. The plates are read on fluorescence plate reader with Dual emission at 615 nm and 665 nm.

[0174] IC_{50} values of compounds against CDK9 (cyclin K) are determined by LanthaScreen™ Eu Kinase Binding Assay at Invitrogen Life Technologies (Grand Island, NY) where total reaction volume is 16 µL/well in low volume, white 384-well plates (#784207, Greiner). 0.16 µL of 100 × test compound in 100% DMSO (at specific solutions) is mixed with 3.84 µL of Kinase Buffer (50 mM HEPES pH 7.5, 0.01% BRIJ-35, 10 mM

$MgCl_2$, 1 mM EGTA), 8.0 µL of 2× Kinase (5 nM)/Antibody (Eu-anti-His, 2 nM) Mixture and 4.0 µL of 4 × Tracer (Tracer 236, 100 nM). The plates are shaken for 30 seconds, and incubated for 60 minutes at room temperature. The plates are read on fluorescence plate reader with Dual emission at 615 nm and 665 nm.

[0175] IC_{50} values of compounds against FMS kinase are determined by LanthaScreen™ Eu Kinase Binding Assay at Invitrogen (Life Technologies Grand Island, NY) where total reaction volume is 10 µL in low-volume 384-well plates (#4511, Corning). Serially diluted compounds (3-fold) are incubated with kinase (1.25 nM) for 10 min, following which a mixture of ATP (10 µM) (#A1852, Sigma, St-Louis, MO) and fluorescent-PolyGT substrate (200 nM) (#PV3610, Invitrogen, Life Technologies Grand Island, NY) is added and incubated in dark at room temperature for 1H. After 1H, 10 µL stop solution containing Terbium labeled antibody (4 nM) (#PV3529, Invitrogen, Life Technologies Grand Island, NY) and EDTA (#E5134, Sigma, St-Louis, MO) (20mM) in TR-FRET dilution buffer (# PV3574, Invitrogen, Life Technologies Grand Island, NY) is added. Readings are taken in a Synergy Neo Plate reader (BioTek, Winooski, VT) at single excitation of 340 nm and Dual emission at 495 nm and 520 nm respectively.

[0176] The following equations are used for LanthaScreen Eu Kinase Binding Assay Data Analysis. Percent inhibition (100 –% activity) is fitted to the "four-parameter logistic model" in XLfit for determination of IC_{50} values.

	Equation
Emission Ratio (ER)	$\frac{\textbf{AF647 Emission (665 nm)}}{\textbf{Europium Emission (615 nm)}}$
% Displacement	$\left\{\frac{\textbf{ER}_{\text{0\% Disp Ctrl}} - \textbf{ER}_{\text{Sample}}}{\textbf{ER}_{\text{0\% Disp Ctrl}} - \textbf{ER}_{\text{100\% Disp Ctrl}}}\right\} * \textbf{100}$
Difference Between Data Points (single point only)	$\lvert \textbf{\% Displacement}_{\text{Point 1}} - \textbf{\% Displacement}_{\text{Point 2}} \rvert$
Test Compound Interference	For each emission wavelength, fluorescence interference is flagged for a compound well that is more than 20% outside the range of the controls.
Z' (using Emission Ratio values)	$1 - \frac{3 * \textbf{Stdev}_{\text{0\% Disp Ctrl}} + 3 * \textbf{Stdev}_{\text{100\% Disp Ctrl}}}{\lvert \textbf{Mean}_{\text{0\% Disp Ctrl}} - \textbf{Mean}_{\text{100\% Disp Ctrl}} \rvert}$

[0177] IC_{50} values of compounds against the PI3Kδ kinase are determined by an assay performed by Reaction Biology Corporation (Malvern, PA). Briefly, this assay is conducted in buffer (Tris-HCl 40 mM (pH7.5), Orthovanadate 3 mM, $MgCl_2$ 20 mM, DTT 2 mM, CHAPS 0.05%, DMSO 1%). PI3Kδ kinase is added to the reaction solution and mixed gently. The test compounds in 100% DMSO (at specific solutions) are mixed with the kinase reaction mixture to achieve the final compounds at pre-defined concentrations (e.g., range – 0.5 nM to 100 μM) by Acoustic technology (Echo550; nanoliter range). After incubating for 10 min at room temp, ATP is added into the reaction mixture to initiate the reaction followed by a 30-min incubation at 30°C. After quenching the reaction with ADP-Glo reagent, the plates are incubated for 40 min. The Detection Mixture is added, and the plate is incubated for an additional 30 min. At the end of incubation, luminescence is measured. For data analysis, the luminescence is converted into μM ADP production based on ADP standard curves. The nonlinear regression to obtain the standard curve and IC_{50} values is performed using GraphPad Prism (GraphPad Software, Inc., San Diego, CA).

[0178] IC_{50} values of compounds against CDK12 (cyclin K) are determined by KinaseProfiler™ radiometric protein kinase assay at Eurofins Pharma Discovery (Dundee, UK). Compounds are prepared to 50x final assay concentration in 100% DMSO. This working stock of the compound is added to the assay well as the first component in each reaction. CDK12/Cyclin K is diluted in buffer (20 mM TRIS, 0.2 mM EDTA, 0.1% β-mercaptoethanol, 0.01% Brij-35, 5% glycerol, 1 mg/ml BSA) prior to addition to the reaction mix. CDK12/Cyclin K is incubated with 20 mM Tris/HCl pH 8.5, 0.2 mM EDTA, 300 μM RSRSRSRSRSRSRSR, 10 mM Magnesium acetate and [γ-^{33}P-ATP] (specific activity and concentration as required). The reaction is initiated by the addition of the Mg/ATP mix. After incubation for 120 minutes at room temperature, the reaction is stopped by the addition of phosphoric acid to a concentration of 0.5%. 10 μl of the stopped reaction is spotted onto a P30 filtermat and washed four times for 4 minutes in 0.425% phosphoric acid and once in methanol prior to drying and scintillation counting. Results are calculated as a percentage of the mean kinase activity in positive control samples. Data are fitted in XLfit for determination of IC_{50} values.

Example B2. Determination of potency of compounds in cancer cell proliferation assay as a single agent.

[0179] The effects of test compounds were studied in two breast cancer cell lines of different subtype. The cancer cells (Table below) are harvested during the logarithmic growth period and counted. Cell concentrations are adjusted to the appropriate number with respective medium and 90 µL cell suspensions are added to 96-well plates. After cells are seeded, the plates are shaken gently to distribute cells evenly and incubated at 37 °C, 5% CO_2 on day 1.

Cell Culture Conditions

No.	Cell Line	Histopathology	Rb Status	Medium
1	MCF-7	Breast adenocarcinoma	Positive	MEM+10%FBS
2	DU4475	Breast carcinoma	Negative	RPMI1640+10%FBS

[0180] Cells are treated with test compounds at 7 to 9 concentrations within a desired concentration range (e.g. 1.1 nM – 10 µM) on day 2 by series diluting the test compound stock solution (10 mM in DMSO) with culture medium. Treatment duration was 144H (with a medium change at 72H) for both MCF-7 and DU4475 cells. Cell viability is assessed by Cell Titer-Glo® as recommended by Promega (Cat. No.: G7572), or by resazurin assay (Sigma Aldrich, Cat. No.: R7017) post treatment.

[0181] Cell viability data are plotted using GraphPad Prism (GraphPad Software, Inc., San Diego, CA). In addition, a nonlinear regression model with a sigmoidal dose response and variable slope within GraphPad Prism is used to calculate the IC_{50} value of individual test compounds.

[0182] The effects of test compounds are studied in additional cell lines of various histotypes, such as A549 lung adenocarcinoma, HCT-116 colorectal carcinoma, ZR-75-30 breast ductal carcinoma, Hs-578T breast epithelia carcinoma and BT-549 breast ductal carcinoma cells. The cancer cells are harvested during the logarithmic growth period and counted. Cell concentrations are adjusted to the appropriate number with suitable medium, and 90 µL cell suspensions are added to 96-well plates. After cells are seeded, the plates are shaken gently to distribute cells evenly and incubated at 37 °C, 5% CO_2 on day 1. Cells are treated with test compounds at typically 7-9 concentrations within a desired concentration range (e.g. 1.5 nM – 10 µM) on day 2 by series diluting the test compound stock solution (10

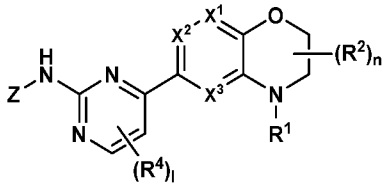
mM in DMSO) with culture medium. Cell viability is assessed by Cell Titer-Glo® as recommended by Promega (Cat. No.: G7572, Promega) typically 48-144H post-treatment, with a medium change as necessary. Cell viability data are plotted using GraphPad Prism (GraphPad Software, Inc., San Diego, CA). In addition, a nonlinear regression model with a sigmoidal dose response and variable slope within GraphPad Prism is used to calculate the IC_{50} value of individual test compounds.

[0183] Additional test compounds are studied in the same and/or other cancer cell lines using similar proliferation methods with possible variations in cell seeding densities and/or incubation durations. The cell cycle phase distribution post treatment of test compounds is studied using flow cytometer using DAPI staining. Cellular senescence is evaluated after continuously treating cells for a long time (e.g., 14 days) followed by staining cells lines for Senescence associated-β-galactosidase (SAβGAL).

[0184] Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it is apparent to those skilled in the art that certain minor changes and modifications will be practiced in light of the above teaching. Therefore, the description and examples should not be construed as limiting the scope of the invention.

CLAIMS

1. A compound of Formula (J):



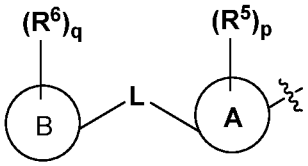
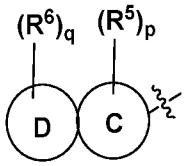
(J),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein:

X^1 is CR^3 or N;

X^2 is CR^3 or N;

X^3 is CR^3 or N;

Z is  or  , wherein

A is C_3-C_6 cycloalkyl, 4- to 7-membered heterocyclyl, 5- to 7-membered heteroaryl, or C_6 aryl, each of which is optionally substituted with one or more R^5;

L is a bond, $-CR^{11}R^{12}-$, -O-, -S-, $-S(O)_2-$, -C(O)-, $-NR^{10}-$, $-S(O)_2NR^{10}-$, or $-NR^{10}SO_2-$;

B is hydrogen, C_3-C_6 cycloalkyl, 3- to 7-membered heterocyclyl, 5- to 7-membered heteroaryl, or C_6 aryl, each of which is optionally substituted with one or more R^6;

C is C_3-C_6 cycloalkyl, 5- to 7-membered heterocyclyl, 5- to 7-membered heteroaryl, or C_6 aryl, each of which is optionally substituted with one or more R^5, wherein C is fused to D; and

D is C_3-C_6 cycloalkyl, 3- to 7-membered heterocyclyl, 5- to 7-membered heteroaryl, or C_6 aryl, each of which is optionally substituted with one or more R^6;

R^1 is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_8 alkoxy, C_3-C_{12} cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 10-membered heteroaryl, C_6-C_{14} aryl, -(C_1-C_3 alkylene)(C_3-C_{12} cycloalkyl), -(C_1-C_3 alkylene)(3- to 12-membered heterocyclyl), $-C(O)R^{10}$, -(C_1-C_3 alkylene)(5- to 10-membered heteroaryl)

or -(C_1-C_3 alkylene)(C_6-C_{14} aryl), wherein R^1 is independently optionally substituted with one or more substituents selected from the group consisting of halogen, oxo, -OR^{13}, -$NR^{13}R^{14}$, -$C(O)R^{13}$, -CN, C_3-C_8 cycloalkyl, and C_1-C_6 alkyl optionally substituted with one or more substituents selected from the group consisting of oxo, -OH and halogen;

each R^2 is independently C_2-C_6 alkenyl, C_2-C_6 alkynyl, -OH, oxo, -$NR^{11}R^{12}$, -CN, -$C(O)R^{10}$, -$C(O)NR^{11}R^{12}$, halogen, or C_1-C_6 alkyl optionally substituted with one or more substituents selected from the group consisting of –CN, -OH or halogen, or

two R^2 or R^1 and R^2 are taken together with the atom or atoms to which they are attached to form a C_3-C_6 cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 10-membered heteroaryl, or C_6-C_{14} aryl, each of which is independently optionally substituted with one or more substituents selected from the group consisting of C_1-C_6 alkyl, -OH, oxo, and halogen;

each of R^3 and R^4 is independently hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, -CN, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, halogen or -OH;

each R^5 is independently C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, oxo, -CN, -OR^{10}, -SR^{10}, -$NR^{11}R^{12}$, -$C(O)R^{10}$, -$C(O)NR^{11}R^{12}$, -$OC(O)NR^{11}R^{12}$, -$NR^{10}C(O)R^{11}$, -$NR^{10}C(O)NR^{11}R^{12}$, -$S(O)R^{10}$, -$S(O)_2R^{10}$, -$NR^{10}S(O)_2R^{11}$, -$S(O)_2NR^{11}R^{12}$, C_3-C_6 cycloalkyl, 3- to 12-membered heterocyclyl, -(C_1-C_3 alkylene)OR^{10}, -(C_1-C_3 alkylene)SR^{10}, -(C_1-C_3 alkylene)$NR^{11}R^{12}$, -(C_1-C_3 alkylene)$C(O)R^{10}$, -(C_1-C_3 alkylene)$C(O)NR^{11}R^{12}$, -(C_1-C_3 alkylene)$NR^{10}C(O)R^{11}$, -(C_1-C_3 alkylene)$NR^{10}C(O)NR^{11}R^{12}$, -(C_1-C_3 alkylene)$S(O)_2R^{10}$, -(C_1-C_3 alkylene)$NR^{10}S(O)_2R^{11}$, -(C_1-C_3 alkylene)$NR^{10}S(O)_2NR^{11}R^{12}$, -($C_1$-$C_3$ alkylene)$S(O)_2NR^{11}R^{12}$, -(C_1-C_3 alkylene)(C_3-C_6 cycloalkyl), -(C_1-C_3 alkylene)(3- to 12-membered heterocyclyl), wherein each R^5 is independently optionally substituted with one or more substituents selected from the group consisting of halogen, oxo, -OR^{13}, -$NR^{13}R^{14}$, -$C(O)R^{13}$, -CN, -(C_1-C_3 alkylene)OR^{13}, -(C_1-C_3 alkylene)$NR^{13}R^{14}$, -(C_1-C_3 alkylene)$C(O)R^{13}$, C_3-C_8 cycloalkyl, and C_1-C_6 alkyl optionally substituted with one or more substituents selected from the group consisting of oxo, -OH, and halogen,

or any two R^5 are taken together with the atom or atoms to which they are attached to form a C_3-C_6 cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 10-membered heteroaryl, or C_6-C_{14} aryl;

each R^6 is independently oxo or R^7, or any two R^6 are taken together with the atom or atoms to which they are attached to form a C_3-C_6 cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 10-membered heteroaryl, or C_6-C_{14} aryl;

each R^7 is independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 6-membered heterocyclyl, $-OR^{10}$, $-NR^{11}R^{12}$, $-NR^{10}C(O)R^{11}$, $-NR^{10}C(O)NR^{11}R^{12}$, $-S(O)_2R^{10}$, $-NR^{10}S(O)_2R^{11}$, $-S(O)_2NR^{11}R^{12}$, $-C(O)R^{10}$, $-C(O)NR^{11}R^{12}$, $-(C_1$-C_3 alkylene)CN, $-(C_1$-C_3 alkylene)OR^{10}, $-(C_1$-C_3 alkylene)SR^{10}, $-(C_1$-C_3 alkylene)$NR^{11}R^{12}$, $-(C_1$-C_3 alkylene)CF_3, $-(C_1$-C_3 alkylene)$C(O)R^{10}$, $-(C_1$-C_3 alkylene)$C(O)NR^{11}R^{12}$, $-(C_1$-C_3 alkylene)$NR^{10}C(O)R^{11}$, $-(C_1$-C_3 alkylene)$NR^{10}C(O)NR^{11}R^{12}$, $-(C_1$-C_3 alkylene)$S(O)_2R^{10}$, $-(C_1$-C_3 alkylene)$NR^{10}S(O)_2R^{11}$, $-(C_1$-C_3 alkylene)$S(O)_2NR^{11}R^{12}$, $-(C_1$-C_3 alkylene)(C_3-C_6 cycloalkyl), or $-(C_1$-C_3 alkylene)(3- to 6-membered heterocyclyl), wherein each R^7 is independently optionally substituted with one or more substituents selected from the group consisting of halogen, oxo, $-OR^{13}$, $-NR^{13}R^{14}$, $-C(O)R^{13}$, -CN, $-(C_1$-C_3 alkylene)OR^{13}, $-(C_1$-C_3 alkylene)$NR^{13}R^{14}$, $-(C_1$-C_3 alkylene)$C(O)R^{13}$, C_3-C_8 cycloalkyl, and C_1-C_6 alkyl optionally substituted with one or more substituents selected from the group consisting of oxo, -OH, and halogen;

each R^{10} is independently hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, $-(C_1$-C_3 alkylene)(C_3-C_6 cycloalkyl), C_6-C_{14} aryl, 5- to 6-membered heteroaryl or 3- to 6-membered heterocyclyl, each of which is independently optionally substituted with one or more substituents selected from the group consisting of halogen, oxo, -CN, $-OR^{15}$, $-NR^{15}R^{16}$, and C_1-C_6 alkyl optionally substituted with one or more substituents selected from the group consisting of halogen, -OH, and oxo;

R^{11} and R^{12} are each independently hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, $-(C_1$-C_3 alkylene)(C_3-C_6 cycloalkyl), C_6-C_{14} aryl, 5- to 6-membered heteroaryl or 3- to 6-membered heterocyclyl, each of which is independently optionally substituted with one or more substituents selected from the group consisting of halogen, oxo, -CN, $-OR^{15}$, $-NR^{15}R^{16}$, and C_1-C_6 alkyl optionally substituted with one or more substituents selected from the group consisting of halogen, -OH, and oxo,

or R^{11} and R^{12} are taken together with the atom to which they attached to form a 3- to 6- membered heterocyclyl optionally substituted with one or more substituents

selected from the group consisting of halogen, oxo, and C_1-C_6 alkyl optionally substituted with one or more substituents selected from the group consisting of halogen, -OH, and oxo;

R^{13} and R^{14} are each independently hydrogen or C_1-C_6 alkyl, wherein the C_1-C_6 alkyl is optionally substituted with one or more substituents selected from the group consisting of halogen, $-OR^{15}$, $-NR^{15}R^{16}$, and oxo,

or R^{13} and R^{14} are taken together with the atom to which they attached to form a 3- to 6- membered heterocyclyl optionally substituted with one or more substituents selected from the group consisting of halogen, oxo, and C_1-C_6 alkyl optionally substituted with one or more substituents selected from the group consisting of halogen, -OH, and oxo; and

R^{15} and R^{16} are each independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl are each independently optionally substituted with one or more substituents selected from the group consisting of halogen, -OH, and oxo,

or R^{15} and R^{16} are taken together with the atom to which they attached to form a 3- to 6- membered heterocyclyl optionally substituted with one or more substituents selected from the group consisting of halogen, oxo, and C_1-C_6 alkyl optionally substituted with one or more substituents selected from the group consisting of halogen, -OH, and oxo;

l is 0, 1, or 2;

p and q are each independently 0, 1, 2 or 3; and

n is 0, 1, 2, 3 or 4,

provided that at least one of (1), (2), (3), and (4) applies:

(1) at least one of X^1, X^2, and X^3 is N or CR^3, wherein R^3 is -CN,

(2) l is 1 and R^4 is -CN,

(3) at least one R^2 is C_1-C_6 alkyl substituted with one or more halogen,

(4) two R^2 or R^1 and R^2 are taken together with the atom or atoms to which they are attached to form a C_3-C_6 cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 10-membered heteroaryl, or C_6-C_{14} aryl, each of which is independently optionally substituted with one or more substituents selected from the group consisting of C_1-C_6 alkyl, -OH, oxo, and halogen.

2. The compound of claim 1, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein X^1 is N.

3. The compound of claim 1, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein X^1 is CR^3.

4. The compound of any one of claims 1-3, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein X^2 is N.

5. The compound of any one of claims 1-3, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein X^2 is CR^3.

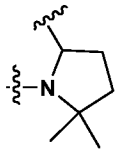
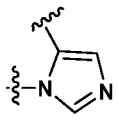
6. The compound of any one of claims 1-5, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein X^3 is N.

7. The compound of any one of claims 1-5, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein X^3 is CR^3.

8. The compound of any one of claims 1-7, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein at least one of X^1, X^2, and X^3 is N or CR^3, wherein R^3 is -CN.

9. The compound of any one of claims 1-8, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein n is 0.

10. The compound of any one of claims 1-8, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein n is 1.

11. The compound of any one of claims 1-8, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^1 and R^2 are taken together with the atoms to which they are attached to form  or  .

12. The compound of any one of claims 1-8, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein n is 2.

13. The compound of claim 12, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein one R^2 is oxo and one R^2 is C_1-C_6 alkyl substituted with one or more halogen.

14. The compound of claim 12, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein two R^2 are attached to a same carbon atom and are taken together with the atom to form a C_3-C_6 cycloalkyl.

15. The compound of any one of claims 1-14, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein *l* is 1.

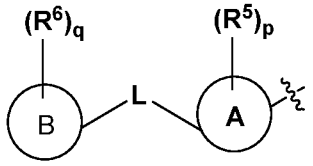
16. The compound of any one of claims 1-15, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^4 is -CN.

17. The compound of any one of claims 1-15, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^4 is halogen.

18. The compound of any one of claims 1-17, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^1 is C_1-C_6 alkyl.

19. The compound of any one of claims 1-18, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^1 is isopropyl.

20. The compound of any one of claims 1-19, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein Z is



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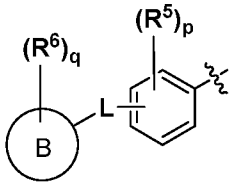
21. The compound of any one of claims 1-20, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein Z is 

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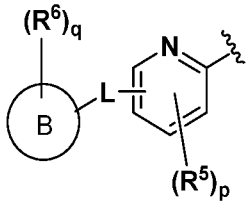

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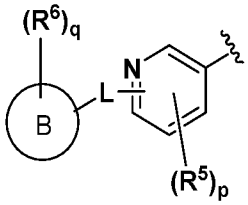

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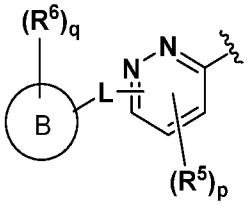

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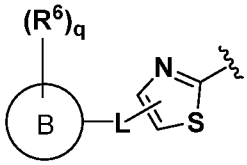
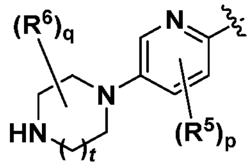
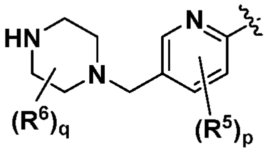
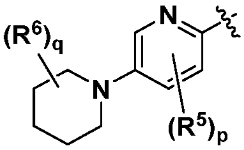
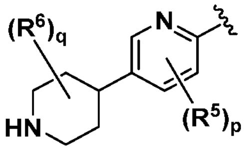
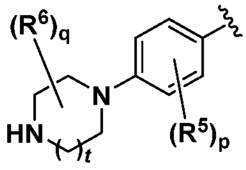
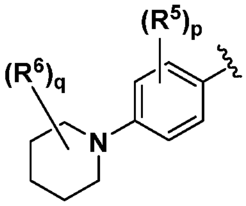
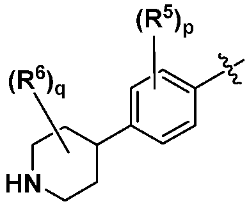
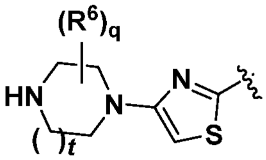
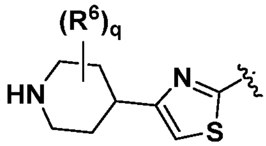


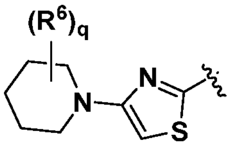
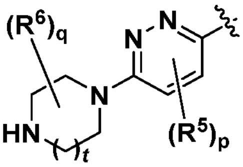
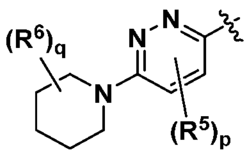
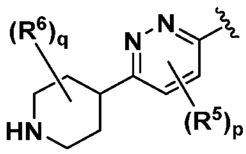
, wherein t is 0, 1, or 2; and t' is 0 or 1.

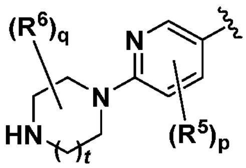
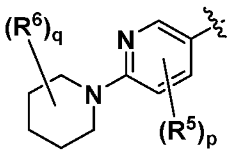
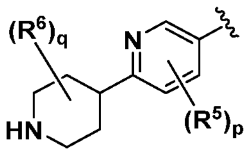
22. The compound of any one of claims 1-21, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein L is a bond or -CH_2-.

23. The compound of any one of claims 1-22, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein Z is  ,

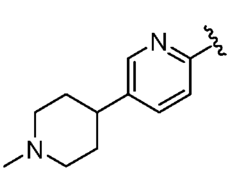
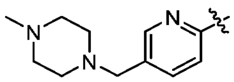
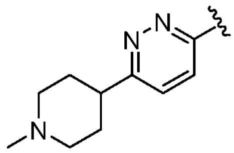
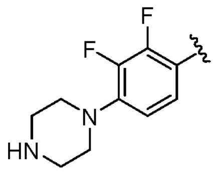
 ,  ,  ,  ,

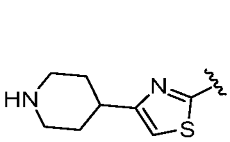
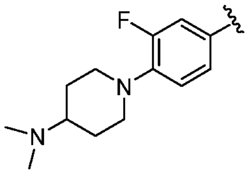
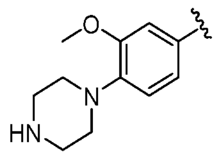
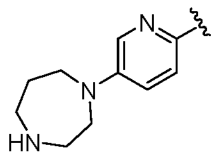
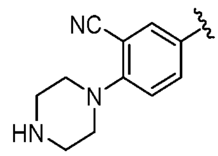
 ,  ,  ,  ,

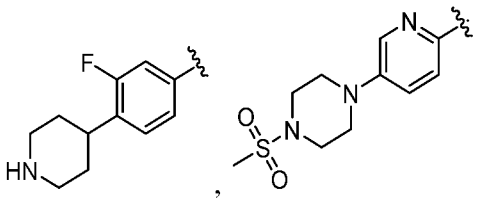
 ,  ,  ,  ,

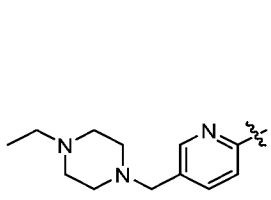
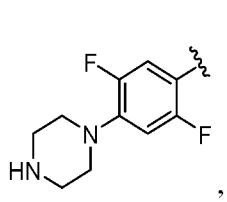
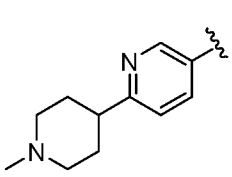
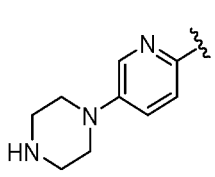
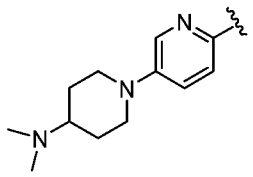
 ,  , or  , wherein t is 0, 1, or 2.

24. The compound of any one of claims 1-23, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein Z is

 ,  ,  ,  ,

 ,  ,  ,  ,  ,







, or 
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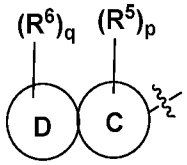
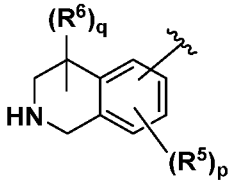
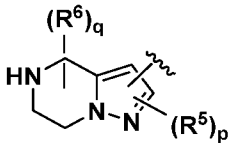
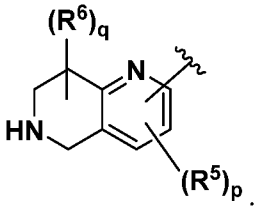
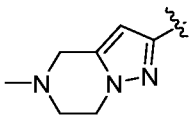
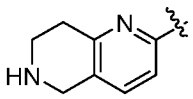
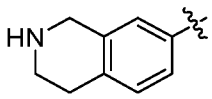
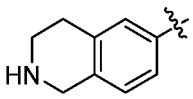
25. The compound of any one of claims 1-19, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein Z is 
.

26. The compound of claim 25, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein Z is 
,


, or 
.

27. The compound of claim 25 or 26, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein Z is 
,


, 
, or 
.

28. A compound, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein the compound is selected from the group consisting of compounds of Table 1.

29. A pharmaceutical composition comprising the compound of any one of claims 1-28, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and a pharmaceutically acceptable carrier or excipient.

30. A method of treating a cancer in an individual in need thereof comprising administering to the individual a therapeutically effective amount of a compound of any one of claims 1-28, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

31. The method of claim 30, where the cancer is a breast cancer, brain cancer, colorectal cancer, lung cancer, gastric cancer, liver cancer, leukemia, lymphoma, mantle cell lymphoma, melanoma, ovarian cancer, pancreatic cancer, prostate cancer, adult hematopoietic or solid tumor, or pediatric tumor.

32. The method of claim 30 or 31, further comprising administering a radiation therapy to the individual.

33. The method of any one of claims 30-32, further comprising administering to the individual a therapeutically effective amount of an additional therapeutic agent.

34. The method of claim 33, wherein the additional therapeutic agent is a cancer immunotherapy agent, an endocrine therapy agent, or a chemotherapeutic agent.

35. The method of claim 33 or 34, wherein the additional therapeutic agent is a cancer immunotherapy.

36. The method of any one of claims 33-35, wherein the additional therapeutic agent is an anti-PD-1 antibody.

37. The method of claim 36, wherein the endocrine therapy agent is an antiestrogen therapy, a selective estrogen receptor degrader (SERD), or an aromatase inhibitor.

38. The method of claim 34, wherein the chemotherapeutic agent is a DNA alkylating agent, a platinum-based chemotherapeutic agent, a taxane, a BTK inhibitor, a PI3K inhibitor, another kinase inhibitor, or a DNA damage repair (DDR) pathway inhibitor.

39. The method of any one of claims 30-38, wherein the cancer comprises a mutated or overexpressed CDK gene.

40. The method of any one of claims 30-39, comprising selecting the individual for treatment based on (i) the presence of one or more mutations or amplifications of the CDK4

or CDK6 or other CDK gene in the cancer, (ii) overexpression of CDK4 or CDK6 or other CDK protein in the cancer, (iii) amplification or overexpression of the genes encoding cyclins, (iv) loss of endogenous INK4 inhibitors by gene deletion, mutation, or promoter hypermethylation, (v) other genetic events leading to overactivity of CDK4 or CDK6 or other CDK, or (vi) phosphorylation of retinoblastoma (Rb) protein in the cancer.

41. A method of arresting the G_1-S checkpoint in a cell, comprising administering a compound of any one of claims 1-28, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, to the cell.

42. A method of inducing senescence in a cell, comprising administering a compound of any one of claims 1-28, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, to the cell.

43. A method of inducing apoptosis in a cell, comprising administering a compound of any one of claims 1-28, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, to the cell.

44. A method of inhibiting CDK4 or CDK6 in a cell, comprising administering a compound of any one of claims 1-28, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, to the cell.

45. A method of inhibiting CDK4 or CDK6, comprising contacting CDK4 or CDK6 with a compound of any one of claims 1-28, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

46. A kit comprising a compound of any one of claims 1-28, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.