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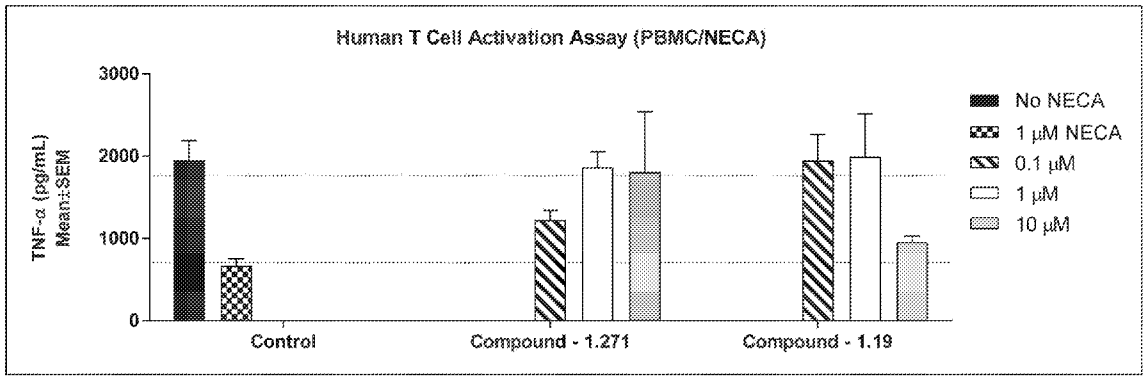


Figure 1

(57) Abstract: Aminopyrazine compounds as modulators of an adenosine receptor are provided. The compounds may find use as therapeutic agents for the treatment of diseases mediated through a G-protein-coupled receptor signaling pathway and may find particular use in oncology.

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HETEROCYCLIC COMPOUNDS AS ADENOSINE ANTAGONISTS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 62/534,176, filed July 18, 2017, the contents of which are incorporated by reference in their entirety.

FIELD OF THE INVENTION

[0002] This disclosure relates generally to therapeutics for treatment mediated through a G-protein–coupled receptor (GPCR) signaling pathway and, more particularly, to compounds that inhibit an adenosine receptor (such as an A_{2A} antagonist). The disclosure also provides pharmaceutically acceptable compositions comprising such compounds and methods of using the compounds or compositions in the treatment of a disease associated with a GPCR signaling pathway.

BACKGROUND OF THE INVENTION

[0003] Adenosine receptors (ARs) are distributed throughout the body and are responsible for numerous biological functions. The seven trans-membrane G-protein-coupled receptors (GPCRs) have been divided into four different subtypes: A_1, A_{2A}, A_{2B}, and A_3. The A_{2A} and A_{2B} ARs stimulate activity of the adenylyl cyclase, inducing an increase of cAMP levels. A_{2A} ARs have a distinct tissue localization, different biochemical pathways, and specific pharmacological profiles.

[0004] Adenosine is one of the human body's most important neuromodulators in both the central and the peripheral nervous systems. Adenosine is released from tumor cells and its concentration in the extracellular fluid of tumors can reach immunosuppressive levels (Blay et al. (1997), *Cancer Res., 57(13),* pp. 2602-5). The extracellular fluid of solid carcinomas contains immunosuppressive concentrations of adenosine. *Id.* This increase in adenosine concentration is a result of increases in CD73 (ecto-5′-nucleotidase) and CD39 (nucleoside triphosphate dephosphorylase) enzymes, which are responsible for directly catabolizing ATP into adenosine. These upregulations are triggered by hypoxia and the generation of HIF-1α. High levels of adenosine around tumor cells act to regulate multiple immune cells (e.g., $CD4^+$ T-cells and cytotoxic $CD8^+$ T-cells) via activation of multiple adenosine receptor subtypes, but particularly

A_{2A} receptors, resulting the suppressing of pro-inflammatory activities and upregulation of anti-inflammatory molecules and immunoregulatory cells (Kumar et al. (2013), Adenosine as an endogenous immunoregulator in cancer pathogenesis: where to go? *Purinergic Signal.*, 9(2), pp 145-65 and Sitkowsky et al., Hostile, hypoxia-A2-adenosinergic tumor biology as the next barrier to overcome for tumor immunologists. *Cancer Immunol. Res. 2(7)*, pp 598-605; Ohta (2016), A Metabolic Immune Checkpoint: Adenosine in Tumor Microenvironment. *Frontiers in Immunology.*, 7 article# 109, pp 1-11). It was demonstrated that chimeric antigen receptor (CAR) T cells upregulate A2ARs upon antigen-specific stimulation in vitro and in vivo (Beavls (2017), Targeting the Adenosine 2A Receptor Enhances Chimeric Antigen Receptor T Cell Efficacy. *J of Clin Invest.* 127 (3): pp 929-941).

[0005] Survival of cancer cells is dependent on their ability to avoid attack by the immune system. In addition, tumor cells can overtake the immune system to facilitate tumor survival and metastasis. Adenosine, whose concentration increases within hypoxic regions of solid tumors, has been recognized as being able to interfere with the recognition of tumor cells by cytolytic effector cells of the immune system. (Tuite and Riss (2013). Recent developments in the pharmacological treatment of Parkinson's disease. *Expert Opin. Investig. Drugs, 12(8)* pp 1335-52, Popoli et al. (2002). Blockade of striatal adenosine A_{2A} receptor reduces, through a presynaptic mechanism, quinolinic acid-induced excitotoxicity: possible relevance to neuroprotective interventions in neurodegenerative diseases of the striatum, *J. Neurosci, 22(5) pp. 1967-75*, Gessi et al. (2011). Adenosine receptors and cancer. *Biochim Biophys Acta, 1808(5),* pp. 1400-12).

[0006] Although all adenosine receptors now have an increasing number of recognized biological roles in tumors, the A_{2A} and A_3 subtypes appear promising targets for therapeutic development. In particular, activation of A_{2A} receptors leads to immunosuppressive effects, which decreases anti-tumoral immunity and thereby encourages tumor growth.

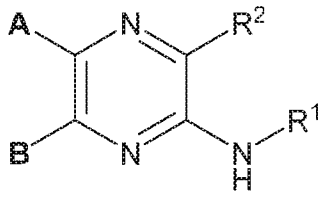
[0007] The A_{2B} receptor is another potential target for therapeutic development. Autocrine/paracrine stimulation of A_{2B} expressed on tumor cells is believed to enhance their metastatic potential and A_{2B} blockade may reduce tumor metastasis in an immune-independent manner (Beavis et al. (2013). Blockade of A_{2A} receptors potently suppresses the metabolism of $CD73^+$ Tumors. *Proc. Natl. Acad. Sci., 110(36)* pp. 14711-6). A_{2B} expression also correlates with relapse-free survival (RFS) in triple negative breast cancer suggesting that this pathway may be

clinically relevant. A_{2B} blockade also has the potential to modulate the immunosuppressive properties of tumor-associated immune cells including dendritic cells and myeloid-derived suppressor cells (MDSCs) (Cekic et al. (2011). Adenosine A2B receptor blockade slows growth of bladder and breast tumors. *J. Immunol. 188(1)*, pp. 198-205; Sorrentino et al. (2015). Myeloid-derived suppressor cells contribute to A_{2B} adenosine receptor-induced VEGF production and angiogenesis in a mouse melanoma model. *Oncotarget 6(29)*, pp. 27478-89; Iannone et al. (2013). Blockade of A_{2B} adenosine receptor reduces tumor growth and immune suppression mediated by myeloid-derived suppressor cells in a mouse model of melanoma. *Neoplasia, 15(12)*, pp. 1400-9.

[0008] There remains a continuing need for new therapies for the treatment of diseases and disorders related to the adenosine signaling pathway.

BRIEF SUMMARY OF THE INVENTION

[0009] In one aspect, provided is a compound of the formula (I):



(I),

or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein **A**, **B**, R^1 and R^2 are as detailed herein. In some embodiments, provided is a compound of formula (I), or a salt thereof.

[0010] In some embodiments, the compound of the formula (I), or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, is of the formula (II), (III) or (IV) or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, as detailed herein. In some embodiments, the compound of the formula (I), or a salt thereof, is of the formula (II), (III) or (IV) or a salt of the foregoing, as detailed herein.

[0011] In another aspect, provided is a method for any one or more of: (a) treating a disease, such as a proliferative disease, in an individual in need thereof; (b) enhancing an immune response in an individual in need thereof; (c) inhibiting tumor metastasis in an individual in need thereof; (d) modulating the activity of a G protein coupled receptor signaling pathway in an individual in need thereof; (e) modulating the activity of an adenosine receptor, such as an A_{2A}

receptor, in an individual in need thereof; and (f) increasing the activity of a natural killer cell in an individual in need thereof, wherein the method comprises administering to the individual an effective amount of a compound of formula (I), or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing. In some embodiments, provided is a method for any one or more of: (a) treating a disease, such as a proliferative disease, in an individual in need thereof; (b) enhancing an immune response in an individual in need thereof; (c) inhibiting tumor metastasis in an individual in need thereof; (d) modulating the activity of a G protein coupled receptor signaling pathway in an individual in need thereof; (e) modulating the activity of an adenosine receptor, such as an A_{2A} receptor, in an individual in need thereof; and (f) increasing the activity of a natural killer cell in an individual in need thereof, wherein the method comprises administering to the individual an effective amount of a compound of formula (I), or a salt thereof. In one aspect, the compound of formula (I) or a salt thereof is administered to the individual in combination with another therapeutic agent. In some embodiments, the compound of formula (I) or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing is administered to the individual in combination with another therapeutic agent. In a further aspect of the methods, the compound of formula (I) or a salt thereof is a compound of the formula (II), (III) or (IV) or a salt of the foregoing. In some embodiments, the compound of formula (I) or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing is a compound of the formula (II), (III) or (IV), or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

[0012] Also provided are pharmaceutical compositions comprising (A) a compound detailed herein, such as a compound of formula (I) or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a compound of formula (II) or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a compound of formula (III) or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a compound of formula (IV) or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and (B) a pharmaceutically acceptable carrier or excipient. In some embodiments, provided are pharmaceutical compositions comprising (A) a compound detailed herein, such as a compound of formula (I) or a salt thereof, or a compound of formula (II) or a salt thereof, or a compound of formula (III) or a salt thereof, or a compound of formula (IV) or a salt thereof, and (B) a pharmaceutically acceptable carrier or excipient. Kits

comprising a compound detailed herein or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing and instructions for use are also provided. Kits comprising a compound detailed herein or a salt thereof and instructions for use are also provided. A compound detailed herein or a tautomer or isomer 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. Compounds as detailed herein or a pharmaceutically acceptable salt thereof are also provided for the manufacture of a medicament for the treatment of cancer.

BRIEF DESCRIPTION OF THE DRAWINGS

[0013] Figure 1 shows the effects of certain compounds on TNF-α production in activated human PBMCs.

[0014] Figure 2 shows the effects of certain compounds on IFN-γ production in activated human PBMCs.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0015] For use herein, unless clearly indicated otherwise, use of the terms "a", "an" and the like refers to one or more.

[0016] "Alkenyl" as used herein refers to an unsaturated linear or branched univalent 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) and having the number of carbon atoms designated (*i.e.*, C_2-C_{10} means two to ten carbon atoms). 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 (a "C_2-C_{20} alkenyl"), having 2 to 8 carbon atoms (a "C_2-C_8 alkenyl"), having 2 to 6 carbon atoms (a "C_2-C_6 alkenyl"), or having 2 to 4 carbon atoms (a "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.

[0017] The term "alkyl" refers to and includes saturated linear and branched univalent hydrocarbon structures and combination thereof, having the number of carbon atoms designated (*i.e.*, C_1-C_{10} means one to ten carbons). Particular alkyl groups are those having 1 to 20 carbon

atoms (a "C_1-C_{20} alkyl"). More particular alkyl groups are those having 1 to 8 carbon atoms (a "C_1-C_8 alkyl"), 3 to 8 carbon atoms (a "C_3-C_8 alkyl"), 1 to 6 carbon atoms (a "C_1-C_6 alkyl"), 1 to 5 carbon atoms (a "C_1-C_5 alkyl"), or 1 to 4 carbon atoms (a "C_1-C_4 alkyl"). Examples of alkyl include, but are not limited to, groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, homologs and isomers of, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like.

[0018] "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 (a "C_1-C_6 alkylene"), 1 to 5 carbon atoms (a "C_1-C_5 alkylene"), 1 to 4 carbon atoms (a "C_1-C_4 alkylene") or 1 to 3 carbon atoms (a "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.

[0019] "Alkynyl" as used herein refers to an unsaturated linear or branched univalent 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) and having the number of carbon atoms designated (*i.e.*, C_2-C_{10} means two to ten carbon atoms). Particular alkynyl groups are those having 2 to 20 carbon atoms (a "C_2-C_{20} alkynyl"), having 2 to 8 carbon atoms (a "C_2-C_8 alkynyl"), having 2 to 6 carbon atoms (a "C_2-C_6 alkynyl"), or having 2 to 4 carbon atoms (a "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.

[0020] The term "aryl" refers to and includes polyunsaturated aromatic hydrocarbon groups. Aryl may contain additional fused rings (*e.g.*, from 1 to 3 rings), including additionally fused aryl, heteroaryl, cycloalkyl, and/or heterocyclyl rings. In one variation, the aryl group contains from 6 to 14 annular carbon atoms. Examples of aryl groups include, but are not limited to, phenyl, naphthyl, biphenyl, and the like.

[0021] The term "cycloalkyl" refers to and includes cyclic univalent hydrocarbon structures, which may be fully saturated, mono- or polyunsaturated, but which are non-aromatic, having the number of carbon atoms designated (*e.g.*, C_1-C_{10} means one to ten carbons). Cycloalkyl can consist of one ring, such as cyclohexyl, or multiple rings, such as adamantyl, but excludes aryl groups. A cycloalkyl comprising more than one ring may be fused, spiro or bridged, or

combinations thereof. A preferred cycloalkyl is a cyclic hydrocarbon having from 3 to 13 annular carbon atoms. A more preferred cycloalkyl is a cyclic hydrocarbon having from 3 to 8 annular carbon atoms (a "C_3-C_8 cycloalkyl"). Examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, norbornyl, and the like.

[0022] "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. 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, e.g., dihaloaryl, dihaloalkyl, trihaloaryl etc. refer to aryl and alkyl substituted with two ("di") or three ("tri") halo groups, which may be but are not necessarily the same halo; thus 4-chloro-3-fluorophenyl is within the scope of dihaloaryl. An alkyl group in which each hydrogen is replaced with a halo group is referred to as a "perhaloalkyl." A preferred perhaloalkyl group is trifluoroalkyl (-CF_3). Similarly, "perhaloalkoxy" refers to an alkoxy group in which a halogen takes the place of each H in the hydrocarbon making up the alkyl moiety of the alkoxy group. An example of a perhaloalkoxy group is trifluoromethoxy (-OCF_3).

[0023] The term "heteroaryl" refers to and includes unsaturated aromatic cyclic groups having from 1 to 10 annular carbon atoms and at least one annular heteroatom, including but not limited to heteroatoms such as nitrogen, oxygen and sulfur, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. A heteroaryl group can be attached to the remainder of the molecule at an annular carbon or at an annular heteroatom. Heteroaryl may contain additional fused rings (*e.g.*, from 1 to 3 rings), including additionally fused aryl, heteroaryl, cycloalkyl, and/or heterocyclyl rings. Examples of heteroaryl groups include, but are not limited to, pyridyl, pyrimidyl, thiophenyl, furanyl, thiazolyl, and the like. Examples of heteroaryl groups also include, but are not limited to, pyridyl, pyrimidyl, thiophenyl, furanyl, thiazolyl, oxazolyl, isoxazolyl, thiophenyl, pyrrolyl, pyrazolyl, 1,3,4-oxadiazolyl, imidazolyl, isothiazolyl, triazolyl, 1,3,4-thiadiazolyl, tetrazolyl, benzofuranyl, benzothiophenyl, pyrazolopyridinyl, indazolyl, benzothiazolyl, benzooxazolyl or benzoimidazolyl and the like.

[0024] In one variation, a heteroaryl containing at least one additional fused ring that is nonaromatic (e.g., cycloakyl or heterocyclyl) is attached to the parent structure at an annular

atom of the additional ring. In another variation, a heteroaryl containing at least one additional ring that is nonaromatic (e.g., cycloakyl or heterocyclyl) is attached to the parent structure at an annular atom of the aromatic ring.

[0025] The term "heterocycle" or "heterocyclyl" refers to a saturated or an unsaturated non-aromatic group having from 1 to 10 annular carbon atoms and from 1 to 4 annular heteroatoms, such as nitrogen, sulfur or oxygen, and the like, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. A heterocyclyl group may have a single ring or multiple condensed rings, but excludes heteroaryl groups. A heterocycle comprising more than one ring may be fused, spiro or bridged, or any combination thereof. In fused ring systems, one or more of the fused rings can be aryl, cycloalyl or heterocyclyl. Examples of heterocyclyl groups include, but are not limited to, tetrahydropyranyl, dihydropyranyl, piperidinyl, piperazinyl, pyrrolidinyl, thiazolinyl, thiazolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, 2,3-dihydrobenzo[b]thiophen-2-yl, 4-amino-2-oxopyrimidin-1(2H)-yl, and the like.

[0026] In one variation, a heterocyclyl containing at least one additional ring (such as a fused additional ring) that does not contain a heteroatom is attached to the parent structure at an annular atom of the additional ring. In another variation, a heterocyclyl containing at least one additional ring (such as a fused additional ring) that does not contain a heteroatom is attached to the parent structure at an annular atom of the ring containing a heteroatom.

[0027] "Oxo" refers to the moiety =O.

[0028] "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. 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.

[0029] 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.

[0030] 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.

[0031] 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.

[0032] 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 salt thereof, 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.

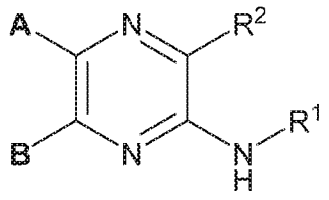
[0033] As used herein, the term "individual" is a mammal, including humans. An individual includes, but is not limited to, human, bovine, horse, feline, canine, rodent, or primate. In some embodiments, the individual is human. The individual (such as a human) may have advanced disease or lesser extent 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).

[0034] Reference to "about" a value or parameter herein includes (and describes) embodiments that are directed to that value or parameter per se. For example, description referring to "about X" includes description of "X".

[0035] It is understood that aspects and variations described herein also include "consisting" and/or "consisting essentially of" aspects and variations.

Compounds

[0036] In one aspect, provided is a compound of the formula (I):



(I),

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

A is 4-hydroxyphenyl optionally further substituted by R^3, 4-hydroxy-2-pyridyl optionally further substituted by R^4, a naphthyl substituted by R^4, a 9- or 10- membered bicylic heterocylyl optionally substituted by R^4, or a 9- or 10-membered bicyclic heteroaryl optionally substituted by R^4;

B is a phenyl optionally substituted by R^3, C_3-C_6 cycloalkyl optionally substituted by R^4, 3- to 6-membered heterocyclyl optionally substituted by R^4 or a 5- to 10-membered heteroaryl optionally substituted by R^4;

R^1 is a 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, 5- to 10-membered heteroaryl, -(C_1-C_3 alkylene)(C_3-C_6 cycloalkyl), -(C_1-C_3 alkylene)(3-6-membered heterocyclyl), -(C_1-C_3 alkylene)(5-6-membered heteroaryl), -(C_1-C_3 alkylene)(C_6 aryl), -$C(O)R^{1a}$, -$C(O)OR^{1a}$, -$C(O)NR^{1b}R^{1c}$, -$NR^{1b}R^{1c}$, –$S(O)_2R^{1a}$, -(C_1-C_3 alkylene)$C(O)NR^{1b}R^{1c}$, -(C_1-C_3 alkylene)$C(O)R^{1a}$ or -(C_1-C_3 alkylene)$NR^{1b}R^{1c}$, wherein the 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, 5- to 10-membered heteroaryl, -(C_1-C_3 alkylene)(C_3-C_6 cycloalkyl), -(C_1-C_3 alkylene)(3-6-membered heterocyclyl), -(C_1-C_3 alkylene)(5-6-membered heteroaryl), and -(C_1-C_3 alkylene)(C_6 aryl) of R^1 are independently optionally substituted by R^4;

each R^{1a} is independently hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, 3-6-membered heterocyclyl, C_6 aryl, 5-6-membered heteroaryl, -(C_1-C_3 alkylene)(C_3-C_6 cycloalkyl), -(C_1-C_3 alkylene)(3-6-membered heterocyclyl), -(C_1-C_3 alkylene)(C_6 aryl) or -(C_1-C_3 alkylene)(5-6-membered heteroaryl), wherein each of which is optionally substituted by methyl, ethyl, halogen, oxo, -CF_3, -OH, -OCH_3, -CN, -$C(O)OCH_3$, -$C(O)OC_2H_5$, -NH_2 or -$NHCH_3$;

each R^{1b} and R^{1c} is independently hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, 3-6-membered heterocyclyl, C_6 aryl, 5-6-membered heteroaryl, -(C_1-C_3 alkylene)(C_3-C_6 cycloalkyl), -(C_1-C_3 alkylene)(3-6-membered heterocyclyl), -(C_1-C_3 alkylene)(C_6 aryl) or -(C_1-C_3 alkylene)(5-6-membered heteroaryl), wherein each of which is optionally substituted by methyl, ethyl, halogen, oxo, $-CF_3$, -OH, $-OCH_3$, -CN, $-C(O)OCH_3$, $-C(O)OC_2H_5$, $-NH_2$ or $-NHCH_3$;

or R^{1b} and R^{1c} are taken together with the nitrogen atom to which they are attached to form a 3- to 6-membered heterocyclyl;

R^2 is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_6-C_{14} aryl, C_5-C_{14} heteroaryl, C_3-C_6 cycloalkyl, 3- to 6-membered heterocyclyl, -CN, halogen, $-OR^{2a}$, $-SR^{2a}$, $-NR^{2b}R^{2c}$, $-C(O)R^{2a}$, $-NR^{2b}C(O)R^{2c}$, $-NR^{2a}C(O)NR^{2b}R^{2c}$, $-C(O)OR^{2a}$, $-C(O)ONR^{2b}R^{2c}$ or $-C(O)NR^{2b}R^{2c}$, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_6-C_{14} aryl, C_3-C_6 cycloalkyl and 3- to 6-membered heterocyclyl of R^2 are independently optionally substituted by R^4;

each R^{2a} is independently hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, 3- to 6-membered heterocyclyl, C_6-aryl, 5- to 6-membered heteroaryl, -(C_1-C_3 alkylene)$N(C_2H_5)_2$, -(C_1-C_3 alkylene)(C_3-C_6 cycloalkyl), -(C_1-C_3 alkylene)(3-6-membered heterocyclyl), -(C_1-C_3 alkylene)(5-6-membered heteroaryl) or -(C_1-C_3 alkylene)(C_6 aryl), wherein each of which is optionally substituted by methyl, ethyl, halogen, oxo, $-CF_3$, -OH, $-OCH_3$, -CN, $-C(O)OCH_3$, $-C(O)OC_2H_5$, $-NH_2$ or $-NHCH_3$;

each R^{2b} and R^{2c} is independently hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, 3- to 6-membered heterocyclyl, C_6-aryl, 5- to 6-membered heteroaryl, -(C_1-C_3 alkylene)$N(C_2H_5)_2$, -(C_1-C_3 alkylene)(C_3-C_6 cycloalkyl), -(C_1-C_3 alkylene)(3-6-membered heterocyclyl), -(C_1-C_3 alkylene)(C_6 aryl) or -(C_1-C_3 alkylene)(5-6-membered heteroaryl), wherein each of which is optionally substituted by methyl, ethyl, halogen, oxo, $-CF_3$, -OH, $-OCH_3$, -CN, $-C(O)OCH_3$, $-C(O)OC_2H_5$, $-NH_2$ or $-NHCH_3$;

or R^{2b} and R^{2c} are taken together with the nitrogen atom to which they are attached to form a 3- to 6-membered heterocyclyl;

each R^3 is independently C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, -CN, $-OR^5$, $-SR^5$, $-NR^6R^7$, $-NO_2$, $-C{=}NH(OR^5)$, $-C(O)R^5$, $-OC(O)R^5$, $-C(O)OR^5$, $-C(O)NR^6R^7$, $-OC(O)NR^6R^7$, $-NR^5C(O)R^6$, $-NR^5C(O)OR^6$, $-NR^5C(O)NR^6R^7$, $-S(O)R^5$, $-S(O)_2R^5$, $-NR^5S(O)R^6$, $-C(O)NR^5S(O)R^6$, $-NR^5S(O)_2R^6$, $-C(O)NR^5S(O)_2R^6$, $-S(O)NR^6R^7$, $-S(O)_2NR^6R^7$, $-P(O)(OR^6)$

(OR^7), C_3-C_6 cycloalkyl, 3-12-membered heterocyclyl, 5- to 10-membered heteroaryl, C_6-C_{14} aryl, -(C_1-C_3 alkylene)CN, -(C_1-C_3 alkylene)OR^5, -(C_1-C_3 alkylene)SR^5, -(C_1-C_3 alkylene)NR^6R^7, -(C_1-C_3 alkylene)CF_3, -(C_1-C_3 alkylene)NO_2, -C=NH(OR^5), -(C_1-C_3 alkylene)C(O)R^5, -(C_1-C_3 alkylene)OC(O)R^5, -(C_1-C_3 alkylene)C(O)OR^5, -(C_1-C_3 alkylene)C(O)NR^6R^7, -(C_1-C_3 alkylene)OC(O)NR^6R^7, -(C_1-C_3 alkylene)NR^5C(O)R^6, -(C_1-C_3 alkylene)NR^5C(O)OR^6, -(C_1-C_3 alkylene)NR^5C(O)NR^6R^7, -(C_1-C_3 alkylene)S(O)R^5, -(C_1-C_3 alkylene)$S(O)_2R^5$, -(C_1-C_3 alkylene)NR^5S(O)R^6, -C(O)(C_1-C_3 alkylene)NR^5S(O)R^6, -(C_1-C_3 alkylene)$NR^5S(O)_2R^6$, -(C_1-C_3 alkylene)C(O)$NR^5S(O)_2R^6$, -(C_1-C_3 alkylene)S(O)NR^6R^7, -(C_1-C_3 alkylene)$S(O)_2NR^6R^7$, -(C_1-C_3 alkylene)P(O)(OR^6)(OR^7), -(C_1-C_3 alkylene)(C_3-C_6 cycloalkyl), -(C_1-C_3 alkylene)(3-12-membered heterocyclyl), -(C_1-C_3 alkylene)(5-10-membered heteroaryl) or -(C_1-C_3 alkylene)(C_6-C_{14} aryl), wherein each R^3 is independently optionally substituted by halogen, oxo, -OR^8, -NR^8R^9, -C(O)R^8, -CN, -S(O)R^8, -$S(O)_2R^8$, -P(O)(OR^8)(OR^9), -(C_1-C_3 alkylene)OR^8, -(C_1-C_3 alkylene)NR^8R^9, -(C_1-C_3 alkylene)C(O)R^8, -(C_1-C_3 alkylene)S(O)R^8, -(C_1-C_3 alkylene)$S(O)_2R^8$, -(C_1-C_3 alkylene)P(O)(OR^8)(OR^9), C_3-C_8 cycloalkyl, or C_1-C_6 alkyl optionally substituted by oxo, -OH or halogen;

each R^4 is independently oxo or R^3;

R^5 is independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{14} aryl, 5-6-membered heteroaryl or 3-6-membered heterocyclyl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{14} aryl, 5-6-membered heteroaryl and 3-6-membered heterocyclyl of R^5 are independently optionally substituted by halogen, oxo, -CN, -OR^9, -NR^9R^{10}, -P(O)(OR^9)(OR^{10}), phenyl optionally substituted by halogen, or C_1-C_6 alkyl optionally substituted by halogen, -OH or oxo;

R^6 and R^7 are each independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{14} aryl, 5-6-membered heteroaryl, -(C_1-C_3 alkylene)(C_6 aryl) or 3-6 membered heterocyclyl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{14} aryl, 5-6-membered heteroaryl, -(C_1-C_3 alkylene)(C_6 aryl) and 3-6 membered heterocyclyl of R^6 and R^7 are independently optionally substituted by halogen, oxo, -CN, -OR^9, -NR^9R^{10} or C_1-C_6 alkyl optionally substituted by halogen, -OH or oxo;

or R^6 and R^7 are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo, -OR^9, -NR^9R^{10} or C_1-C_6 alkyl optionally substituted by halogen, oxo or -OH;

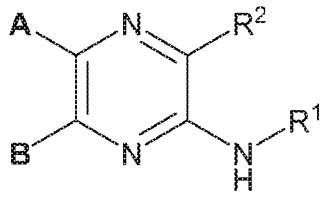
R^8 and R^9 in R^3 are each independently hydrogen, C_1-C_6 alkyl optionally substituted by halogen or oxo, C_2-C_6 alkenyl optionally substituted by halogen or oxo, or C_2-C_6 alkynyl optionally substituted by halogen or oxo;

or R^8 and R^9 in R^3 are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo or C_1-C_6 alkyl optionally substituted by halogen or oxo; and

R^9 and R^{10} in R^5, R^6 and R^7 are each independently hydrogen, C_1-C_6 alkyl optionally substituted by halogen or oxo, C_2-C_6 alkenyl optionally substituted by halogen or oxo, or C_2-C_6 alkynyl optionally substituted by halogen or oxo;

or R^9 and R^{10} in R^5, R^6 and R^7 are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo or C_1-C_6 alkyl optionally substituted by oxo or halogen.

[0037] In some embodiments, provided is a compound of the formula (I):



(I),

or a salt thereof, wherein:

A is 4-hydroxyphenyl optionally further substituted by R^3, 4-hydroxy-2-pyridyl optionally further substituted by R^4, or a 9- or 10-membered bicyclic heteroaryl optionally substituted by R^4;

B is a phenyl optionally substituted by R^3, or a 5- to 6-membered heteroaryl optionally substituted by R^4;

R^1 is a 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, $-C(O)R^{1a}$, $-C(O)OR^{1a}$, $-C(O)NR^{1b}R^{1c}$, or $-NR^{1b}R^{1c}$, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl and 3- to 6-membered heterocyclyl of R^1 are independently optionally substituted by R^4;

each R^{1a} is independently hydrogen, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl;

each R^{1b} and R^{1c} is independently hydrogen, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl;

or R^{1b} and R^{1c} are taken together with the nitrogen atom to which they are attached to form a 3- to 6-membered heterocyclyl;

R^2 is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_6-C_{14} aryl, -CN, halogen, $-OR^{2a}$, $-NR^{2b}R^{2c}$, $-C(O)R^{2a}$, $-C(O)OR^{2a}$, or $-C(O)NR^{2b}R^{2c}$, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl and C_6-C_{14} aryl of R^2 are independently optionally substituted by R^4;

each R^{2a} is independently hydrogen, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl;

each R^{2b} and R^{2c} is independently hydrogen, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl;

or R^{2b} and R^{2c} are taken together with the nitrogen atom to which they are attached to form a 3- to 6-membered heterocyclyl;

each R^3 is independently C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, -CN, $-OR^5$, $-SR^5$, $-NR^6R^7$, $-NO_2$, $-C{=}NH(OR^5)$, $-C(O)R^5$, $-OC(O)R^5$, $-C(O)OR^5$, $-C(O)NR^6R^7$, $-OC(O)NR^6R^7$, $-NR^5C(O)R^6$, $-NR^5C(O)OR^6$, $-NR^5C(O)NR^6R^7$, $-S(O)R^5$, $-S(O)_2R^5$, $-NR^5S(O)R^6$, $-C(O)NR^5S(O)R^6$, $-NR^5S(O)_2R^6$, $-C(O)NR^5S(O)_2R^6$, $-S(O)NR^6R^7$, $-S(O)_2NR^6R^7$, $-P(O)(OR^6)(OR^7)$, C_3-C_6 cycloalkyl, 3-12-membered heterocyclyl, 5- to 10-membered heteroaryl, C_6-C_{14} aryl, -(C_1-C_3 alkylene)CN, -(C_1-C_3 alkylene)OR^5, -(C_1-C_3 alkylene)SR^5, -(C_1-C_3 alkylene)NR^6R^7, -(C_1-C_3 alkylene)CF_3, -(C_1-C_3 alkylene)NO_2, -(C_1-C_3 alkylene)$C{=}NH(OR^5)$, -(C_1-C_3 alkylene)$C(O)R^5$, -(C_1-C_3 alkylene)$OC(O)R^5$, -(C_1-C_3 alkylene)$C(O)OR^5$, -(C_1-C_3 alkylene)$C(O)NR^6R^7$, -(C_1-C_3 alkylene)$OC(O)NR^6R^7$, -(C_1-C_3 alkylene)$NR^5C(O)R^6$, -(C_1-C_3 alkylene)$NR^5C(O)OR^6$, -(C_1-C_3 alkylene)$NR^5C(O)NR^6R^7$, -(C_1-C_3 alkylene)$S(O)R^5$, -(C_1-C_3 alkylene)$S(O)_2R^5$, -(C_1-C_3 alkylene)$NR^5S(O)R^6$, -$C(O)$(C_1-C_3 alkylene)$NR^5S(O)R^6$, -(C_1-C_3 alkylene)$NR^5S(O)_2R^6$, -(C_1-C_3 alkylene)$C(O)NR^5S(O)_2R^6$, -(C_1-C_3 alkylene)$S(O)NR^6R^7$, -(C_1-C_3 alkylene)$S(O)_2NR^6R^7$, -(C_1-C_3 alkylene)$P(O)(OR^6)(OR^7)$, -(C_1-C_3 alkylene)(C_3-C_6 cycloalkyl), -(C_1-C_3 alkylene)(3-12-membered heterocyclyl), -(C_1-C_3 alkylene)(5-10-membered heteroaryl) or -(C_1-C_3 alkylene)(C_6-C_{14} aryl), wherein each R^3 is independently optionally substituted by halogen, oxo, $-OR^8$, $-NR^8R^9$, $-C(O)R^8$, -CN, $-S(O)R^8$, $-S(O)_2R^8$, $-P(O)(OR^8)(OR^9)$, -(C_1-C_3 alkylene)OR^8, -(C_1-C_3 alkylene)NR^8R^9, -(C_1-C_3 alkylene)$C(O)R^8$, -(C_1-C_3 alkylene)$S(O)R^8$, -(C_1-C_3 alkylene)$S(O)_2R^8$, -(C_1-C_3 alkylene)$P(O)(OR^8)(OR^9)$, C_3-C_8 cycloalkyl, or C_1-C_6 alkyl optionally substituted by oxo, -OH or halogen;

each R^4 is independently oxo or R^3;

R^5 is independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{14} aryl, 5-6-membered heteroaryl or 3-6-membered heterocyclyl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{14} aryl, 5-6-membered heteroaryl and 3-6-membered heterocyclyl of R^5 are independently optionally substituted by

halogen, oxo, -CN, -OR^9, -NR^9R^{10}, -$P(O)(OR^9)(OR^{10})$, phenyl optionally substituted by halogen, or C_1-C_6 alkyl optionally substituted by halogen, -OH or oxo;

R^6 and R^7 are each independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{14} aryl, 5-6-membered heteroaryl or 3-6 membered heterocyclyl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{14} aryl, 5-6-membered heteroaryl and 3-6 membered heterocyclyl of R^6 and R^7 are independently optionally substituted by halogen, oxo, -CN, -OR^9, -NR^9R^{10} or C_1-C_6 alkyl optionally substituted by halogen, -OH or oxo;

or R^6 and R^7 are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo, -OR^9, -NR^9R^{10} or C_1-C_6 alkyl optionally substituted by halogen, oxo or -OH;

R^8 and R^9 are each independently hydrogen, C_1-C_6 alkyl optionally substituted by halogen or oxo, C_2-C_6 alkenyl optionally substituted by halogen or oxo, or C_2-C_6 alkynyl optionally substituted by halogen or oxo;

or R^8 and R^9 are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo or C_1-C_6 alkyl optionally substituted by halogen or oxo; and

R^9 and R^{10} are each independently hydrogen, C_1-C_6 alkyl optionally substituted by halogen or oxo, C_2-C_6 alkenyl optionally substituted by halogen or oxo, or C_2-C_6 alkynyl optionally substituted by halogen or oxo;

or R^9 and R^{10} are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo or C_1-C_6 alkyl optionally substituted by oxo or halogen.

[0038] In some embodiments, the compound of formula (I) or a salt thereof is other than a compound selected from Table 1 or a salt thereof. In some embodiments, the compound of formula (I) or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing is other than a compound seletec from Table 1 or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

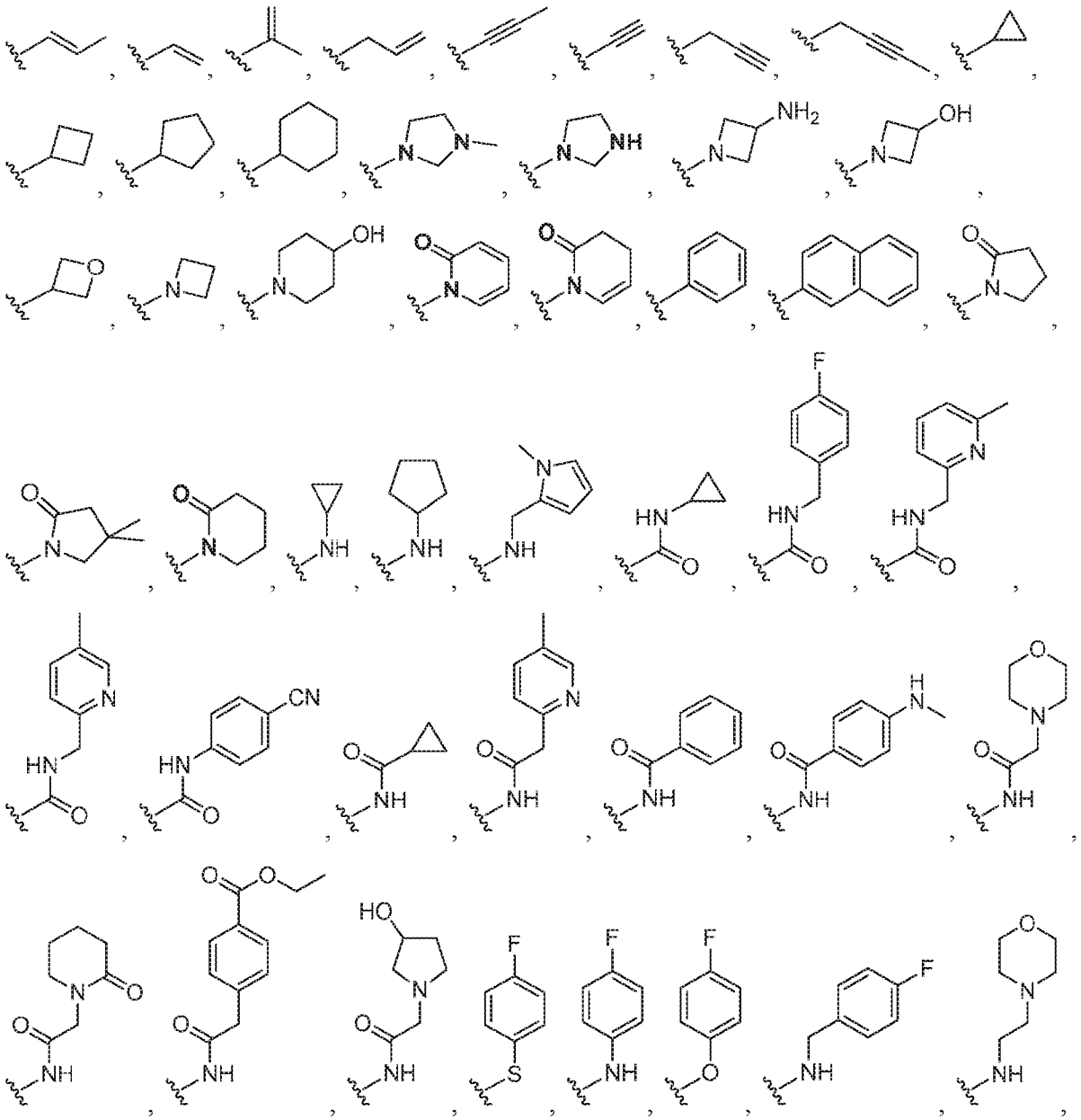
Table 1

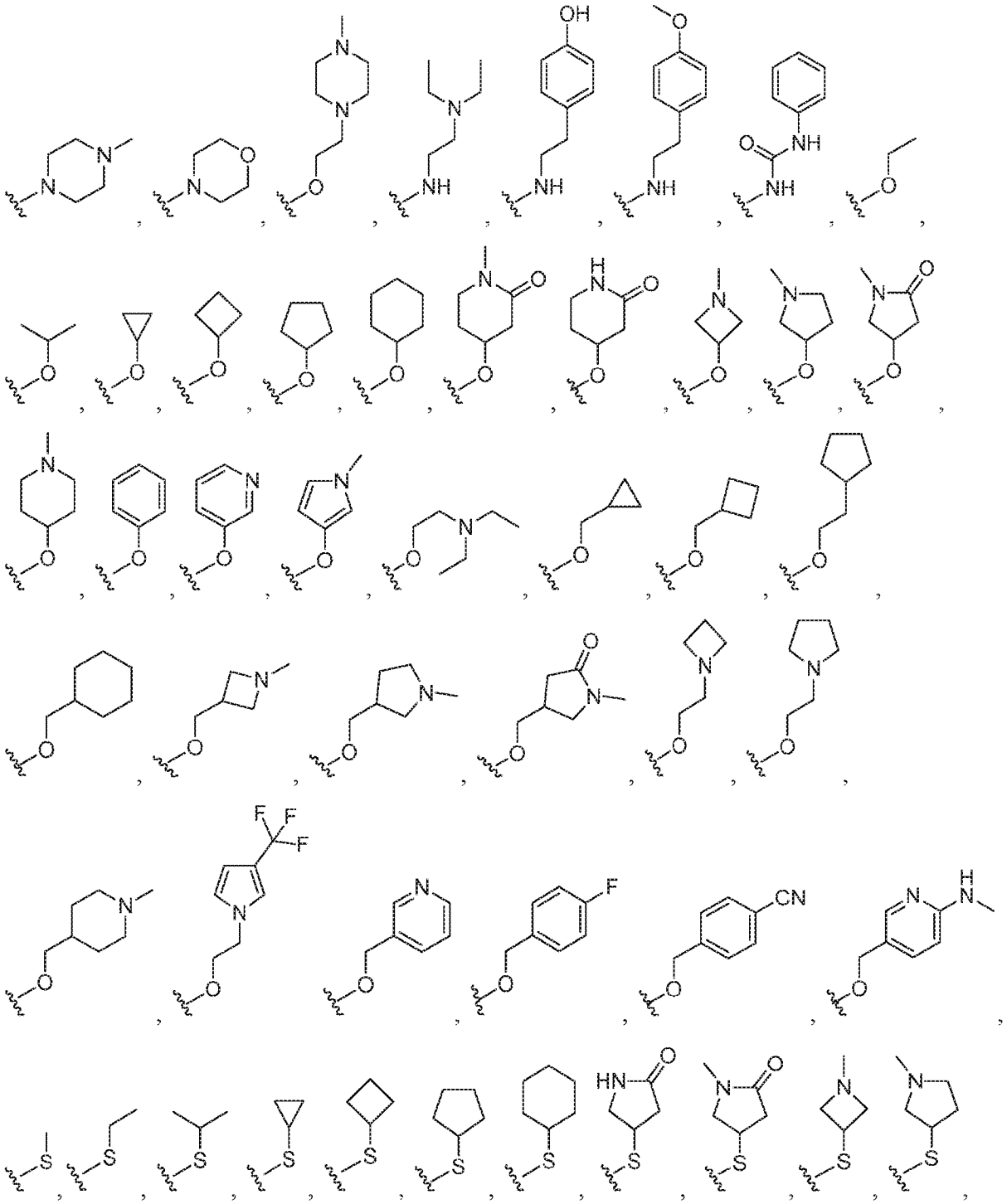
Compound No.	Compound Name

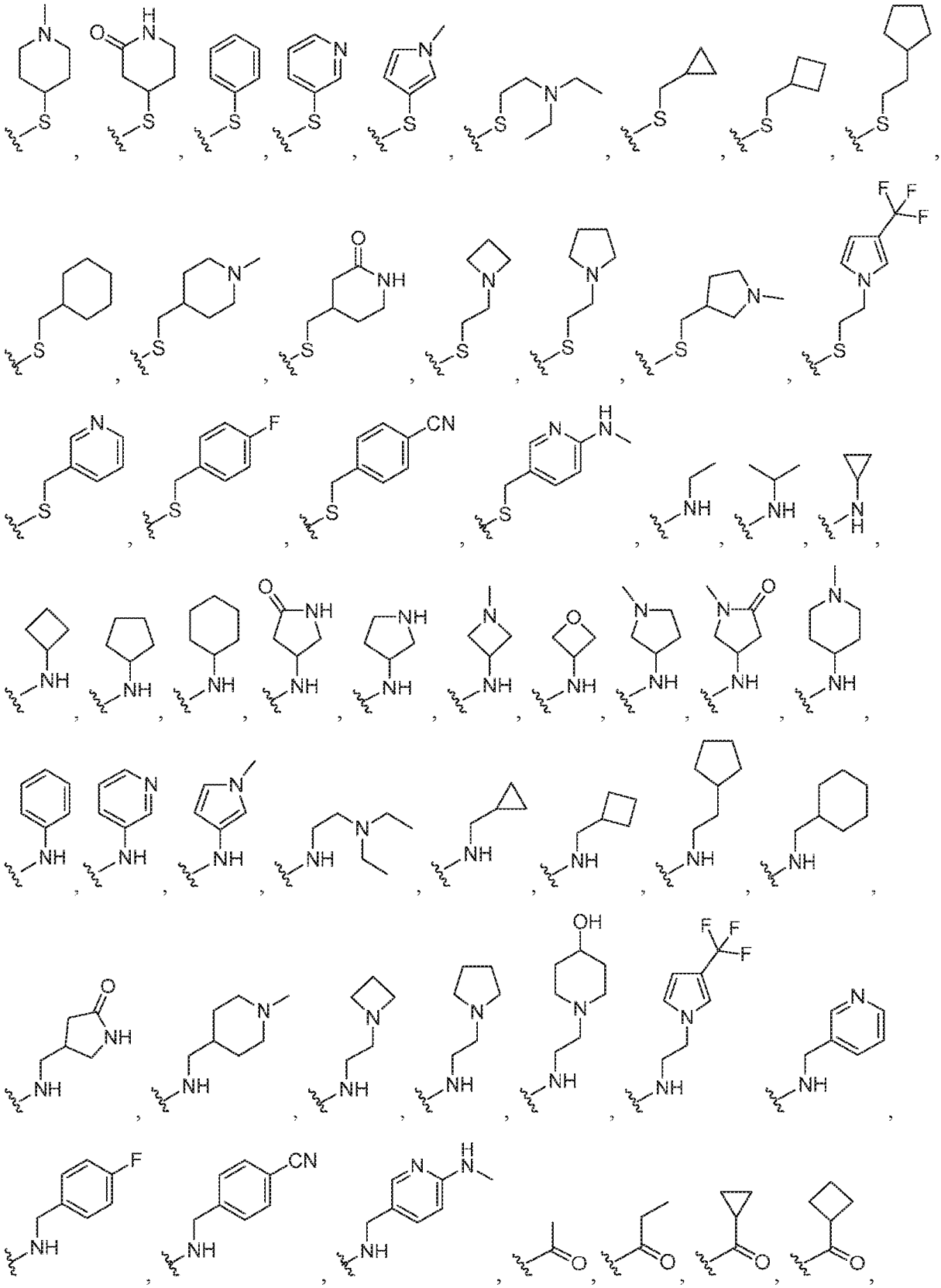
1x	5-(1-ethyl-1H-indol-5-yl)-6-(3-pyridinyl)-2-pyrazinamine
2x	5-(1-ethyl-1H-indol-5-yl)-6-(2H-tetrazol-5-yl)-2-pyrazinamine
3x	2-[6-amino-3-(1-ethyl-2-fluoro-1H-indol-5-yl)-2-pyrazinyl]-4-fluorophenol
4x	5-(1-ethyl-1H-indol-5-yl)-6-(3-thienyl)-2-pyrazinamine
5x	2-[6-amino-3-(1-ethyl-1H-indol-5-yl)-2-pyrazinyl]-6-fluorophenol
6x	5-(1-ethyl-1H-indol-5-yl)-6-(1H-pyrazol-3-yl)-2-pyrazinamine
7x	2-[6-amino-3-(1-ethyl-2-methyl-1H-indol-5-yl)-2-pyrazinyl]-4-fluorophenol
8x	5-[6-amino-3-(1-ethyl-1H-indol-5-yl)-2-pyrazinyl]-4(3H)-pyrimidinone
9x	5-(2-benzofuranyl)-6-(4-pyridinyl)-2,3-pyrazinediamine
10x	2-[6-amino-3-(1-ethyl-2-methyl-1H-benzimidazol-5-yl)-2-pyrazinyl]-4-fluorophenol
11x	5-(1-ethyl-1H-indol-5-yl)-6-(1H-pyrrol-2-yl)-2-pyrazinamine
12x	2-[6-amino-3-(1-ethyl-1H-indol-5-yl)-2-pyrazinyl]-4-fluorophenol
13x	3-[6-amino-3-(1-ethyl-1H-indol-5-yl)-2-pyrazinyl]-2(1H)-pyridinone
14x	5-(1-ethyl-1H-indol-5-yl)-6-[5-fluoro-2-(phenylmethoxy)phenyl]-2-pyrazinamine
15x	2-[6-amino-3-(1-ethyl-1H-benzimidazol-5-yl)-2-pyrazinyl]-4-fluorophenol
16x	5-(1-ethyl-1H-indol-5-yl)-6-(2-thienyl)-2-pyrazinamine
17x	2-[6-amino-3-(1-ethyl-1H-indol-5-yl)-2-pyrazinyl]phenol
18x	5,6-bis(1-phenyl-1H-benzimidazol-2-yl)-2,3-pyrazinediamine

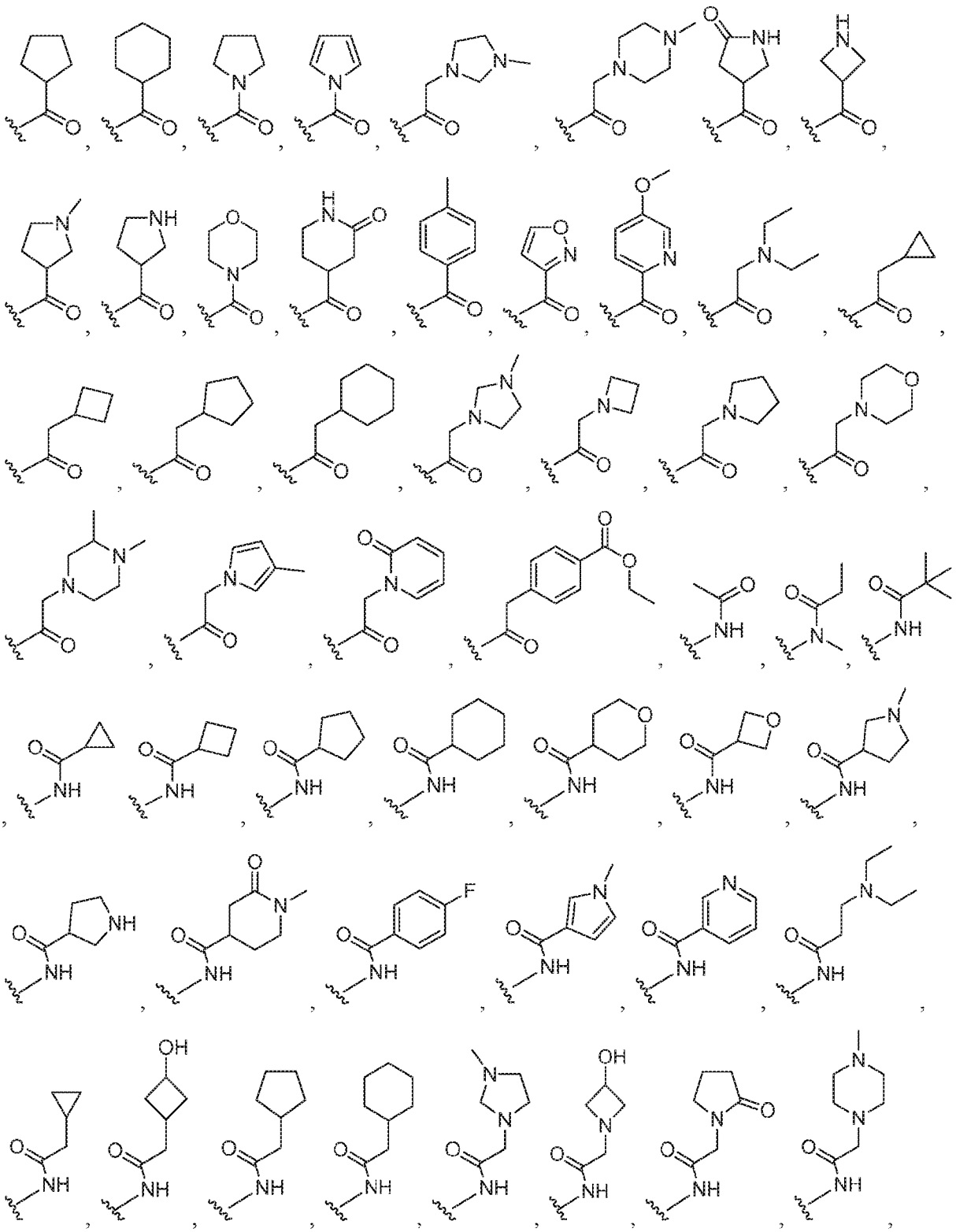
[0039] In some embodiments, R^1 is a hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 6-membered heterocyclyl, 5- to 10-membered heteroaryl, $-C(O)R^{1a}$, $-C(O)OR^{1a}$, $-C(O)NR^{1b}R^{1c}$, or $-S(O)_2R^{1a}$, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 6-membered heterocyclyl, and 5- to 10-membered heteroaryl are optionally substituted with R^4. In some embodiments, R^1 is hydrogen, C_1-C_6 alkyl or $-C(O)R^{1a}$. In certain embodiments, R^1 is hydrogen. In certain embodiments, R^1 is $-C(O)R^{1a}$ where R^{1a} is C_1-C_6 alkyl (e.g., methyl) or C_3-C_6 cycloalkyl. It is understood that each R^1 may be combined with each R^2, **A** and/or **B** the same as if each and every combination of R^1 with R^2, **A** and/or **B** were specifically and individually listed.

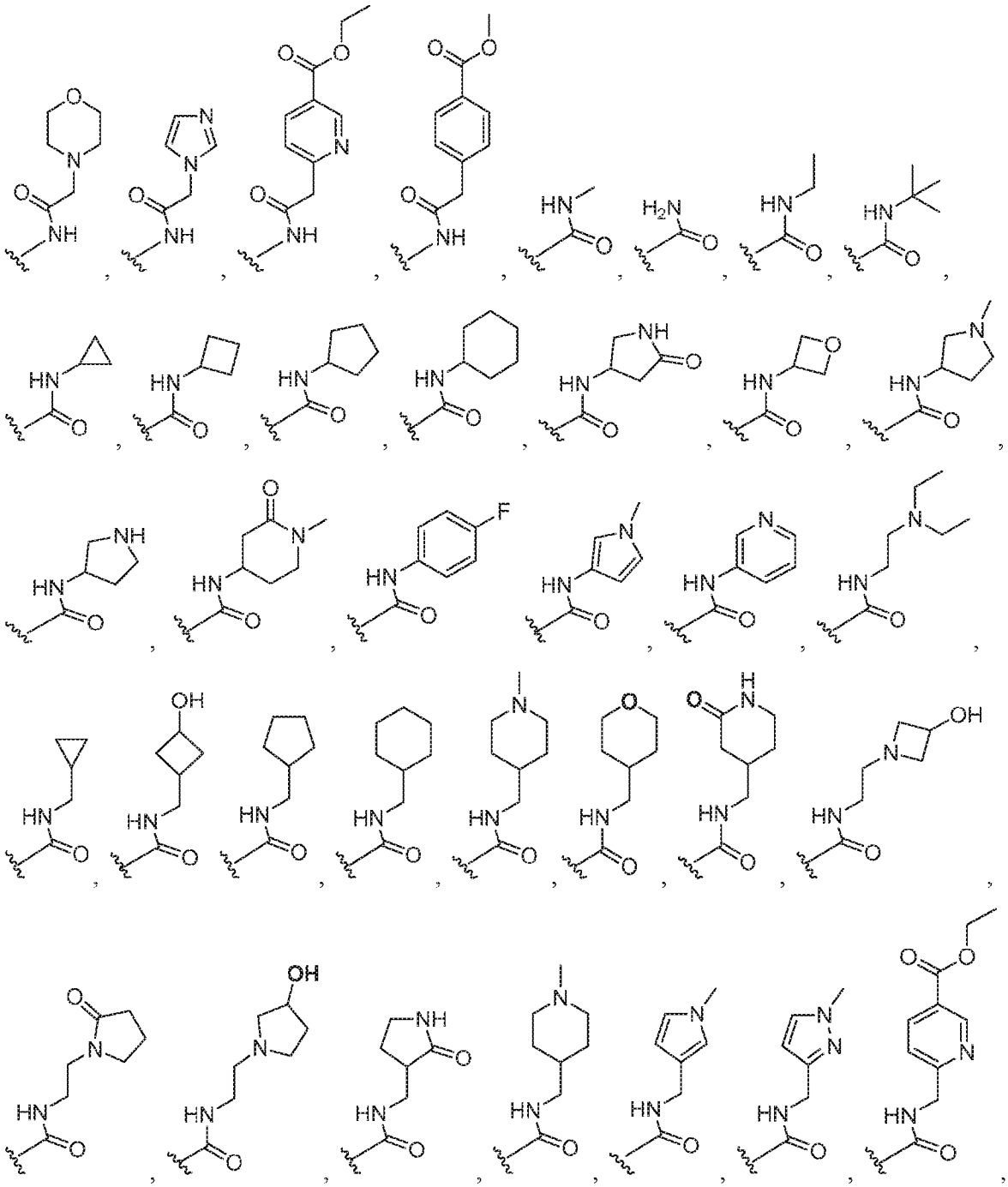
[0040] In some embodiments R^2 is selected from the group consisting of: hydrogen, fluoro, chloro, bromo, -CN, methyl, ethyl, isopropyl, propyl, tert-butyl, isopropenyl, $-OCH_3$, $-C(O)OCH_3$, $-C(O)OH$, $-C(O)ONH_2$, $-CH_2NH_2$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, -OH, $-CF_3$, $-OCF_3$,

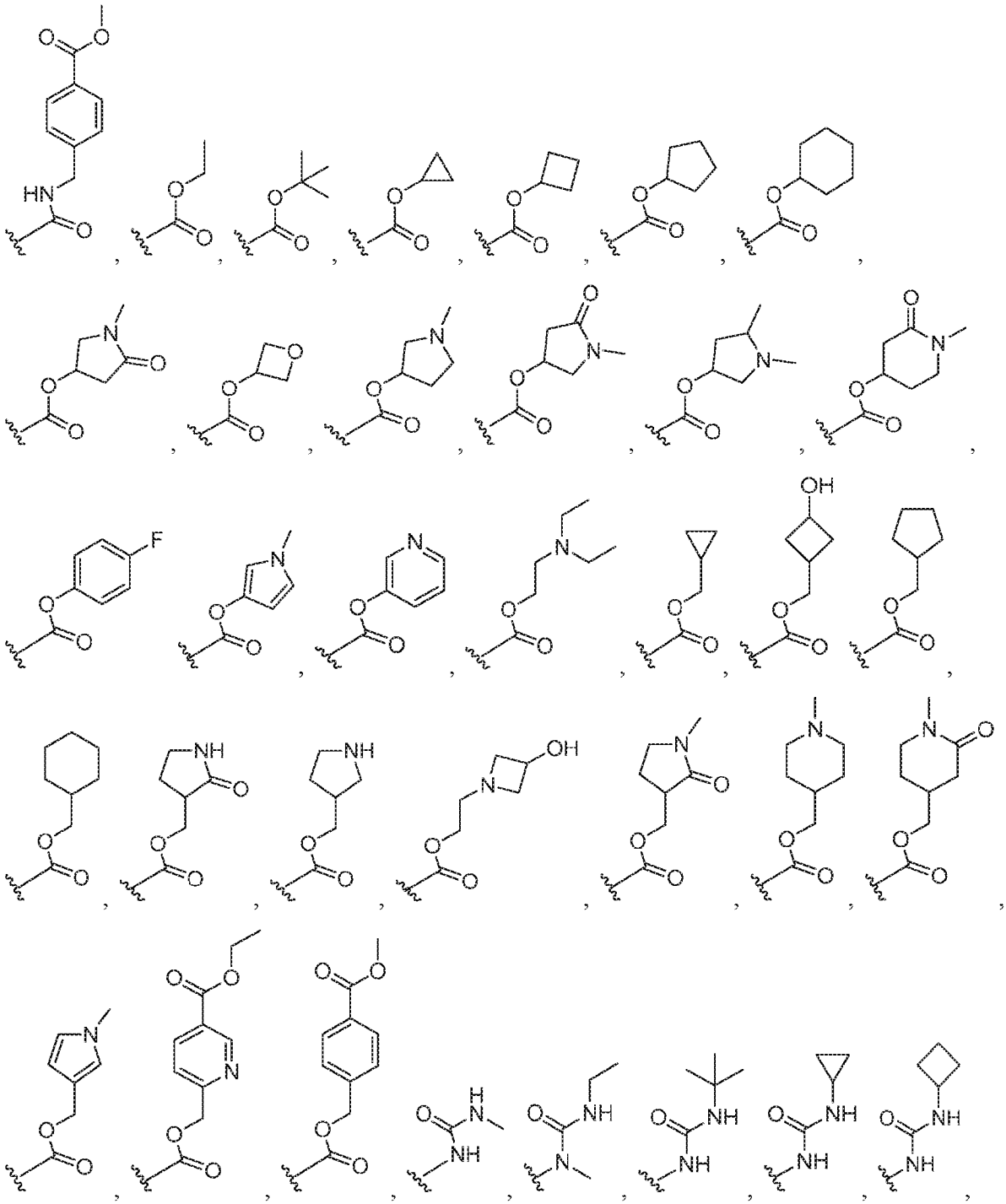


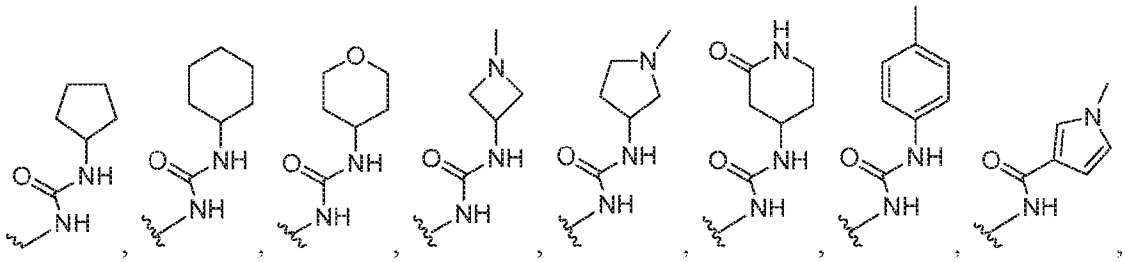
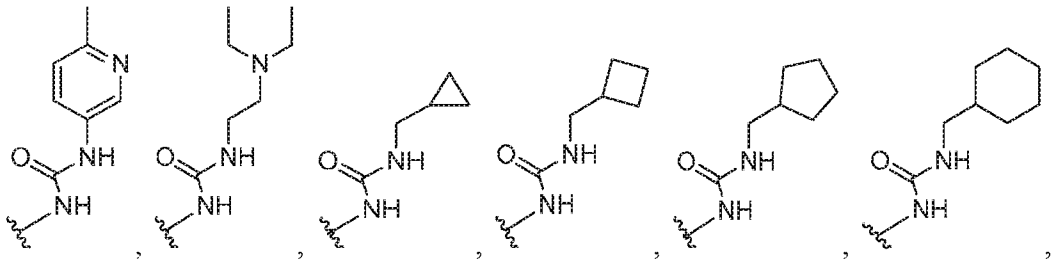
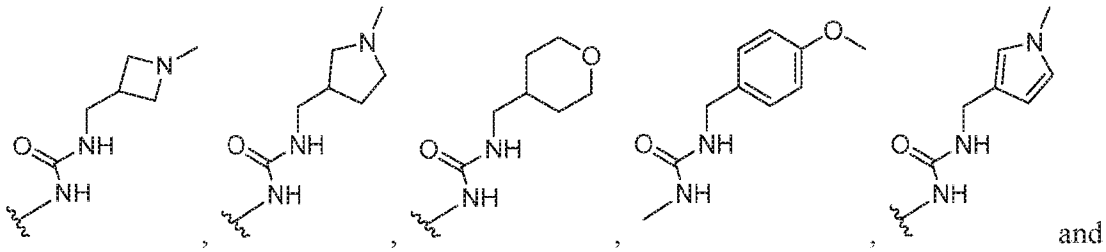
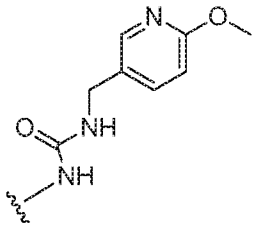




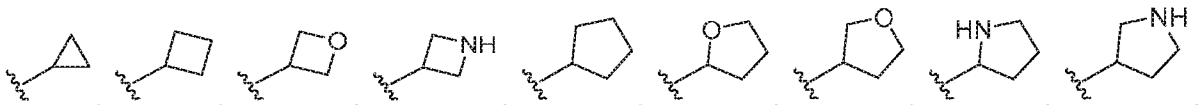
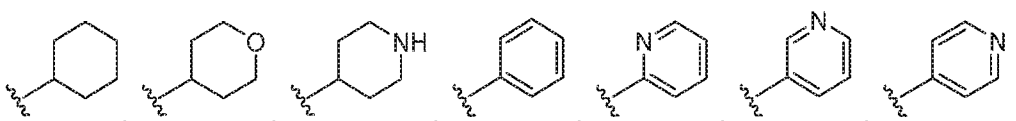
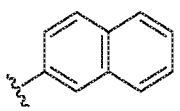




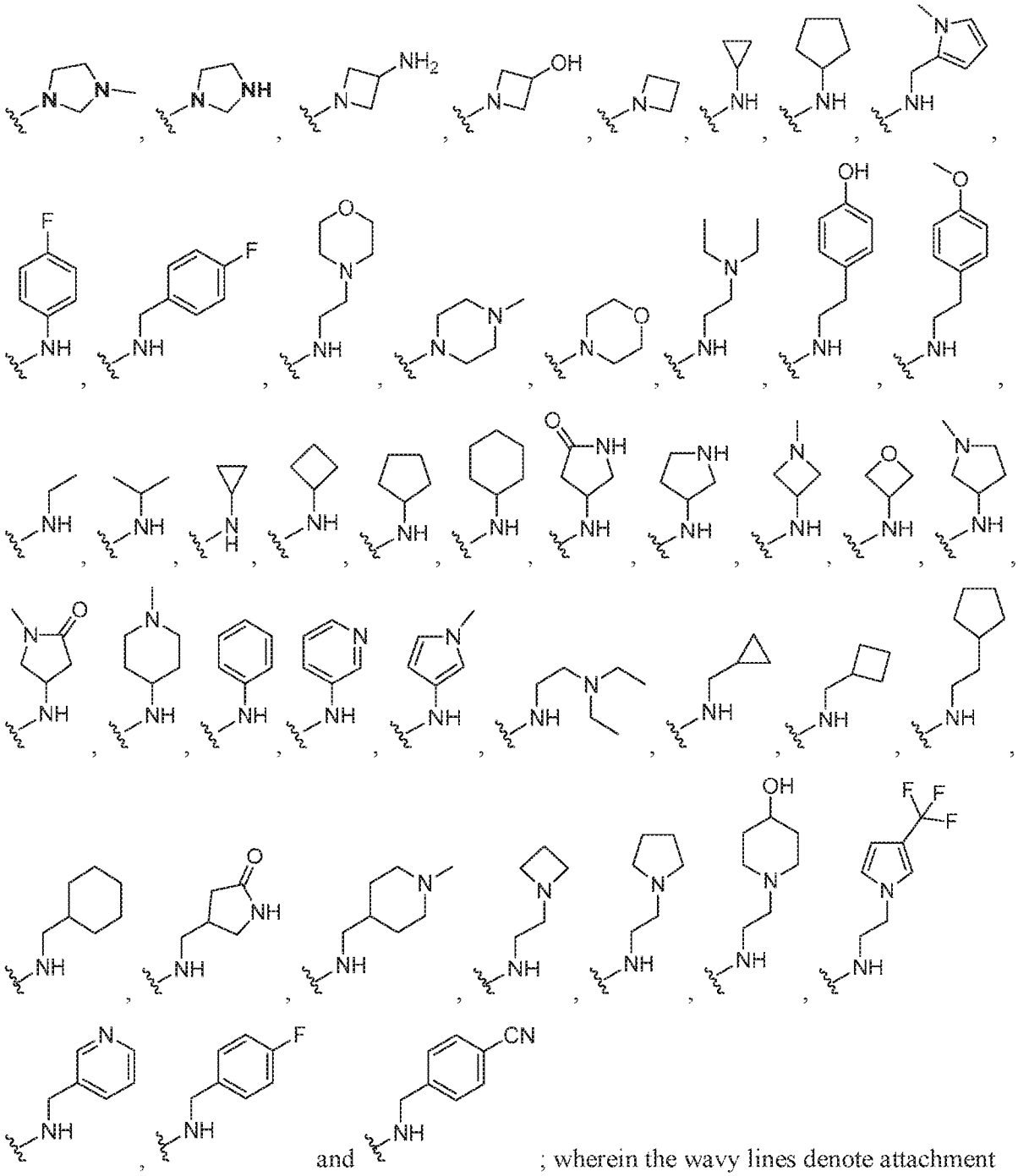





and

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

[0041] In some embodiments R^2 is selected from the group consisting of: hydrogen, fluoro, chloro, bromo, -CN, methyl, ethyl, isopropyl, propyl, tert-butyl, isopropenyl, $-OCH_3$, $-C(O)OCH_3$, $-C(O)OH$, $-C(O)ONH_2$, $-CH_2NH_2$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, -OH, $-CF_3$, $-OCF_3$,

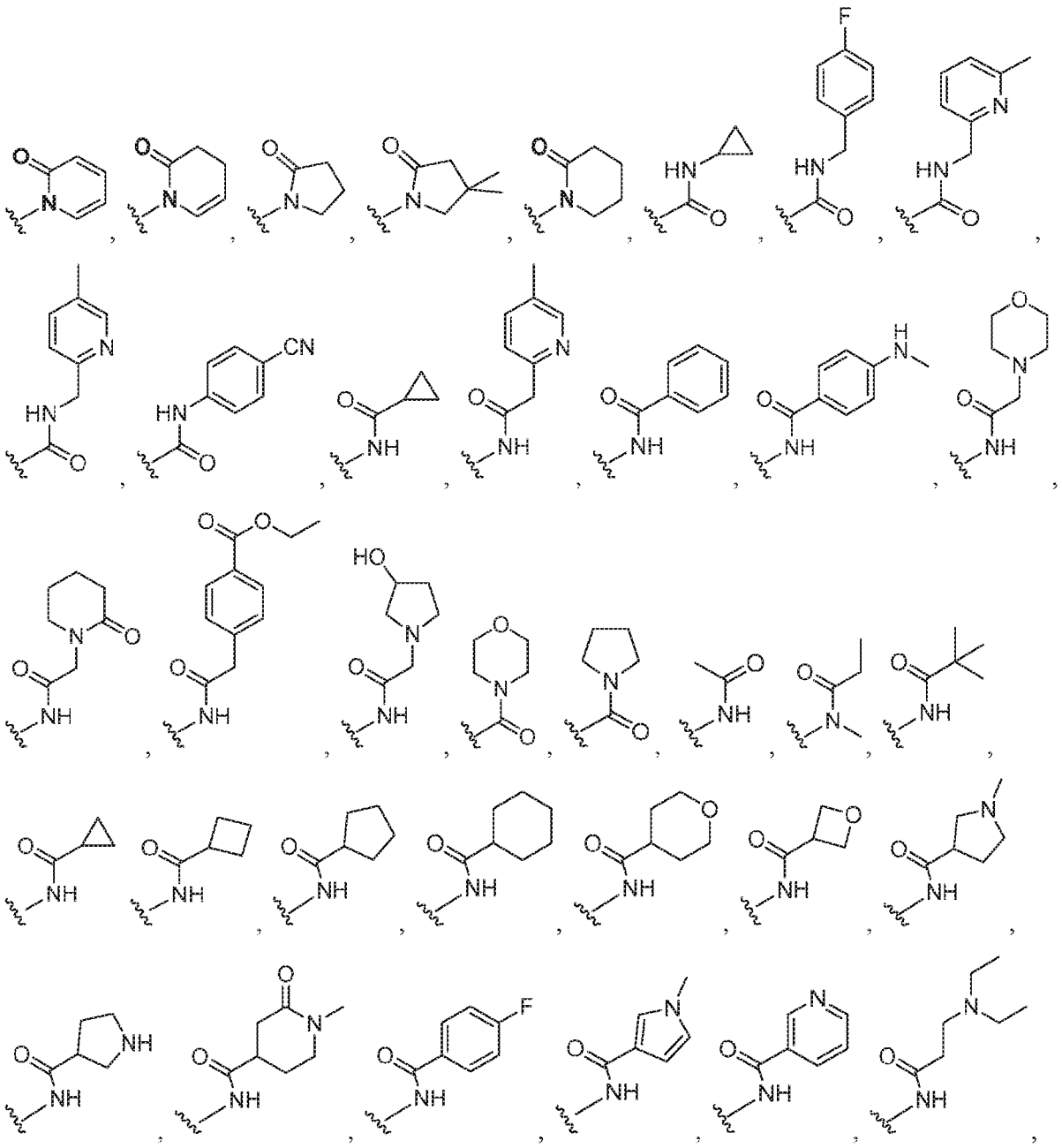


and

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

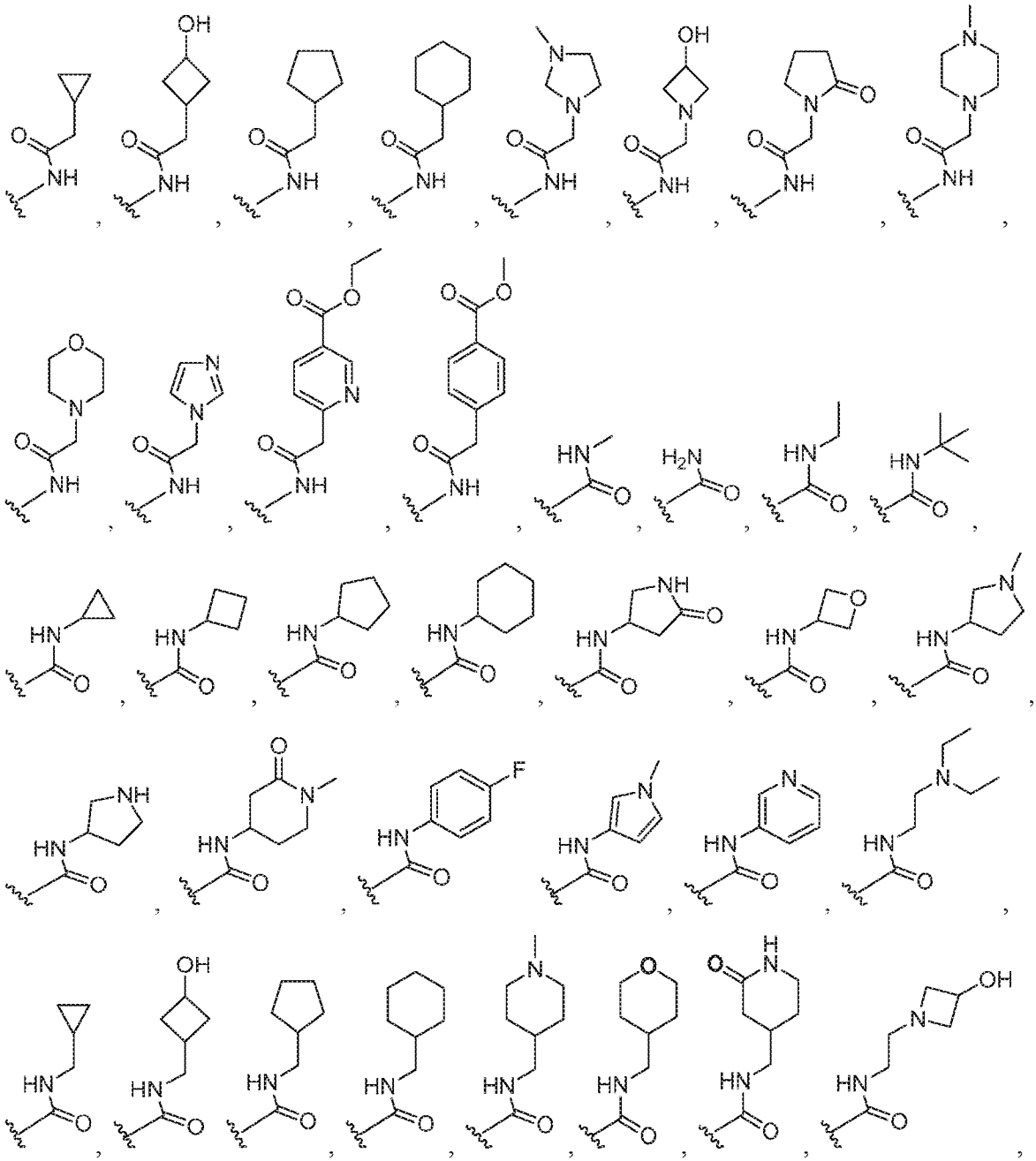
[0042] In some embodiments R^2 is selected from the group consisting of: hydrogen, fluoro, chloro, bromo, -CN, methyl, ethyl, isopropyl, propyl, tert-butyl, isopropenyl, $-OCH_3$, $-C(O)OCH_3$, $-C(O)OH$, $-C(O)ONH_2$, $-CH_2NH_2$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, -OH, $-CF_3$, $-OCF_3$,

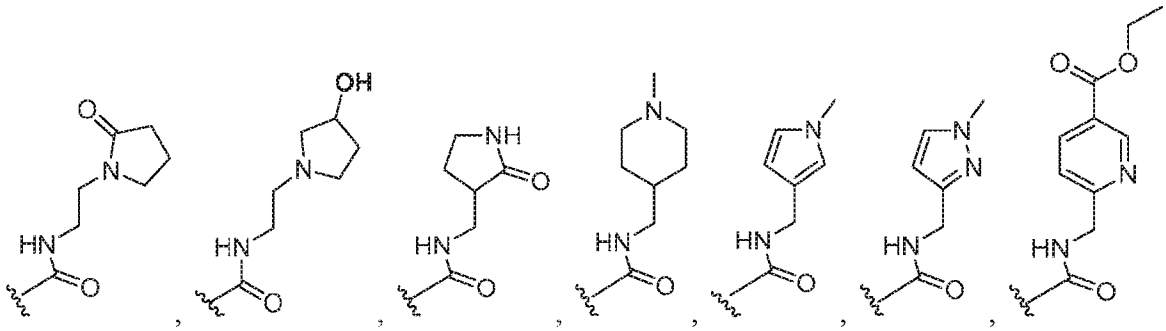
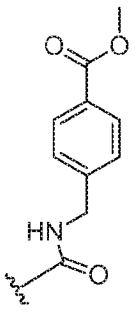


and ; wherein the wavy lines denote attachment points to the parent molecule.

[0043] In some embodiments R^2 is selected from the group consisting of: hydrogen, fluoro, chloro, bromo, -CN, methyl, ethyl, isopropyl, propyl, tert-butyl, isopropenyl $-OCH_3$, $-C(O)OCH_3$, $-C(O)OH$, $-C(O)ONH_2$, $-CH_2NH_2$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-OH$, $-CF_3$, $-OCF_3$,

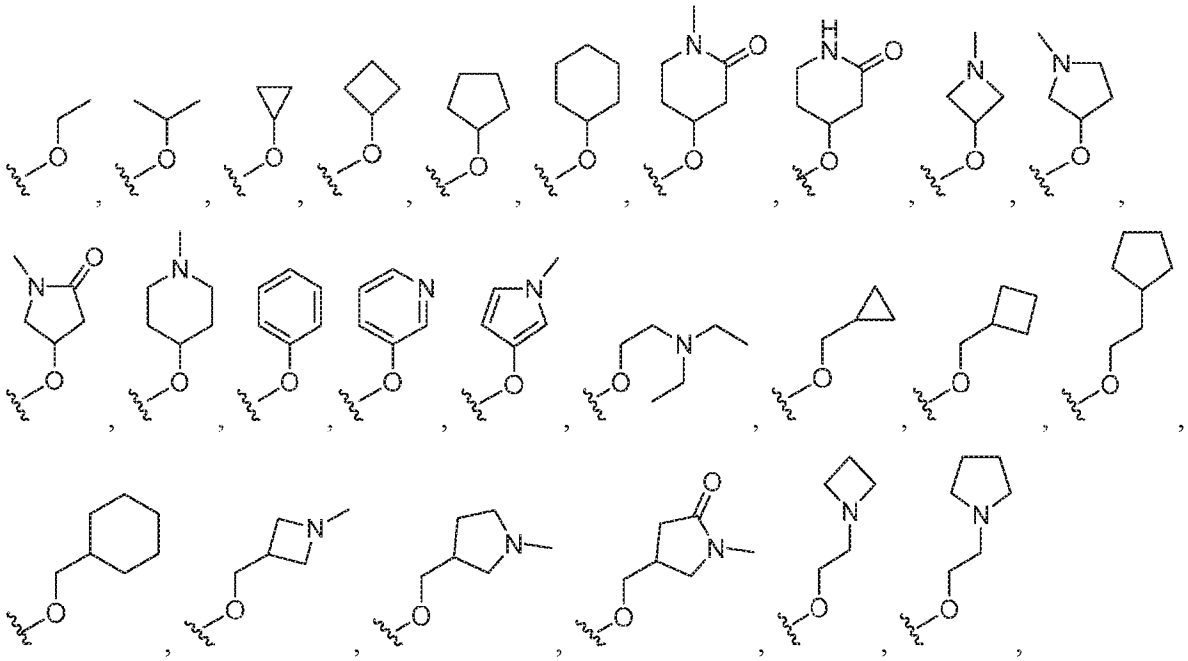


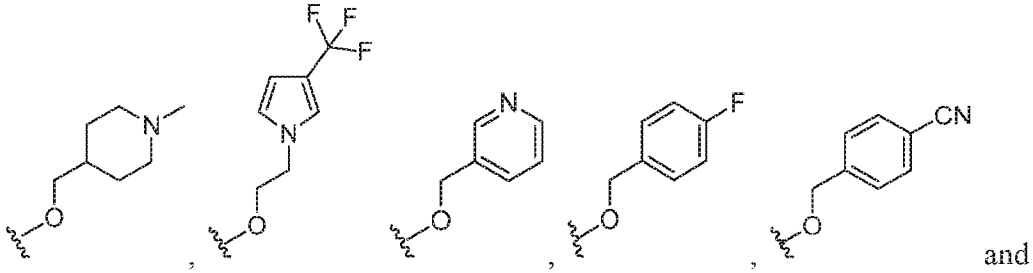


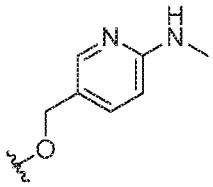



and ; wherein the wavy lines denote attachment points to the parent molecule.

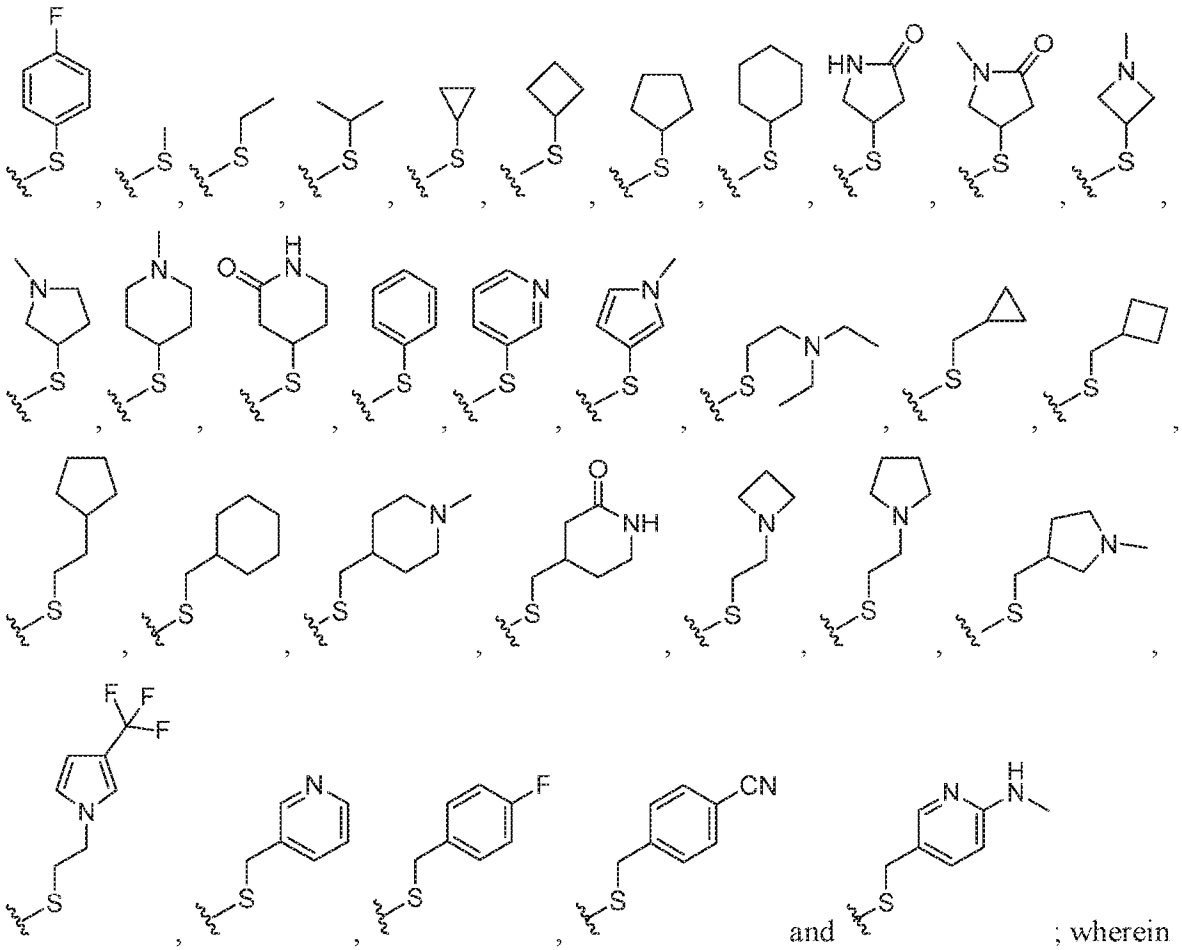
[0044] In some embodiments R^2 is selected from the group consisting of: hydrogen, fluoro, chloro, bromo, -CN, methyl, ethyl, isopropyl, propyl, tert-butyl, isopropenyl, $-OCH_3$, $-C(O)OCH_3$, $-C(O)OH$, $-C(O)ONH_2$, $-CH_2NH_2$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, -OH, $-CF_3$, $-OCF_3$,



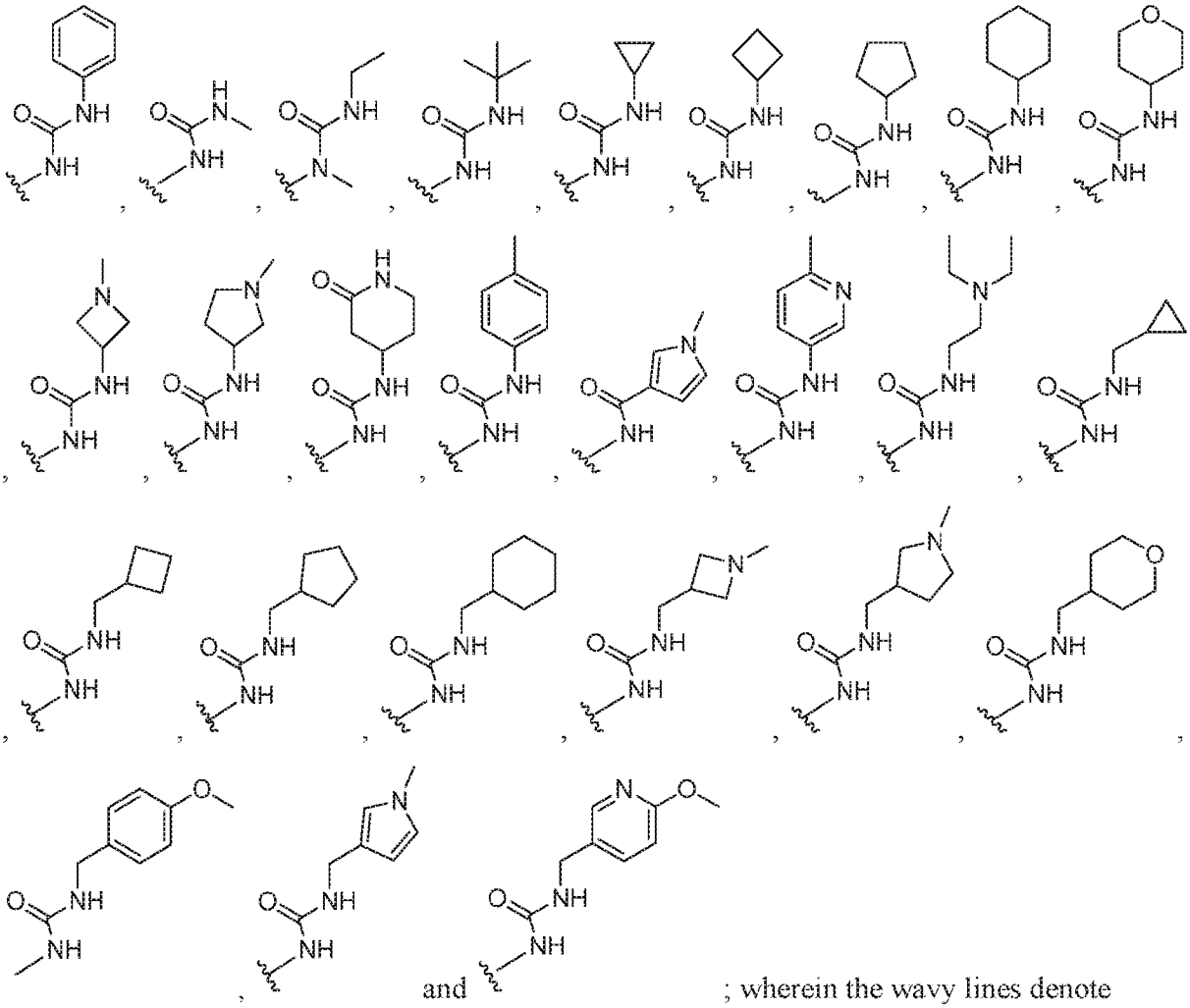

and


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

[0045] In some embodiments R^2 is selected from the group consisting of: hydrogen, fluoro, chloro, bromo, -CN, methyl, ethyl, isopropyl, propyl, tert-butyl, isopropenyl $-OCH_3$, $-C(O)OCH_3$, $-C(O)OH$, $-C(O)ONH_2$, $-CH_2NH_2$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, -OH, $-CF_3$, $-OCF_3$,

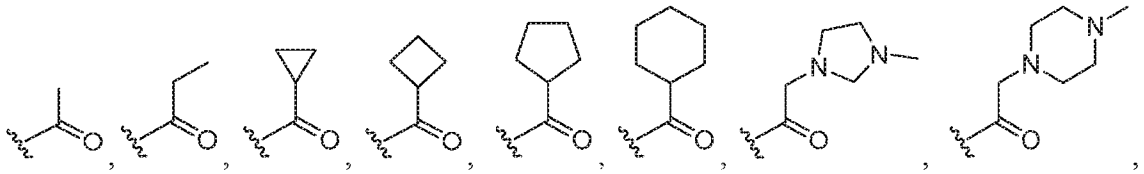

; wherein the wavy lines denote attachment points to the parent molecule.

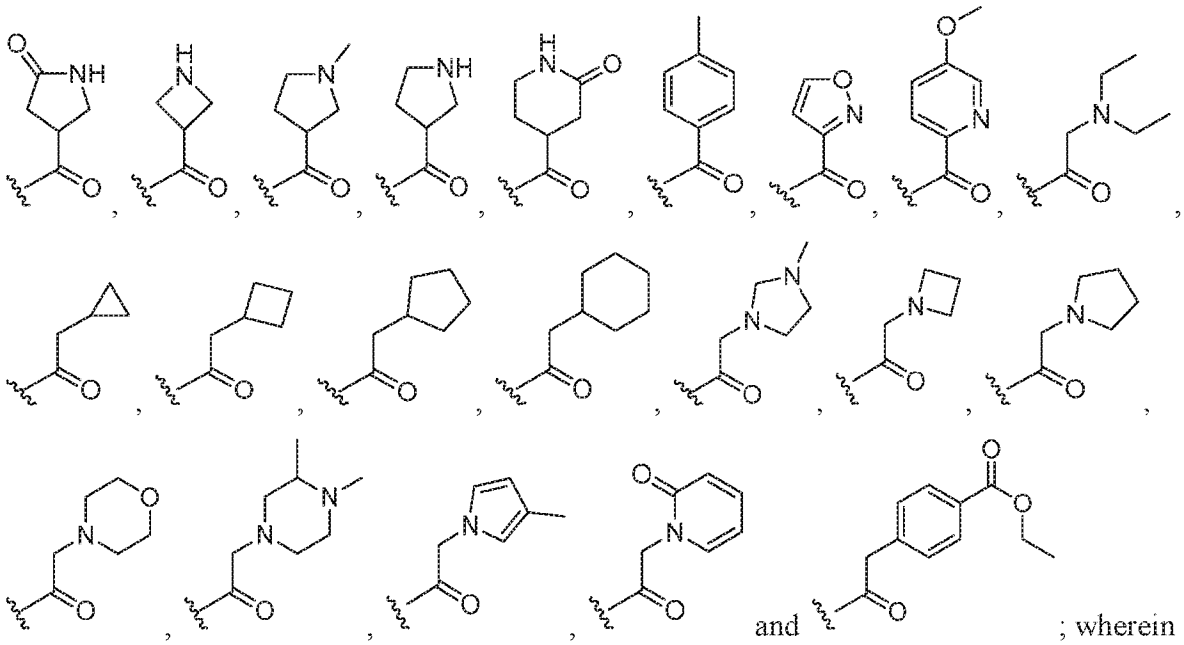
[0046] In some embodiments R^2 is selected from the group consisting of: hydrogen, fluoro, chloro, bromo, -CN, methyl, ethyl, isopropyl, propyl, tert-butyl, isopropenyl, $-OCH_3$, $-C(O)OCH_3$, $-C(O)OH$, $-C(O)ONH_2$, $-CH_2NH_2$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, -OH, $-CF_3$, $-OCF_3$,



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

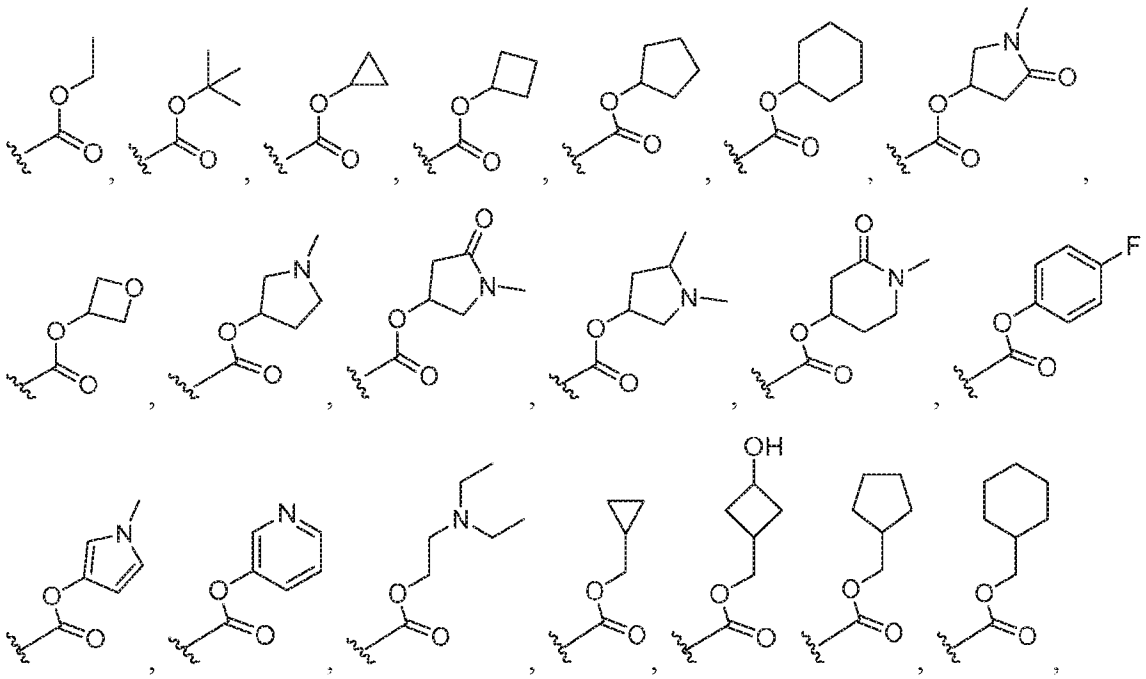
[0047] In some embodiments R^2 is selected from the group consisting of: hydrogen, fluoro, chloro, bromo, -CN, methyl, ethyl, isopropyl, propyl, tert-butyl, isopropenyl, $-OCH_3$, $-C(O)OCH_3$, $-C(O)OH$, $-C(O)ONH_2$, $-CH_2NH_2$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, -OH, $-CF_3$, $-OCF_3$,

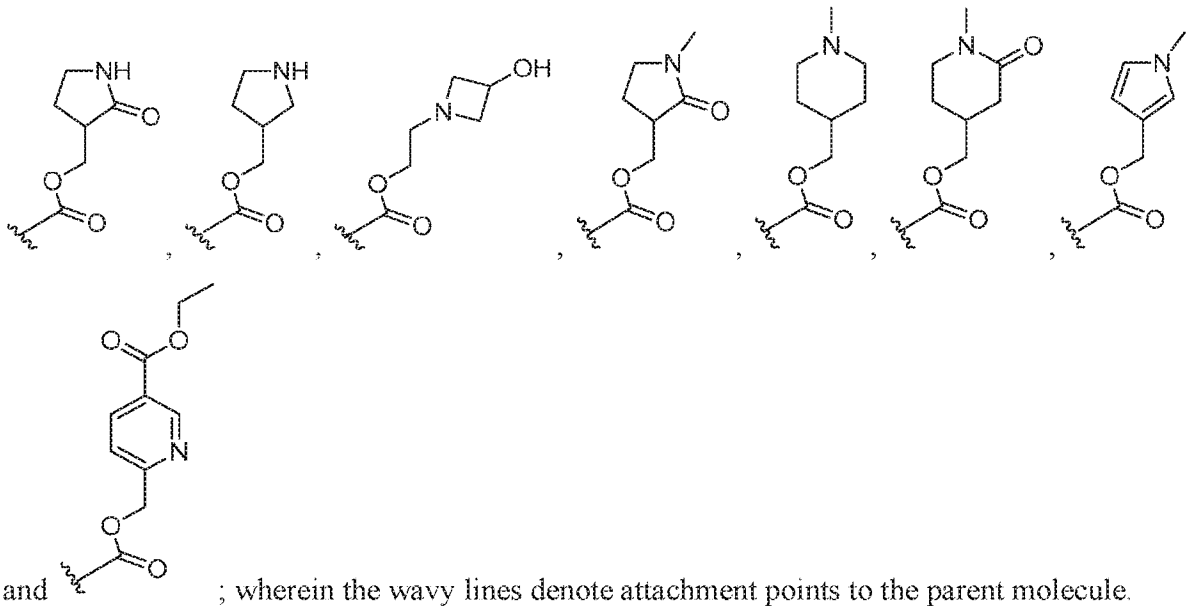




; wherein the wavy lines denote attachment points to the parent molecule.

[0048] In some embodiments R^2 is selected from the groups consisting of: hydrogen, fluoro, chloro, bromo, -CN, methyl, ethyl, isopropyl, propyl, tert-butyl, isopropenyl, $-OCH_3$, $-C(O)OCH_3$, -C(O)OH, $-C(O)ONH_2$, $-CH_2NH_2$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, -OH, $-CF_3$, $-OCF_3$,





and ; wherein the wavy lines denote attachment points to the parent molecule.

[0049] It is understood that each R^2 may be combined with each R^1, A and/or B the same as if each and every combination of R^2 with R^1, A and/or B were specifically and individually listed. In some embodiments R^2 is hydrogen, C_1-C_6 alkyl, -CN, halogen, -OR^{2a}, –$C(O)R^{2a}$, -$C(O)ONR^{2b}R^{2c}$, -$C(O)NR^{2b}R^{2c}$, -$NR^{2b}R^{2c}$, -$NR^{2b}C(O)R^{2c}$, -$NR^{2a}C(O)NR^{2b}R^{2c}$, -SR^{2a} or –$C(O)OR^{2a}$. In some embodiments, R^2 is hydrogen. In some embodiments, R^2 is C_1-C_6 alkyl (e.g., methyl). In some embodiments, R^2 is –CN. In some embodiments, R^2 is halogen (e.g., bromo). In some embodiments, R^2 is –OR^{2a} and in certain aspects R^{2a} is C_1-C_6 alkyl (e.g., methyl). In some embodiments, R^2 is $C(O)R^{2a}$ and in certain aspects R^{2a} is C_1-C_6 alkyl (e.g., methyl) or C_3-C_6 cycloalkyl. In some embodiments, R^2 is $C(O)OR^{2a}$ and in certain aspects R^{2a} is hydrogen or C_1-C_6 alkyl (e.g., methyl). In some embodiments, R^2 is -$C(O)NR^{2b}R^{2c}$ and in certain aspects R^{2b} and R^{2c} are independently hydrogen or C_1-C_6 alkyl (e.g., methyl) or C_3-C_6 cycloalkyl. In some embodiments, R^2 is -$NR^{2b}C(O)R^{2c}$ and in certain aspects R^{2b} and R^{2c} are independently hydrogen or C_1-C_6 alkyl (e.g., methyl) or C_3-C_6 cycloalkyl. In some embodiments, R^2 is -$NR^{2a}C(O)NR^{2b}R^{2c}$ and in certain aspects R^{2a} is hydrogen or C_1-C_6 alkyl (e.g., methyl) and R^{2b} and R^{2c} are independently hydrogen or C_1-C_6 alkyl (e.g., methyl) or C_3-C_6 cycloalkyl. In some embodiments, R^2 is -SR^{2a} and in certain aspects R^{2a} is C_1-C_6 alkyl (e.g., methyl).

[0050] In some embodiments R^2 is hydrogen, C_1-C_6 alkyl, -CN, halogen, -OR^{2a}, –$C(O)R^{2a}$, or –$C(O)OR^{2a}$. In some embodiments, R^2 is hydrogen. In some embodiments, R^2 is C_1-C_6 alkyl (e.g., methyl). In some embodiments, R^2 is –CN or halogen (e.g., bromo). In some embodiments, R^2

is –OR^{2a} and in certain aspects R^{2a} is C_1-C_6 alkyl (e.g., methyl). In some embodiments, R^2 is $C(O)R^{2a}$ and in certain aspects R^{2a} is C_1-C_6 alkyl (e.g., methyl) or C_3-C_6 cycloalkyl. In some embodiments, R^2 is $C(O)OR^{2a}$ and in certain aspects R^{2a} is hydrogen or C_1-C_6 alkyl (e.g., methyl).

[0051] In some embodiments, R^1 and R^2 are each hydrogen. In one such variation, R^1 and R^2 are each hydrogen and A is 4-hydroxyphenyl optionally further substituted by R^3 or 4-hydroxy-2-pyridyl optionally further substituted by R^4. In another variation, R^1 and R^2 are each hydrogen and B is unsubstituted phenyl. In another variation, R^1 and R^2 are each hydrogen and B is a 5- to 10-membered heteroaryl substituted by 1 to 3 R^4 wherein each R^4 is independently oxo or R^3. In a further variation, R^1 and R^2 are each hydrogen and A is an unsubstituted 9- or 10-membered bicyclic heteroaryl containing at least one annular nitrogen atom. In a further variation, R^1 and R^2 are each hydrogen, A is a 9- or 10-membered bicyclic heteroaryl containing at least one annular nitrogen atom and which is optionally substituted by R^4 and B is unsubstituted phenyl or a 5- to 10-membered heteroaryl substituted by 1 to 3 R^4 wherein each R^4 is independently oxo or R^3. In another embodiment, R^1 is hydrogen and R^2 is C_1-C_6 alkyl, -CN, halogen or -OR^{2a}. In one aspect, R^1 is hydrogen and R^2 is bromo, methyl, -CN, -OH, -$CONH_2$, -COOH or methoxy.

[0052] In some embodiments, R^1 and R^2 are hydrogen. In one such variation, R^1 and R^2 are hydrogen and **A** is 4-hydroxyphenyl optionally further substituted by R^3 or 4-hydroxy-2-pyridyl optionally further substituted by R^4. In another variation, R^1 and R^2 are hydrogen and B is unsubstituted phenyl. In another variation, R^1 and R^2 are hydrogen and **B** is a 5- to 6-membered heteroaryl substituted by 1 to 3 R^4 wherein each R^4 is independently R^3. In a further variation, R^1 and R^2 are hydrogen and **A** is an unsubstituted 9- or 10-membered bicyclic heteroaryl containing at least one annular nitrogen atom. In a further variation, R^1 and R^2 are hydrogen, **A** is a 9- or 10-membered bicyclic heteroaryl containing at least one annular nitrogen atom and which is optionally substituted by R^4 and **B** is unsubstituted phenyl or a 5- to 6-membered heteroaryl substituted by 1 to 3 R^4 wherein each R^4 is independently R^3. In another embodiment, R^1 is hydrogen and R^2 is C_1-C_6 alkyl, -CN, halogen or -OR^{2a}. In one aspect, R^1 is hydrogen and R^2 is bromo, methyl, -CN or methoxy.

[0053] In some embodiments, R^1 is hydrogen and R^2 is -CN. In one such variation, R^1 is hydrogen, R^2 is –CN, A is a 9- or 10-membered bicyclic heteroaryl containing at least one annular nitrogen atom (e.g., quinolinyl or indazolyl) and which is optionally substituted by R^4

and B is unsubstituted phenyl or a 5- to 6-membered heteroaryl (e.g., pyrazolyl, pyridyl or pyridone) substituted by 1 to 3 R^4 wherein each R^4 is independently oxo or R^3. In some embodiments, R^1 is hydrogen, R^2 is Br, A is a 9- or 10-membered bicyclic heteroaryl containing at least one annular nitrogen atom (e.g., quinolinyl or indazolyl) and which is optionally substituted by R^4 and B is unsubstituted phenyl or a 5- to 6-membered heteroaryl (e.g., pyrazolyl, pyridyl or pyridone) substituted by 1 to 3 R^4 wherein each R^4 is independently oxo or R^3. In some embodiments, both R^1 and R^2 are hydrogen, A is a 9- or 10-membered bicyclic heteroaryl containing at least one annular nitrogen atom (e.g., quinolinyl or indazolyl) and which is optionally substituted by R^4 and B is unsubstituted phenyl or a 5- to 6-membered heteroaryl (e.g., pyrazolyl, pyridyl or pyridone) substituted by 1 to 3 R^4 wherein each R^4 is independently oxo or R^3. In these variations R^4 is independently oxo, methyl, methoxy, chloro or –CN.

[0054] In some embodiments, **A** is 4-hydroxyphenyl optionally further substituted by R^3, 4-hydroxy-2-pyridyl optionally further substituted by R^4, or a 9- or 10-membered bicyclic heteroaryl optionally substituted by R^4.

[0055] In some embodiments, **A** is 4-hydroxyphenyl optionally further substituted by R^3 or 4-hydroxy-2-pyridyl optionally further substituted by R^4. In some embodiments, **A** is 4-hydroxyphenyl optionally further substituted by R^3. In some embodiments, **A** is 4-hydroxy-2-pyridyl optionally further substituted by R^4. In some embodiments, **A** is a 9- or 10-membered bicyclic heteroaryl optionally substituted by R^4. In some embodiments, **A** is a 9- or 10-membered bicyclic heteroaryl optionally substituted by R^4, wherein one ring is saturated. In some embodiments, **A** is a 9- or 10-membered bicyclic heteroaryl optionally substituted by R^4, wherein both rings are unsaturated. In some embodiments, A is selected from the group consisting of benzimidazolyl, benzoxazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, indazolyl, quinoxalinyl, quinazolinyl, cinnolinyl, naphthyridinyl and naphthyl. In some embodiments, A is selected from the group consisting of benzimidazolyl, benzoxazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, indazolyl, quinoxalinyl, quinazolinyl, cinnolinyl, naphthyridinyl and naphthyl, each of which is optionally substituted by R^4. In yet further embodiments, **A** is a 9- or 10-membered bicyclic heteroaryl optionally substituted by R^4, comprising a first and second ring, wherein the first ring has a greater number of ring atoms than the second ring. In certain embodiments, the point of attachment of **A** to the parent molecule is on the first ring having a greater number of ring atoms. In other embodiments, the point of attachment of **A** to the parent

molecule is on the second ring having a smaller number of ring atoms. In some embodiments, **A** is a 9- or 10-membered bicyclic heteroaryl optionally substituted by R^4, wherein the two rings are selected from the group consisting of: a 5-membered ring and a 6-membered ring or two 6-membered rings.

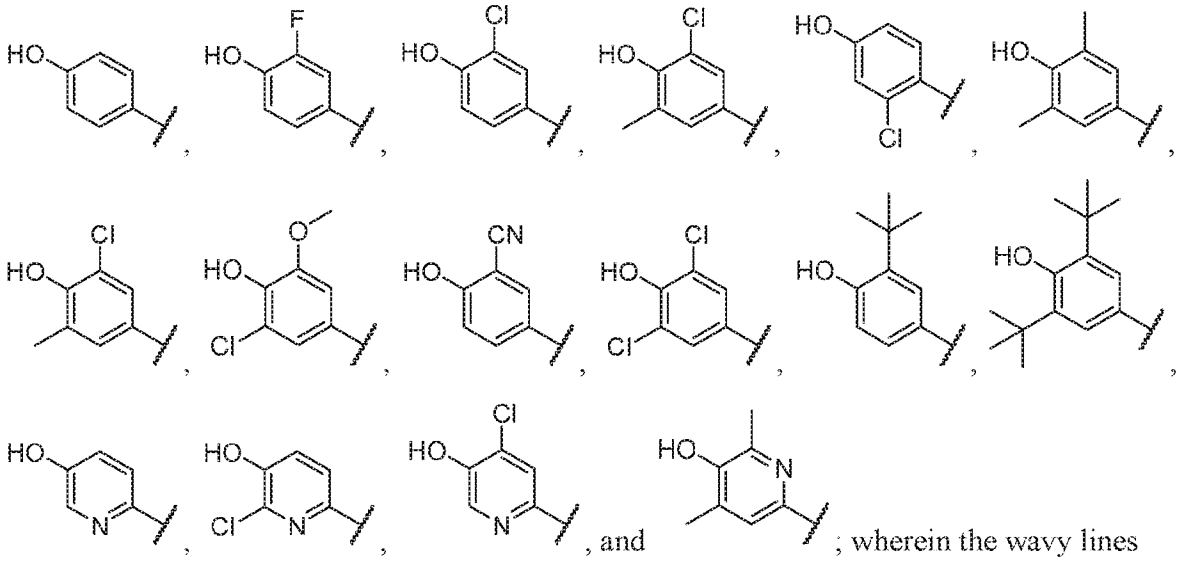
[0056] In one aspect, when A is a 9- or 10-membered bicyclic heteroaryl optionally substituted by R^4, A is an unsubstituted 9- or 10-membered bicyclic heteroaryl containing at least one annular nitrogen atom, a 9- or 10-membered bicyclic heteroaryl containing at least two annular nitrogen atoms and optionally substituted by R^4 which R^4 groups are connected to the parent structure via a carbon atom, or a 10-membered bicyclic heteroaryl optionally substituted by R^4.

[0057] In some embodiments, **A** is 4-hydroxyphenyl optionally further substituted by R^3 where R^3 is selected from the group consisting of halogen, -CN, $-OR^5$, $-SR^5$, $-NR^6R^7$, $-NO_2$, $-C(O)R^5$, $-C(O)OR^5$, $-C(O)NR^6R^7$, $-C(O)NR^5S(O)_2R^6$, $-OC(O)R^5$, $-OC(O)NR^6R^7$, $-NR^5C(O)R^6$, $-NR^5C(O)NR^6R^7$, $-S(O)R^5$, $-S(O)_2R^5$, C_3-C_6 cycloalkyl and C_1-C_6 alkyl optionally substituted by halogen. In some embodiments, **A** is 4-hydroxyphenyl further substituted by 1 to 3 R^3 where each R^3 is independently selected from the group consisting of halogen, -CN, $-OR^5$, $-SR^5$, $-NR^6R^7$, $-NO_2$, $-C(O)R^5$, $-C(O)OR^5$, $-C(O)NR^6R^7$, $-C(O)NR^5S(O)_2R^6$, $-OC(O)R^5$, $-OC(O)NR^6R^7$, $-NR^5C(O)R^6$, $-NR^5C(O)NR^6R^7$, $-S(O)R^5$, $-S(O)_2R^5$, C_3-C_6 cycloalkyl and C_1-C_6 alkyl optionally substituted by halogen. In some embodiments, **A** is 4-hydroxyphenyl optionally further substituted by R^3 where R^3 is selected from the group consisting of halogen, $-OR^5$ and C_1-C_6 alkyl optionally substituted by halogen. In some embodiments, **A** is 4-hydroxyphenyl further substituted by 1 to 3 R^3 where each R^3 is independently selected from the group consisting of halogen, $-OR^5$ and C_1-C_6 alkyl optionally substituted by halogen. In some embodiments, **A** is 4-hydroxyphenyl further substituted by 1 to 3 R^3 where each R^3 is independently selected from the group consisting of fluoro, chloro, $-O$-C_1-C_6alkyl and C_1-C_6 alkyl optionally substituted by halogen.

[0058] In some embodiments, **A** is 4-hydroxy-2-pyridyl optionally further substituted by R^4 where R^4 is selected from the group consisting of halogen, -CN, $-OR^5$, $-SR^5$, $-NR^6R^7$, $-NO_2$, $-C(O)R^5$, $-C(O)OR^5$, $-C(O)NR^6R^7$, $-C(O)NR^5S(O)_2R^6$, $-OC(O)R^5$, $-OC(O)NR^6R^7$, $-NR^5C(O)R^6$, $-NR^5C(O)NR^6R^7$, $-S(O)R^5$, $-S(O)_2R^5$, C_3-C_6 cycloalkyl and C_1-C_6 alkyl optionally substituted by halogen. In some embodiments, **A** is 4-hydroxy-2-pyridyl optionally further substituted by 1 to 3 R^4, where each R^4 is independently selected from the group consisting of halogen, -CN, $-OR^5$,

$-SR^5$, $-NR^6R^7$, $-NO_2$, $-C(O)R^5$, $-C(O)OR^5$, $-C(O)NR^6R^7$, $-C(O)NR^5S(O)_2R^6$, $-OC(O)R^5$, $-OC(O)NR^6R^7$, $-NR^5C(O)R^6$, $-NR^5C(O)NR^6R^7$, $-S(O)R^5$, $-S(O)_2R^5$, C_3-C_6 cycloalkyl and C_1-C_6 alkyl optionally substituted by halogen. In some embodiments, **A** is 4-hydroxy-2-pyridyl further substituted by 1 to 3 R^4 where each R^4 is independently selected from the group consisting of halogen, $-OR^5$ and C_1-C_6 alkyl optionally substituted by halogen. In some embodiments, **A** is 4-hydroxyphenyl further substituted by 1 to 3 R^4 where each R^4 is independently selected from the group consisting of fluoro, chloro, $-O$-C_1-C_6alkyl and C_1-C_6 alkyl optionally substituted by halogen.

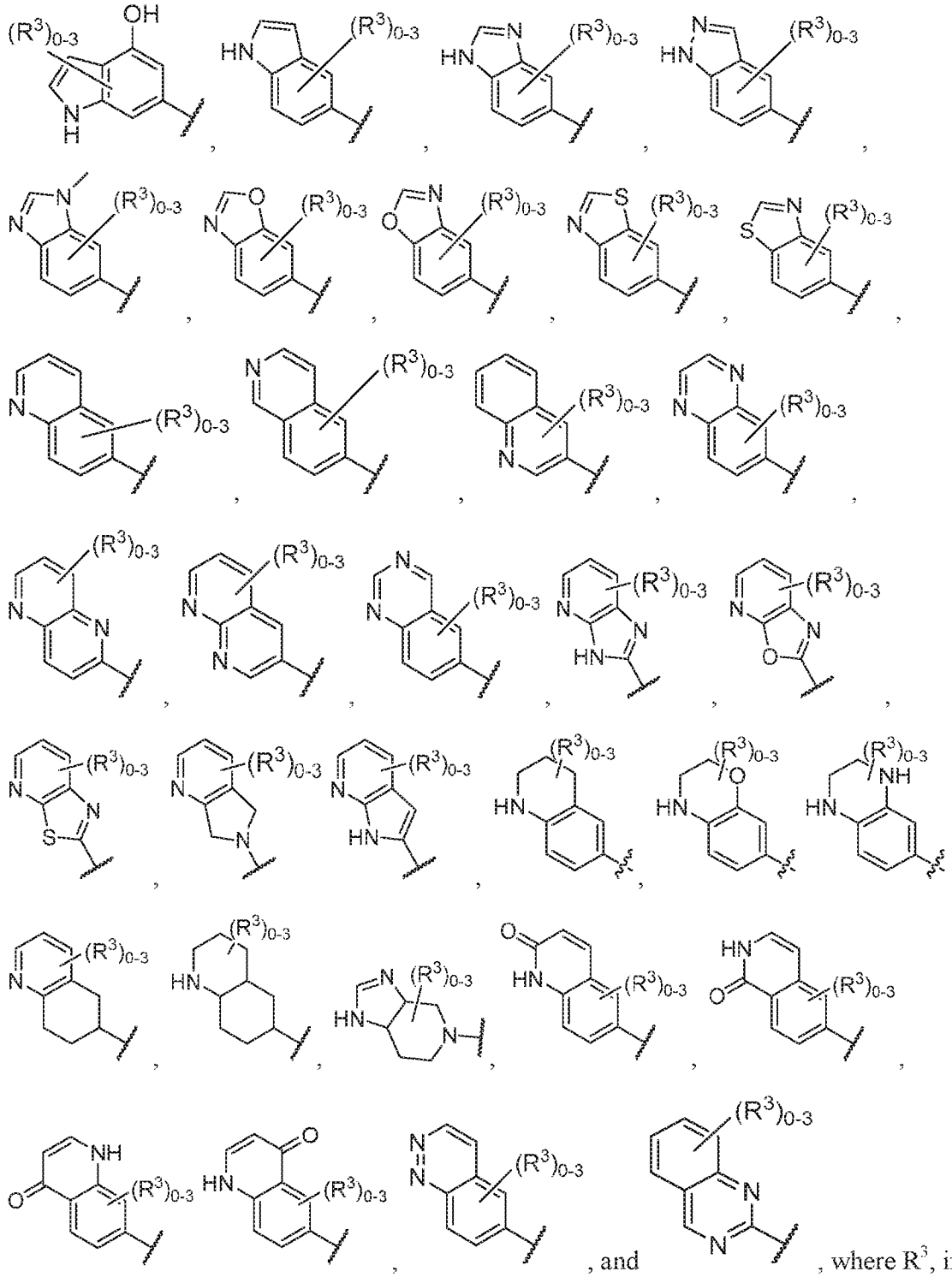
[0059] In some embodiments, **A** is a 4-hydroxyphenyl or a 4-hydroxy-2-pyridyl substituted with 1 to 3 R^3 groups, which may be the same or different. In some of these embodiments, **A** is selected from the group consisting of:



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

[0060] In some embodiments, A is a 9- or 10-membered bicyclic heteroaryl substituted with 0 to 3 R^4 groups which may be the same or different, and which may be present on either one ring or both rings. In one such aspect, A is a 9- or 10-membered bicyclic heteroaryl substituted with 0 to 3 R^3 groups which may be the same or different, and which may be present on either one ring or both rings. In one such aspect, A is a 9- or 10-membered bicyclic heteroaryl substituted with 1 R^3 group. In another such aspect, A is a 9- or 10-membered bicyclic heteroaryl substituted with 2 R^3 groups, which may be the same or different. In another such aspect, A is a 9- or 10-

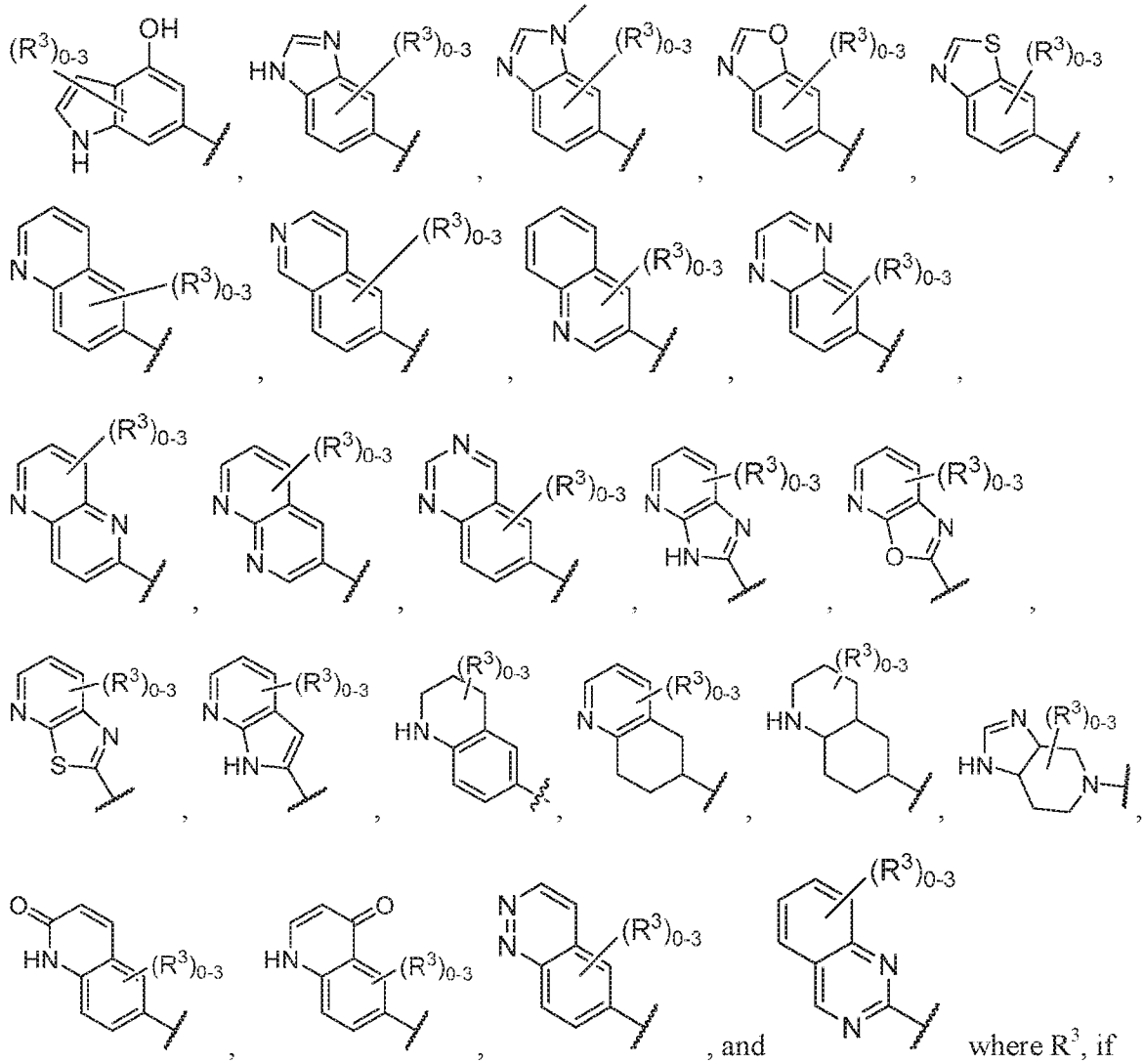
membered bicyclic heteroaryl substituted with 3 R^3 groups, which may be the same or different. In some embodiments, A is selected from the group consisting of:



, where R^3, if present, is attached at any available position on the bicyclic ring system. In one aspect, at

least one R^3 is present and is attached at a position on the ring bearing the wavy line (on the ring that is the attachment point of the bicyclic ring to the parent molecule). In one aspect, at least one R^3 is present and is attached at a position on the ring that does not bear the wavy line (on the ring that is fused to the ring which is the attachment point of the bicyclic ring to the parent molecule).

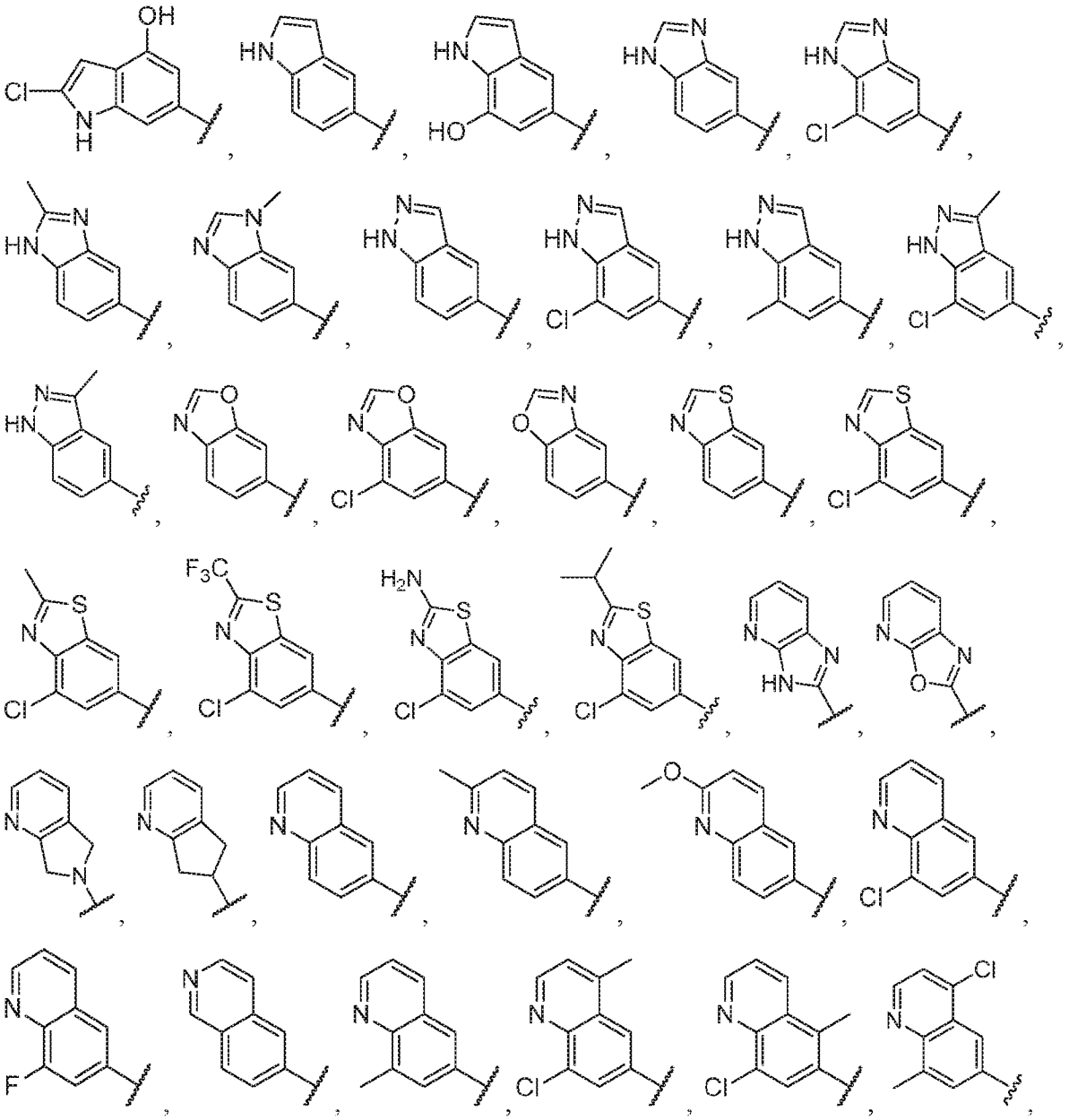
[0061] In some embodiments, **A** is a 9- or 10-membered bicyclic heteroaryl substituted with 0 to 3 R^3 groups which may be the same or different, and which may be present on either one ring or both rings. In some embodiments, A is selected from the group consisting of:

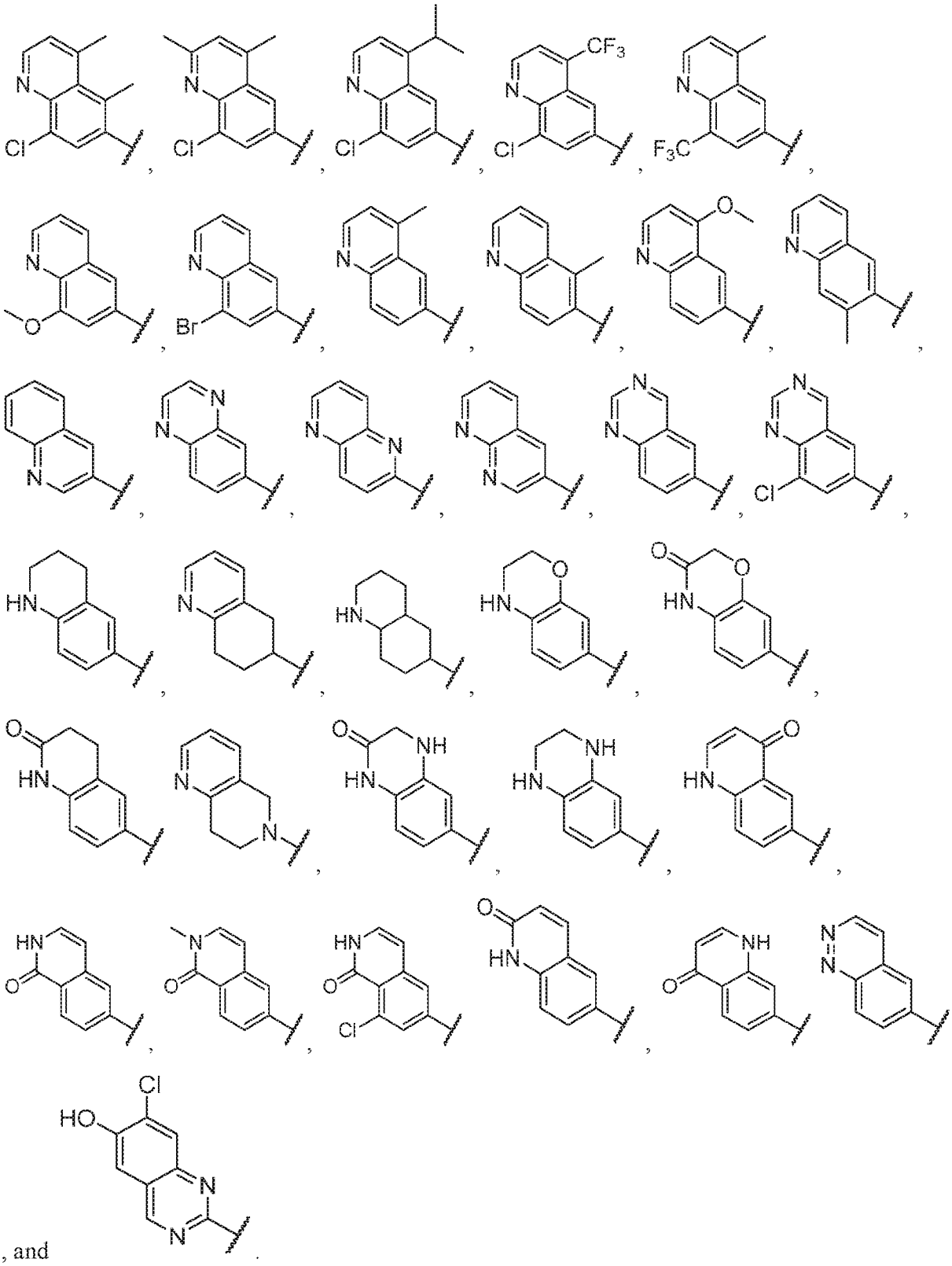


where R^3, if present, is attached at any available position on the bicyclic ring system. In one aspect, at least one R^3 is present and is attached at a position on the ring bearing the wavy line (on the

ring that is the attachment point of the bicyclic ring to the parent molecule). In one aspect, at least one R^3 is present and is attached at a position on the ring that does not bear the wavy line (on the ring that is fused to the ring which is the attachment point of the bicyclic ring to the parent molecule).

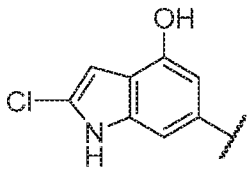
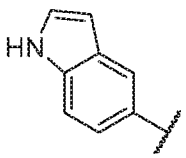
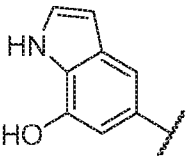
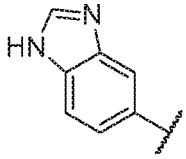
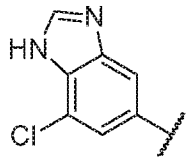
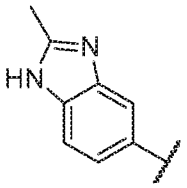
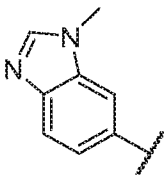
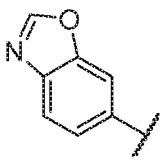
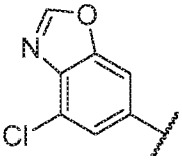
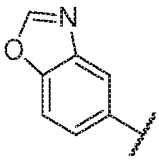
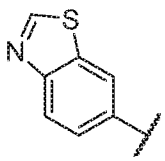
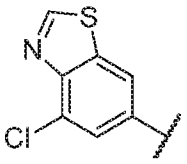
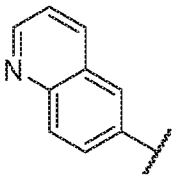
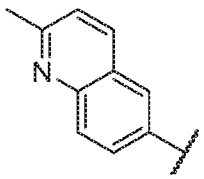
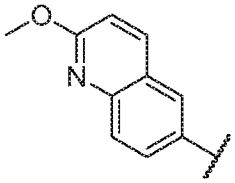
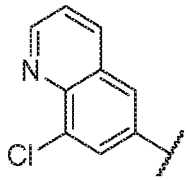
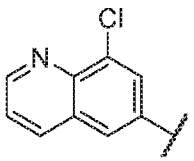
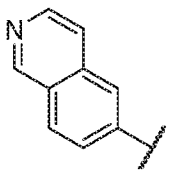
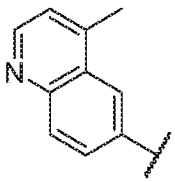
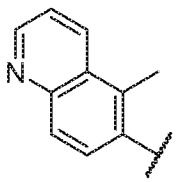
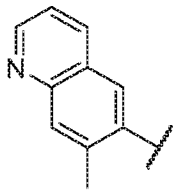
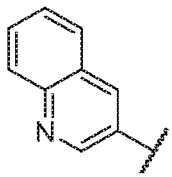
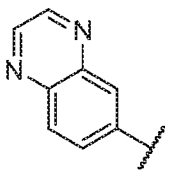
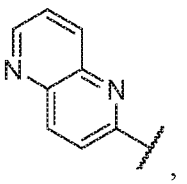
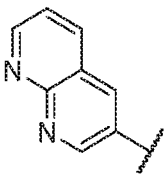
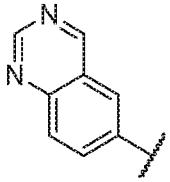
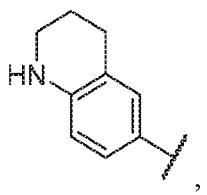
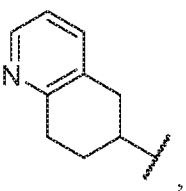
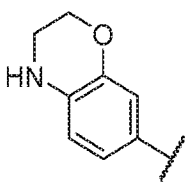
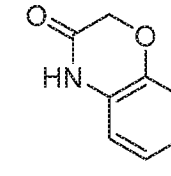
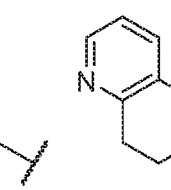
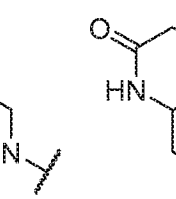
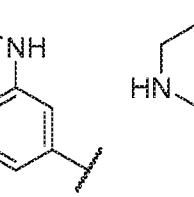
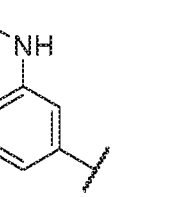
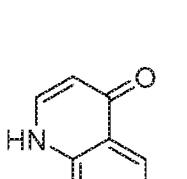
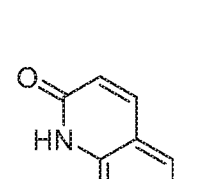
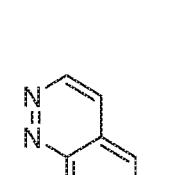
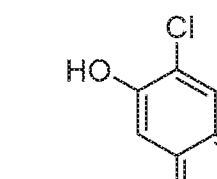
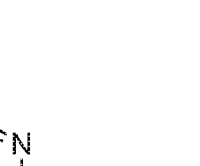
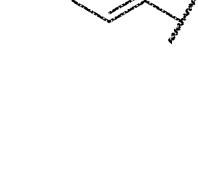
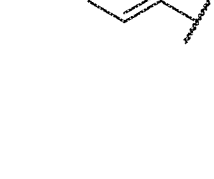
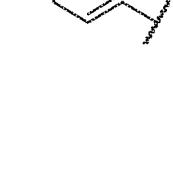
[0062] In some embodiments, A is selected from the group consisting of:

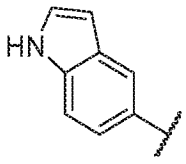




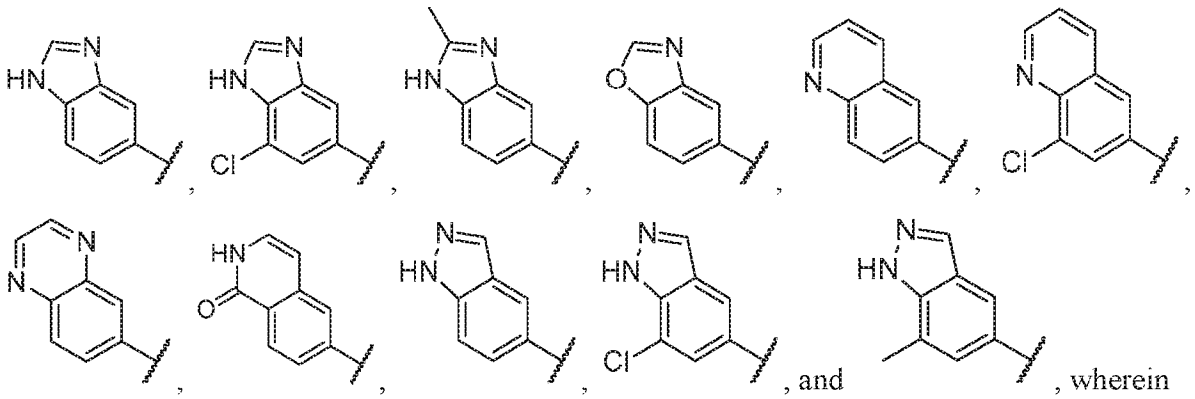
, and

[0063] In some embodiments, **A** is selected from the group consisting of:

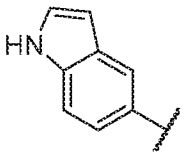









































 , and .



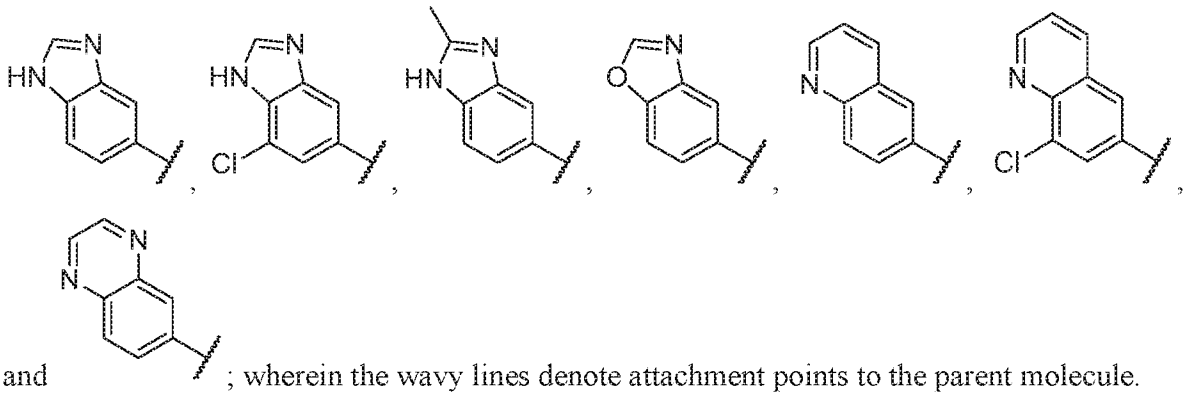
[0064] In certain embodiments, A is selected from the group consisting of:



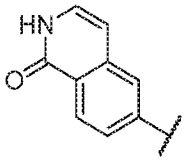
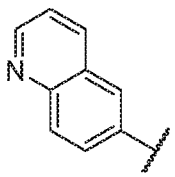
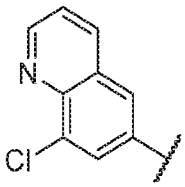
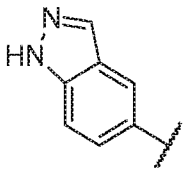
, wherein the wavy lines denote attachment points to the parent molecule.

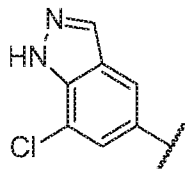


[0065] In certain embodiments, **A** is selected from the group consisting of:



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

[0066] In some embodiments, A is  . In some embodiments, A is  . In some embodiments, A is  . In some embodiments, A is  . In some

embodiments, A is  . In some embodiments, A is naphthyl substituted with halogen, -CN, or hydroxy.

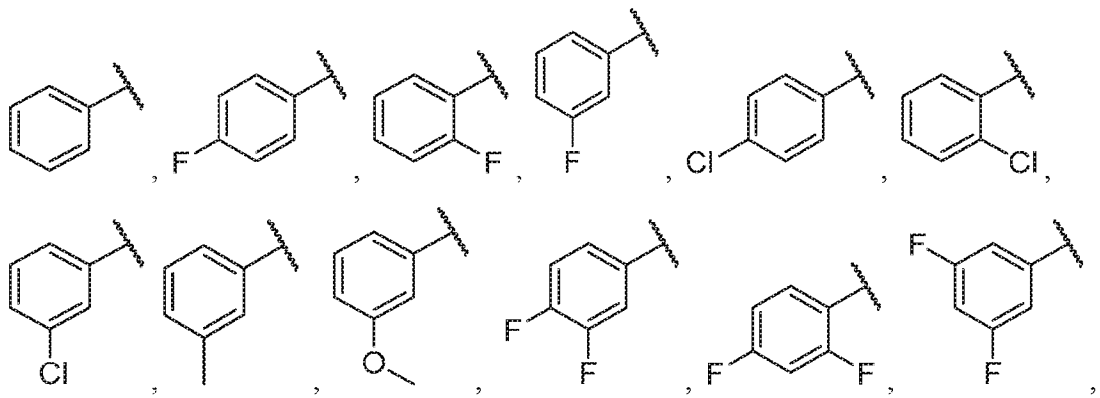
[0067] It is understood that each description of **A** may be combined with each description of R^1 and/or R^2 the same as if each and every combination were specifically and individually listed. For example, in one embodiment, A is as described in any of the embodiments, aspects or variations herein and R^1 and R^2 are each H. It is similarly understood that each description of **A** may be combined with each description of **B** (and further with each description of R^1 and R^2) the same as if each and every combination were specifically and individually listed. For example, in one aspect, it is understood that each description of **A** may be combined in one aspect with a variation in which R^1 and R^2 are each hydrogen. In one aspect, it is understood that each description of **A** may be combined in one aspect with a variation in which R^1 and R^2 are each hydrogen and B is a 5- to 10-membered heteroaryl optionally substituted by R^4.

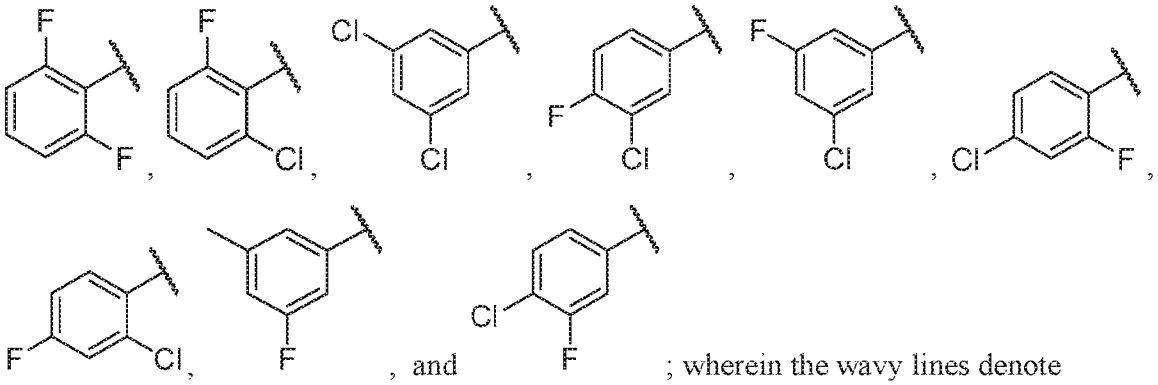
[0068] In some embodiments, B is an unsubstituted phenyl. In some embodiments, B is a phenyl optionally substituted by R^3. In some embodiments, B is a phenyl substituted by 1 to 3 R^3 which R^3 groups may be the same or different. In other embodiments, B is a 5- to 10-membered heteroaryl optionally substituted by R^4. In other embodiments, B is a 5- to 10-membered heteroaryl substituted by 1 to 3 R^4 which R^4 may be the same or different. In some embodiments, the 5- to 10-membered heteroaryl of B is a 5-membered heteroaryl selected from the group consisting of furanyl, oxazolyl, thiophenyl, pyrazolyl, isoxazolyl, 1,3,4-oxadiazolyl, imidazolyl, thiazolyl, isothiazolyl, triazolyl, 1,3,4-thiadiazolyl and tetrazolyl, which 5-membered heteroaryl is optionally substituted by 1 to 3 R^4 which R^4 groups may be the same or different. In other embodiments, the 5- to 10-membered heteroaryl of B is a 6-membered heteroaryl selected from the group consisting of pyridyl, pyridazinyland pyrimidinyl which 6-membered heteroaryl is optionally substituted to 1 to 3 R^4 which R^4 groups may be the same or different. In some embodiments, the 5- to 10-membered heteroaryl of B is a bicyclic heteroaryl selected from the group consisting of benzofuranyl, benzothiophenyl, pyrazolopyridinyl, indazolyl, benzothiazolyl, benzooxazolyl or benzoimidazolyl, each of bicyclic heteroaryl is optionally substituted by 1 to 3 R^4 which R^4 groups may be the same or different.

[0069] In some embodiments, **B** is an unsubstituted phenyl. In some embodiments, **B** is a phenyl optionally substituted by R^3. In some embodiments, **B** is a phenyl substituted by 1 to 3 R^3 which R^3 groups may be the same or different. In other embodiments, **B** is a 5- to 6-membered heteroaryl optionally substituted by R^4. In other embodiments, **B** is a 5- to 6-membered heteroaryl substituted by 1 to 3 R^4 which R^4 may be the same or different. In some embodiments, the 5- to 6-membered heteroaryl of **B** is a 5-membered heteroaryl selected from the group consisting of furanyl, oxazolyl, thiophenyl, pyrazolyl, isoxazolyl, 1,3,4-oxadiazolyl, imidazolyl, thiazolyl, isothiazolyl, triazolyl, 1,3,4-thiadiazolyl and tetrazolyl, which 5-membered heteroaryl is optionally substituted by 1 to 3 R^4 which R^4 groups may be the same or different. In other embodiments, the 5- to 6-membered heteroaryl of **B** is a 6-membered heteroaryl selected from the group consisting of pyridyl and pyrimidinyl which 6-membered heteroaryl is optionally substituted to 1 to 3 R^4 which R^4 groups may be the same or different.

[0070] In some embodiments of **B** in which **B** is a phenyl substituted by R^3, such as when **B** is a phenyl substituted by 1 to 3 R^3 which may be the same or different, each R^3 of **B** in one aspect is independently selected from the group consisting of halogen, $-OR^5$, $-NR^6R^7$, $-C(O)R^5$, C_3-C_6 cycloalkyl and C_1-C_6 alkyl optionally substituted by halogen. In other embodiments, each R^3 of **B** is independently selected from the group consisting of halogen and C_1-C_6 alkyl optionally substituted by halogen (e.g., CF_3).

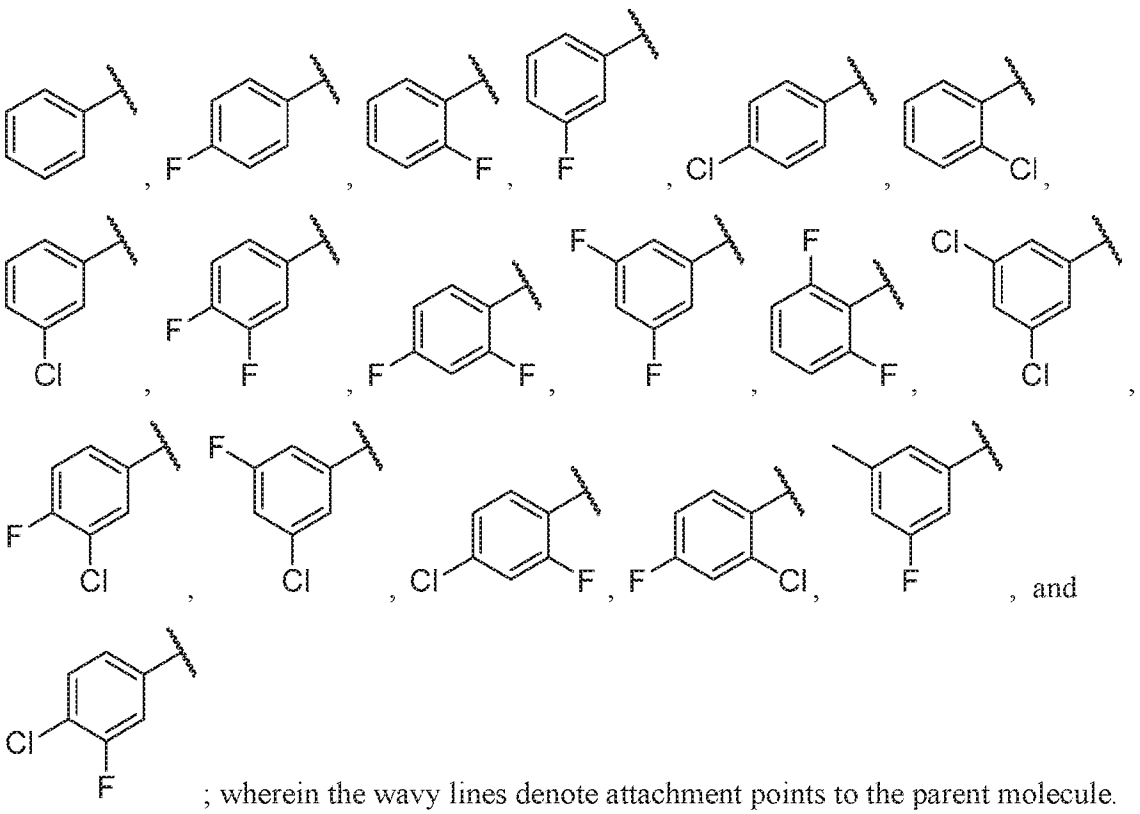
[0071] In some embodiments, B is a phenyl substituted with 1 to 3 halo groups which may be the same or different. In some embodiments, B is phenyl, fluoro-phenyl, di-fluoro-phenyl, chloro-phenyl, di-chloro-phenyl or (fluoro)(chloro)-phenyl. In some embodiments, B is selected from the group consisting of:





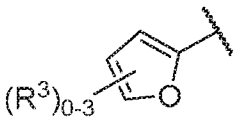
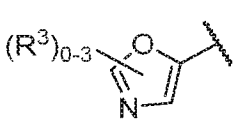
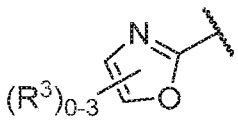
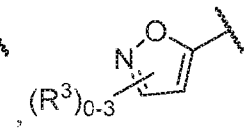
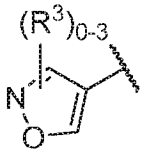
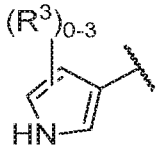
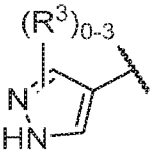
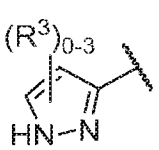
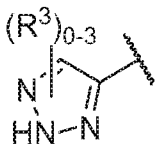
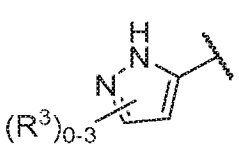
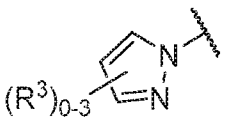
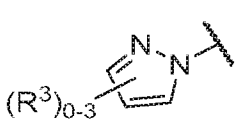
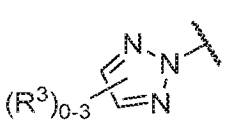
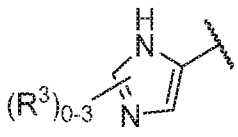
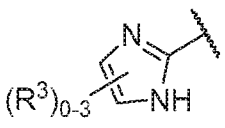
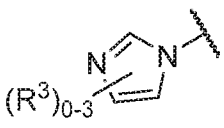
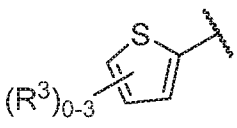
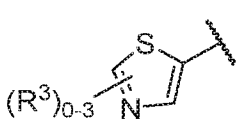
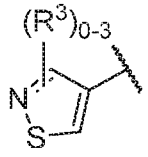
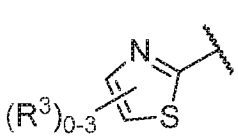
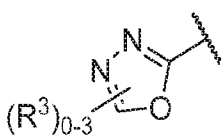
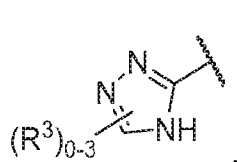
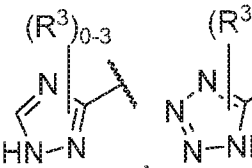
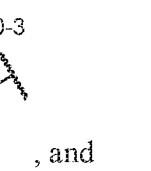
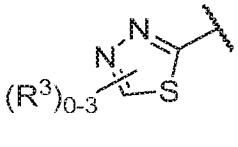
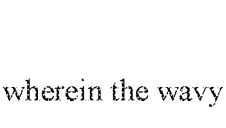
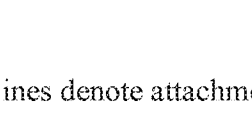
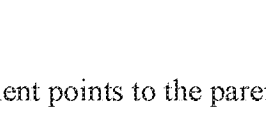
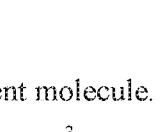
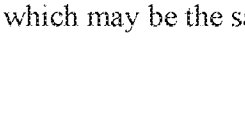
; wherein the wavy lines denote attachment points to the parent molecule.

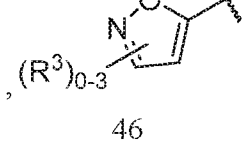
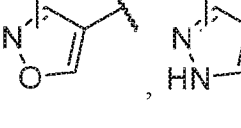
[0072] In some embodiments, **B** is a phenyl substituted with 1 to 3 halo groups which may be the same or different. In some embodiments, **B** is phenyl, fluoro-phenyl, di-fluoro-phenyl, chloro-phenyl, di-chloro-phenyl or (fluoro)(chloro)-phenyl. In some embodiments, **B** is selected from the group consisting of:

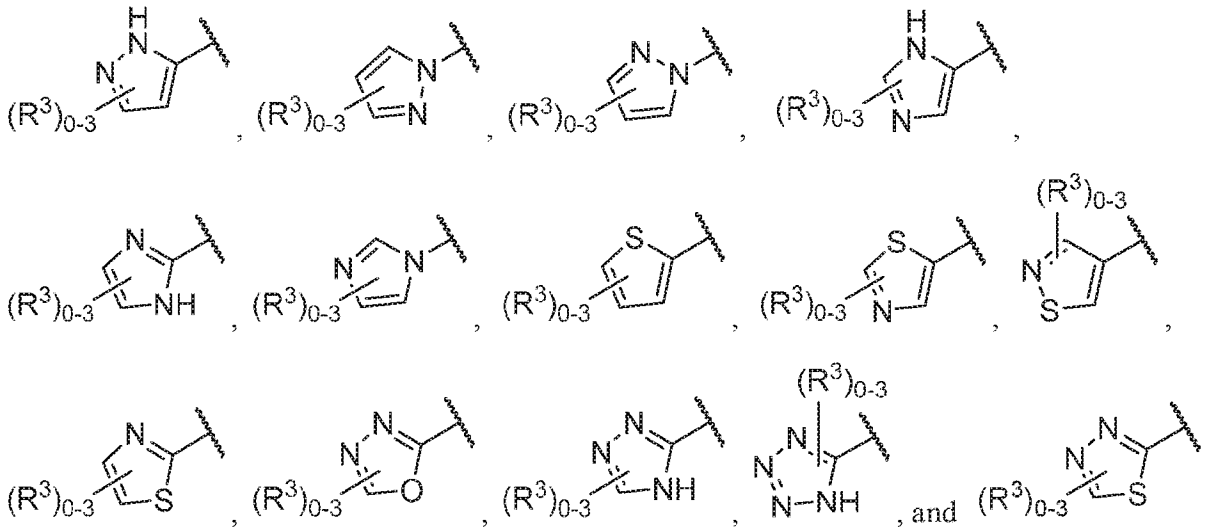


; wherein the wavy lines denote attachment points to the parent molecule.

[0073] In some embodiments, B is a 5-membered heteroaryl substituted with 0 to 3 R^4 groups which may be the same or different. In some embodiments, B is a 5-membered heteroaryl substituted with 0 to 3 R^3 groups which may be the same or different. In one such aspect, B is a

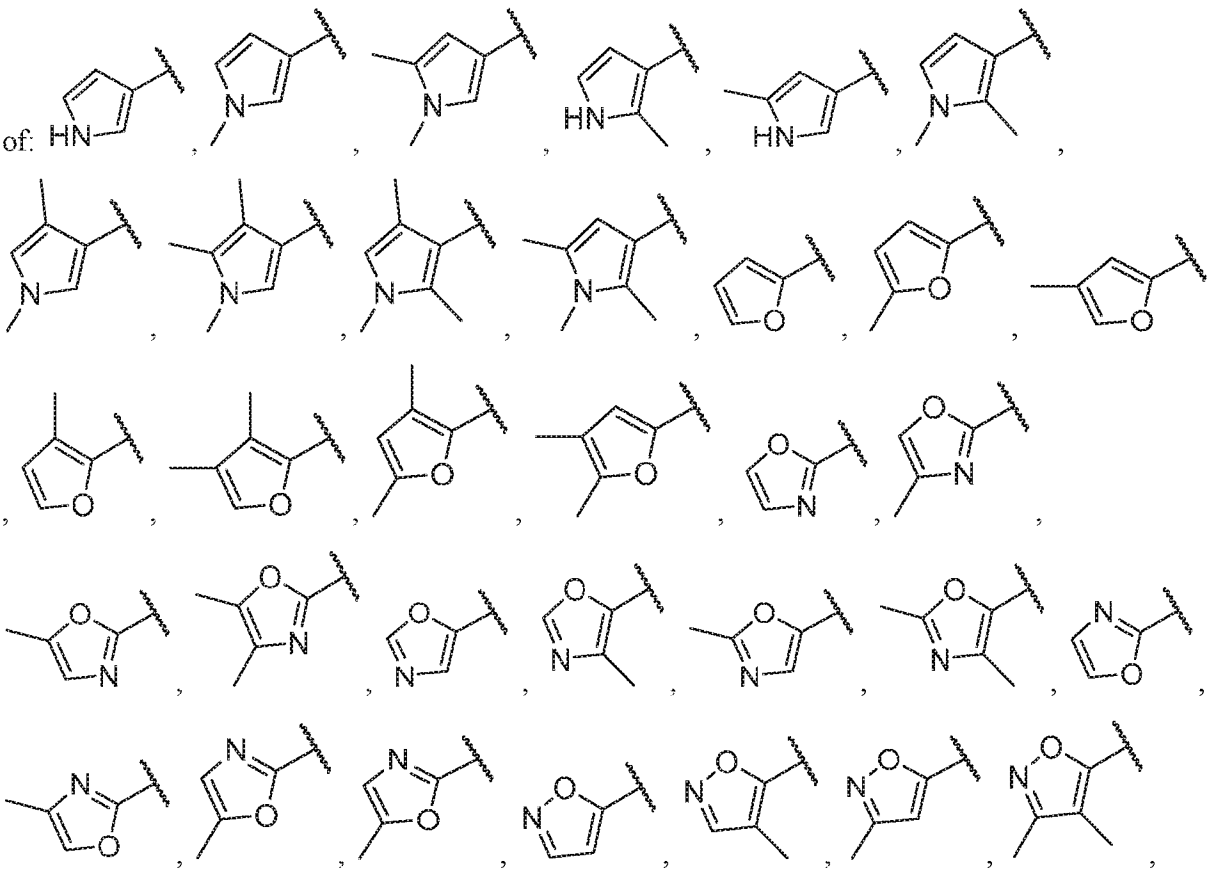
5-membered heteroaryl substituted with 1 R^3 group. In another such aspect, B is a 5-membered heteroaryl substituted with 2 R^3 groups, which may be the same or different. In another such aspect, B is a 5-membered heteroaryl substituted with 3 R^3 groups, which may be the same or different. In some embodiments, B is a 5-membered heteroaryl selected from the group consisting of:  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  ; wherein the wavy lines denote attachment points to the parent molecule.

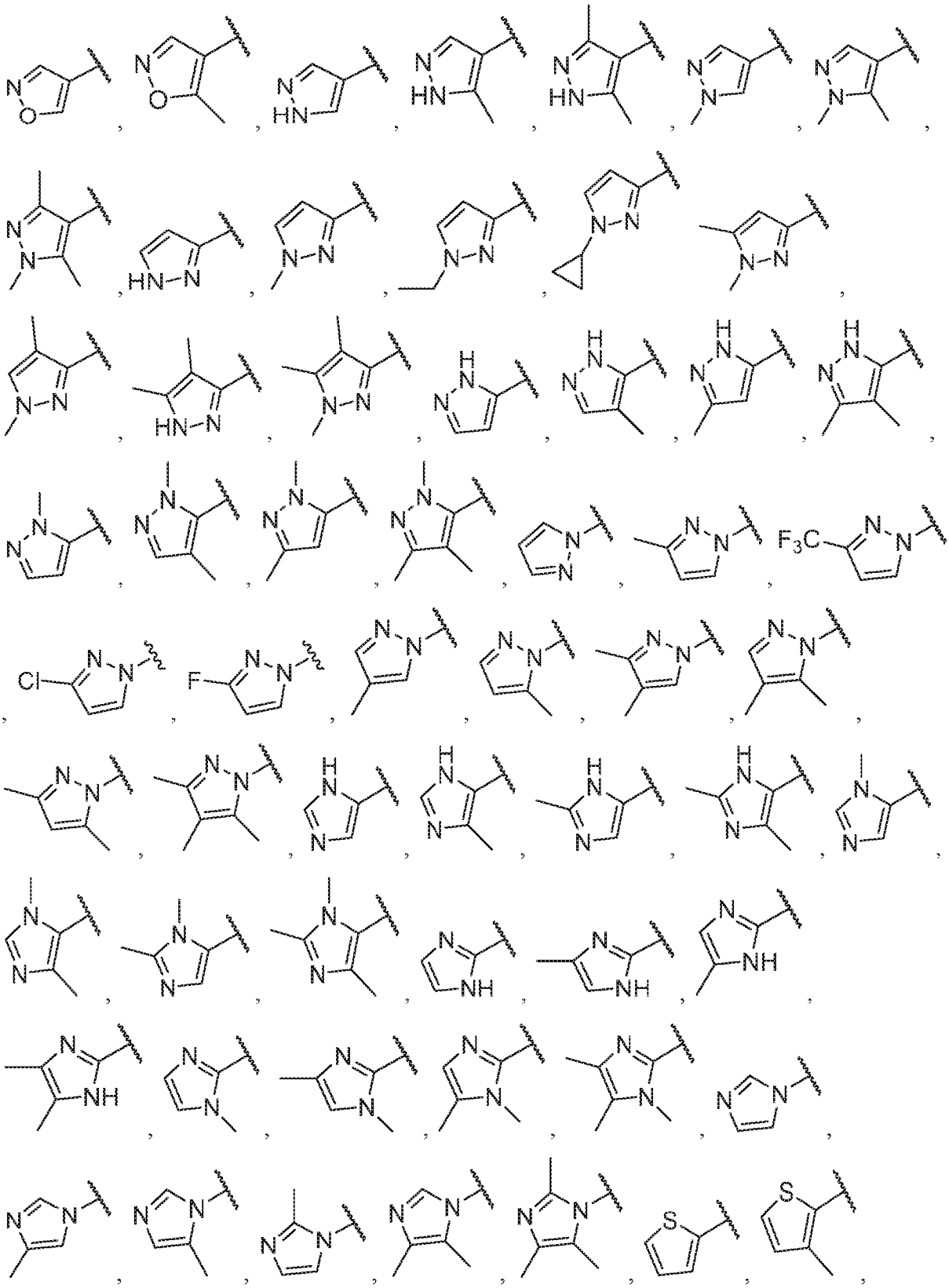
[0074] In some embodiments, **B** is a 5-membered heteroaryl substituted with 0 to 3 R^3 groups which may be the same or different. In some embodiments, **B** is a 5-membered heteroaryl selected from the group consisting of:  ,  , , , , , ,

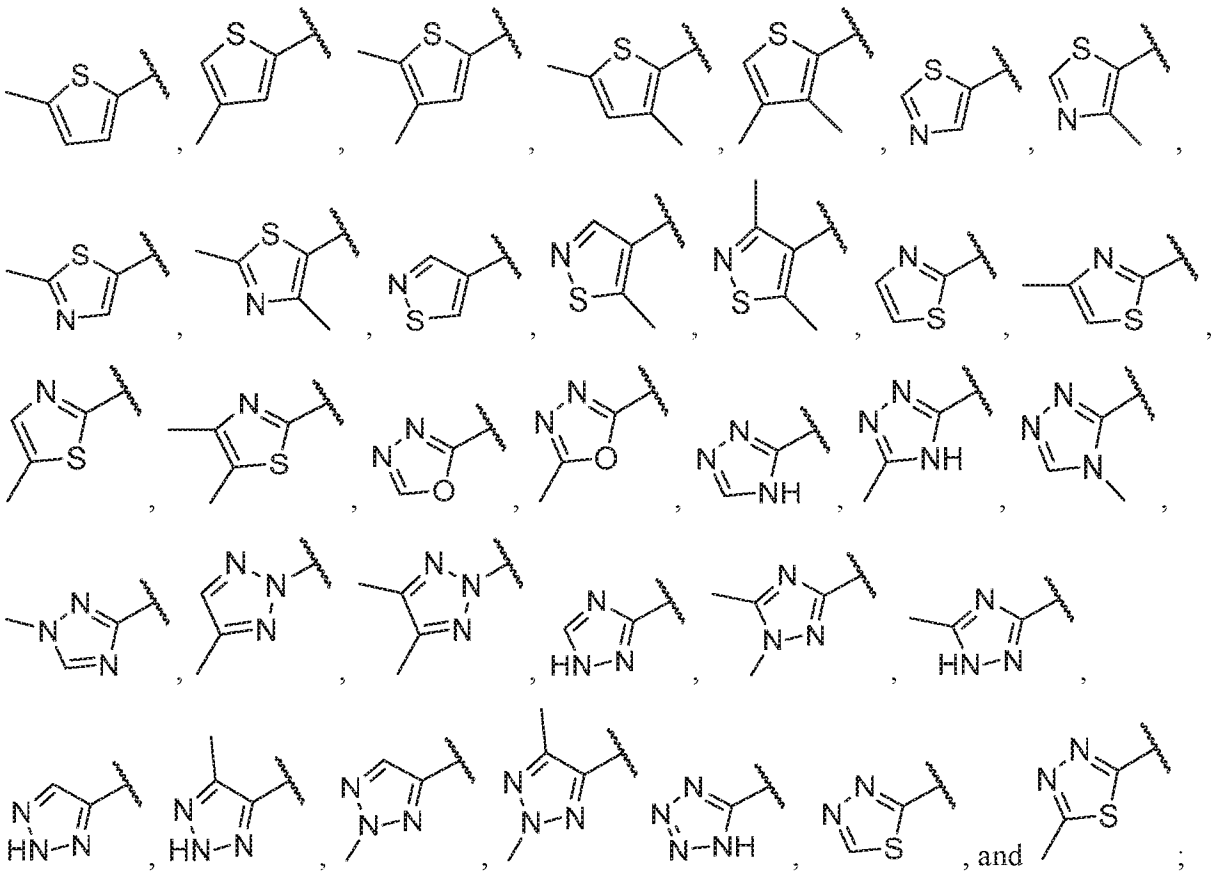


; wherein the wavy lines denote attachment points to the parent molecule.

[0075] In some embodiments, B is a 5-membered heteroaryl selected from the group consisting of:

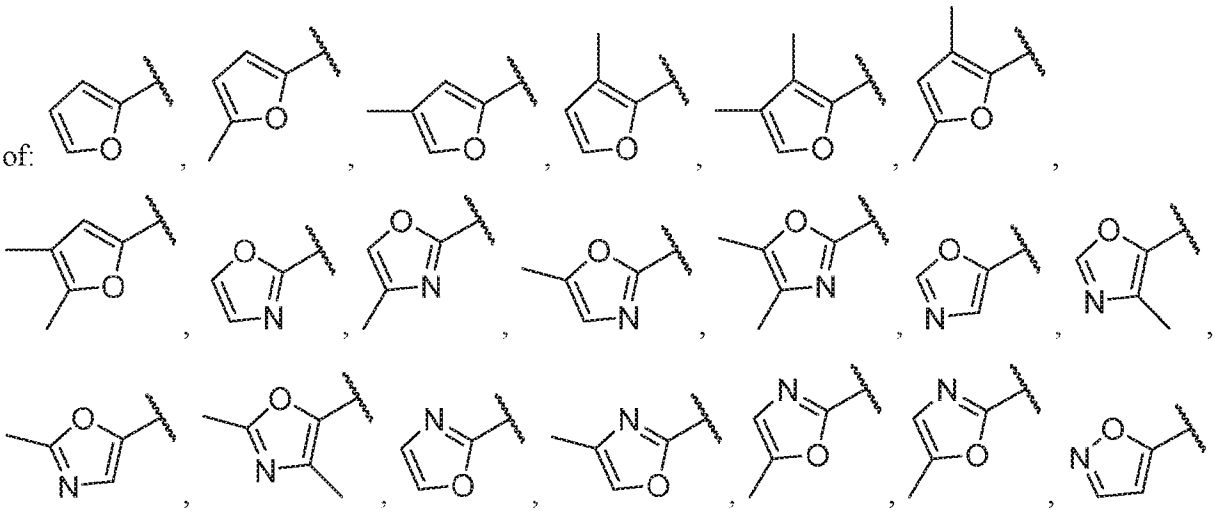


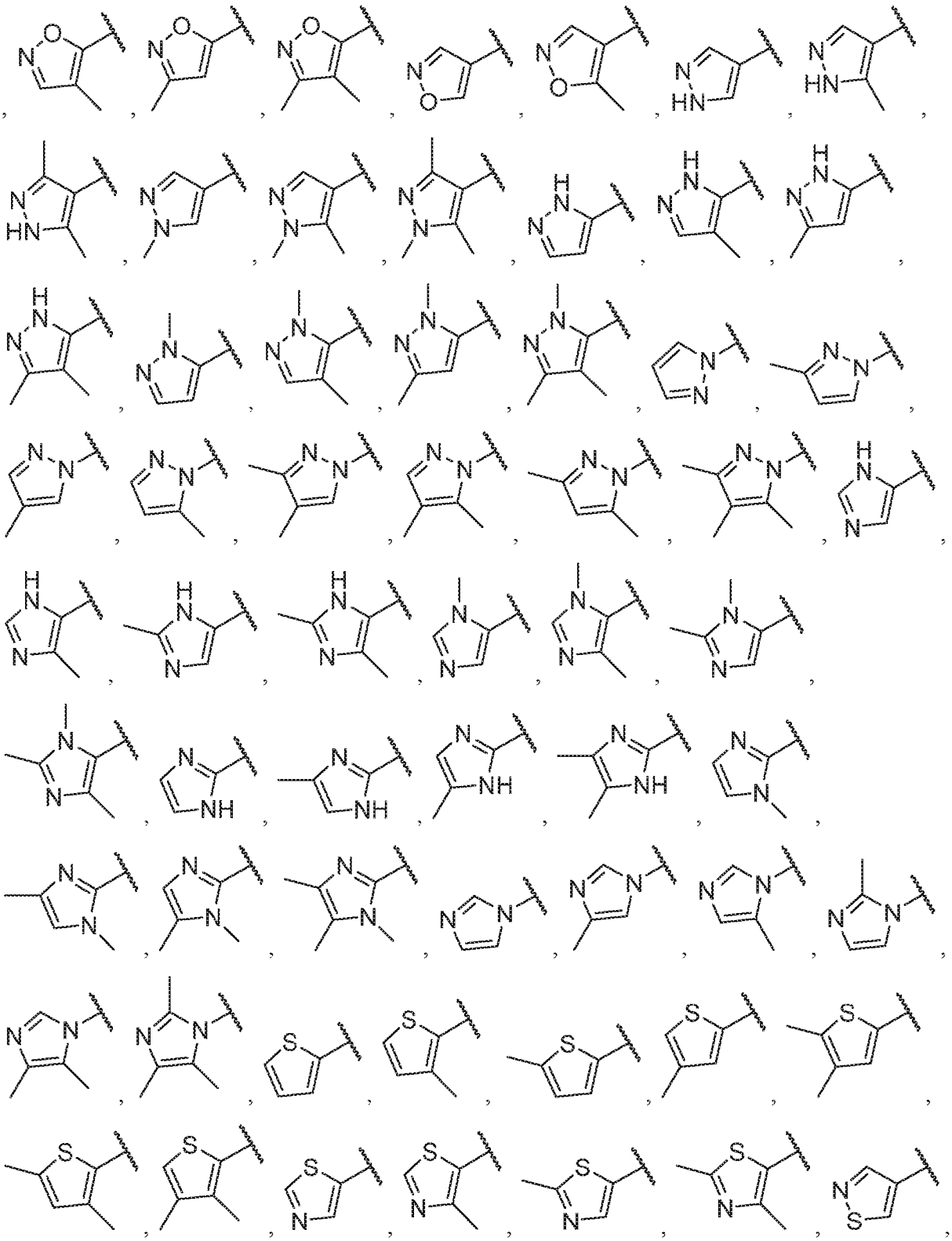


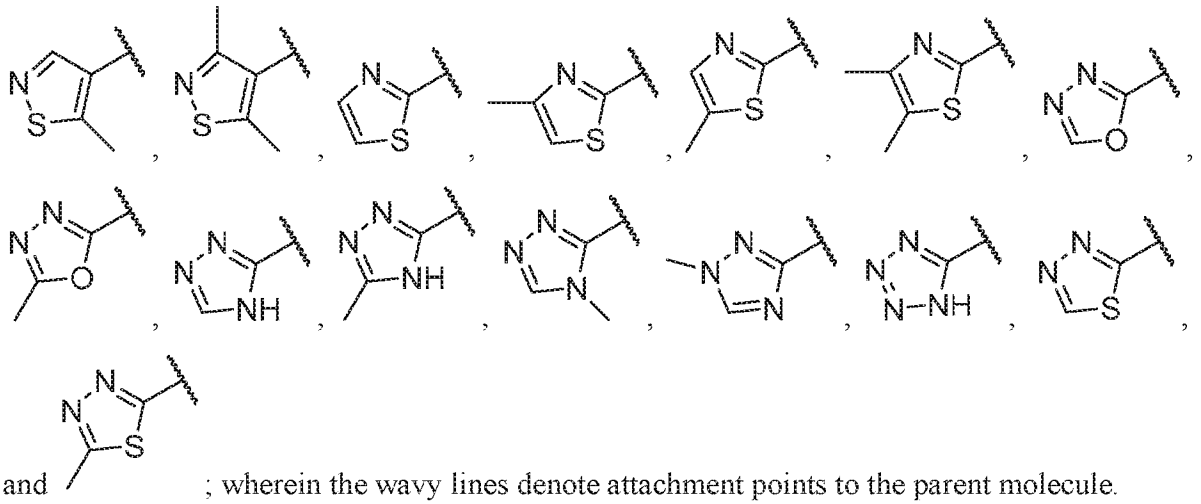


wherein the wavy lines denote attachment points to the parent molecule.

[0076] In some embodiments, **B** is a 5-membered heteroaryl selected from the group consisting of:

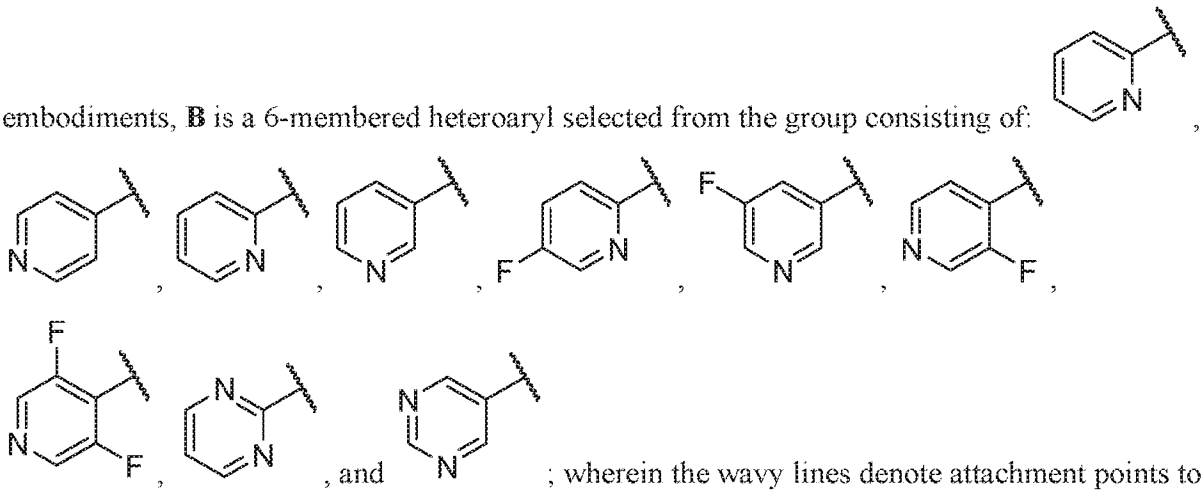






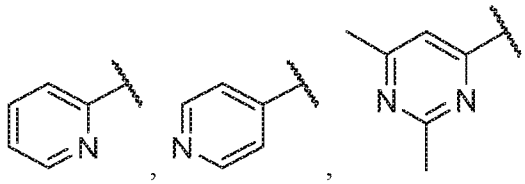
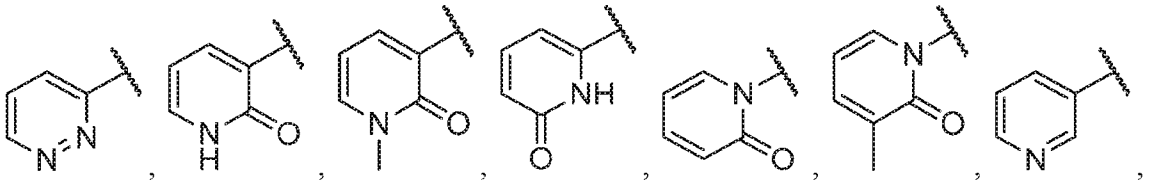
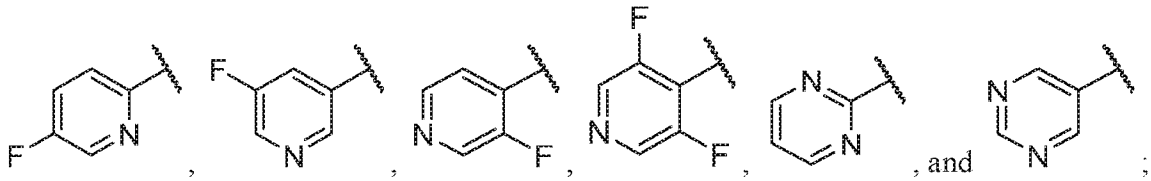
and ; wherein the wavy lines denote attachment points to the parent molecule.

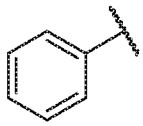
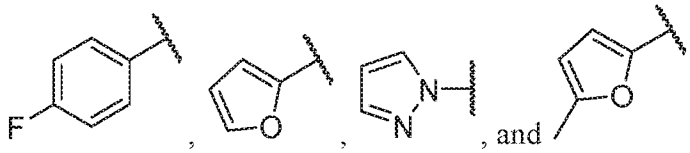
[0077] In some embodiments, **B** is a pyridyl or pyrimidyl optionally substituted by 1 to 3 R^4, which R^4 may be the same or different. In some embodiments, **B** is a pyridyl or pyrimidyl optionally substituted by 1 to 3 halo groups which may be the same or different. In some embodiments, **B** is a 6-membered heteroaryl selected from the group consisting of:

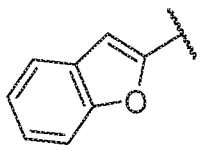
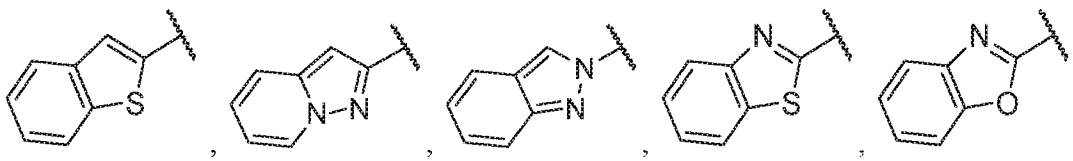
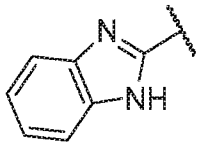


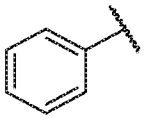
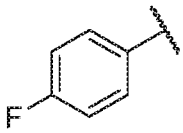
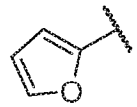
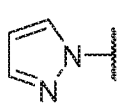
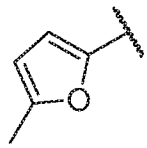
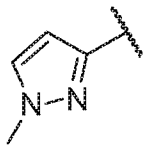
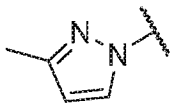
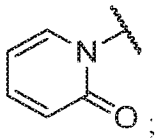
, and ; wherein the wavy lines denote attachment points to the parent molecule.

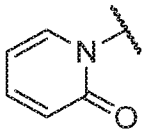
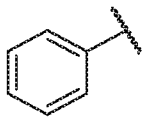
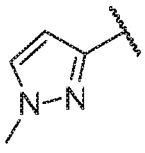
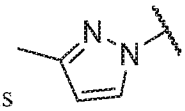
[0078] In some embodiments, B is a pyridyl or pyrimidyl optionally substituted by 1 to 3 R^4, which R^4 may be the same or different. In some embodiments, B is a pyridyl or pyrimidyl optionally substituted by 1 to 3 R^3, which R^3 may be the same or different. In some embodiments, B is a pyridyl or pyrimidyl optionally substituted by 1 to 3 halo groups which may be the same or different. In some embodiments, B is a 6-membered heteroaryl selected from the

group consisting of:  ,  ,  , and ; wherein the wavy lines denote attachment points to the parent molecule.

[0079] In some embodiments, **B** is selected from the group consisting of:  ,  , and ; wherein the wavy lines denote attachment points to the parent molecule.

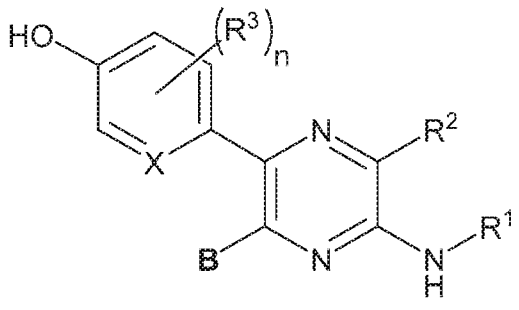
[0080] In some embodiments, B is a bicycle heteroaryl optionally substituted by 1 to 3 R^4, which may be the same or different, and which may be present on either one ring or both rings. In some embodiments, B is a bicylic heteroaryl selected from the group consisting of:,  ,  , or  ; wherein the wavy lines denote attachment points to the parent molecule.

[0081] In some embodiments, B is selected from the group consisting of:  ,  ,  ,  ,  ,  ,  , and  ; wherein the wavy lines denote attachment points to the parent molecule.

[0082] In some embodiments, B is  . In some embodiments, B is  . In some embodiments, B is  . In some embodiments, B is  .

[0083] It is understood that each description of **B** may be combined with each description of R^1 and/or R^2 the same as if each and every combination were specifically and individually listed. It is similarly understood that each description of **B** may be combined with each description of **A** (and further with each description of R^1 and R^2) the same as if each and every combination were specifically and individually listed. For example, in one aspect, it is understood that each description of **B** may be combined in one aspect with a variation in which R^1 and R^2 are each hydrogen. In one such variation, **B** is as defined in any variation herein, R^1 and R^2 are each hydrogen and **A** is 4-hydroxyphenyl optionally further substituted by R^3 or 4-hydroxy-2-pyridyl optionally further substituted by R^4. In another variation, **B** is as defined in any variation herein, R^1 and R^2 are as defined in any variation herein and **A** is 4-hydroxyphenyl optionally further substituted by R^3 or 4-hydroxy-2-pyridyl optionally further substituted by R^4. In another variation, B is as defined in any variation herein, R^1 and R^2 are each hydrogen and A is 9- or 10-membered bicyclic heteroaryl (eg., quinolinyl or indazolyl) optionally substituted by R^4. In another variation, B is as defined in any variation herein, R^1 and R^2 are as defined in any variation herein and A is 9- or 10-membered bicyclic heteroaryl (eg., quinolinyl or indazolyl) optionally substituted by R^4.

[0084] In some embodiments, the compound of formula (I) is of the formula (II):



(II)

or a salt thereof, wherein R^1, R^2 and **B** are as defined for formula (I) or any embodiment or aspect or other variation thereof,

X is N, CH or CR^3;

each R^3 is independently halogen, -CN, $-OR^5$, $-SR^5$, $-NR^6R^7$, $-NO_2$, $-C(O)R^5$, $-C(O)OR^5$, $-C(O)NR^6R^7$, $-C(O)NR^5S(O)_2R^6$, $-OC(O)R^5$, $-OC(O)NR^6R^7$, $-NR^5C(O)R^6$, $-NR^5C(O)NR^6R^7$, $-S(O)R^5$, $-S(O)_2R^5$, C_3-C_6 cycloalkyl, or C_1-C_6 alkyl optionally substituted by halogen;

each R^5 is independently hydrogen, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl;

R^6 and R^7 are each independently hydrogen, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl;

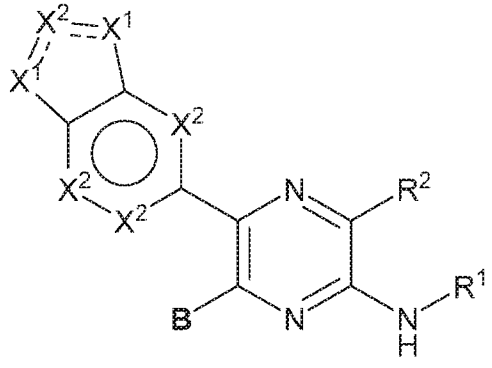
or R^6 and R^7 are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl; and

n is 0, 1, 2 or 3.

[0085] In some embodiments, provided is a compound of formula (II), or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

[0086] In some embodiments of the compound of formula (II), R^3 is selected from the group consisting of halogen, $-OR^5$ and C_1-C_6 alkyl optionally substituted by halogen.

[0087] In some embodiments, the compound of formula (I) is a compound of formula (IIIa):



(IIIa),

or a salt thereof, wherein R^1, R^2 and B are as defined for formula (I);

each X^1 is independently O, S, NH, NR^{4a}, CH_2, CHR^{4b}, $CR^{4b}R^{4b}$, N, CH or CR^{4b};

each X^2 is independently NH, NR^{4a}, CHR^{4b}, $CR^{4b}R^{4b}$, CH, CR^{4b} or N;

each $\overline{\quad}$ is a single or double bond, provided that when $X^1\overline{\quad}X^2$ is a double bond, $X^2\overline{\quad}X^1$ is a single bond and when $X^2\overline{\quad}X^1$ is a double bond, $X^1\overline{\quad}X^2$ is a single bond;

R^{4a} is C_1-C_6 alkyl;

each R^{4b} is independently halogen, -CN, $-OR^5$, $-SR^5$, $-NR^6R^7$, $-NO_2$, $-C(O)R^5$, $-C(O)OR^5$, $-C(O)NR^6R^7$, $-C(O)NR^5S(O)_2R^6$, $-OC(O)R^5$, $-OC(O)NR^6R^7$, $-NR^5C(O)R^6$, $-NR^5C(O)NR^6R^7$, $-S(O)R^5$, $-S(O)_2R^5$, C_3-C_6 cycloalkyl, or C_1-C_6 alkyl optionally substituted by halogen;

where each R^5 is independently hydrogen, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl; and

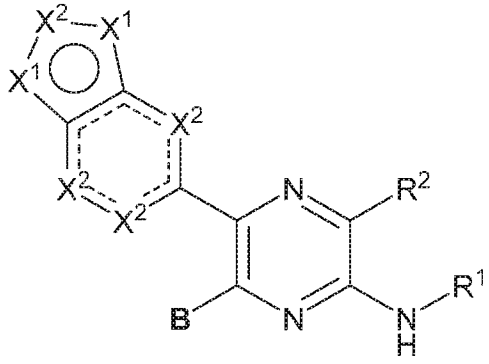
R^6 and R^7 are each independently hydrogen, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl;

or R^6 and R^7 are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl,

provided the compound is other than a compound selected from Table 1 or a salt thereof.

[0088] In some embodiments, provided is a compound of formula (IIIa), or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

[0089] In some embodiments, the compound of formula (I) is a compound of formula (IIIb):



(IIIb),

or a salt thereof, wherein R^1, R^2 and B are as defined for formula (I);

each X^1 is independently O, S, NH, NR^{4a}, CH_2, CHR^{4b}, $CR^{4b}R^{4b}$, N, CH or CR^{4b};

each X^2 is independently NH, NR^{4a}, CH_2, CHR^{4b}, $CR^{4b}R^{4b}$, CH, CR^{4b} or N;

each $\overline{\quad}$ is a single or double bond;

R^{4a} is C_1-C_6 alkyl;

each R^{4b} is independently halogen, -CN, -OR^5, -SR^5, -NR^6R^7, -NO_2, -C(O)R^5, -C(O)OR^5, -C(O)NR^6R^7, -C(O)$NR^5S(O)_2R^6$, -OC(O)R^5, -OC(O)NR^6R^7, -$NR^5C(O)R^6$, -$NR^5C(O)NR^6R^7$, -S(O)R^5, -$S(O)_2R^5$, C_3-C_6 cycloalkyl, or C_1-C_6 alkyl optionally substituted by halogen;

where each R^5 is independently hydrogen, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl; and

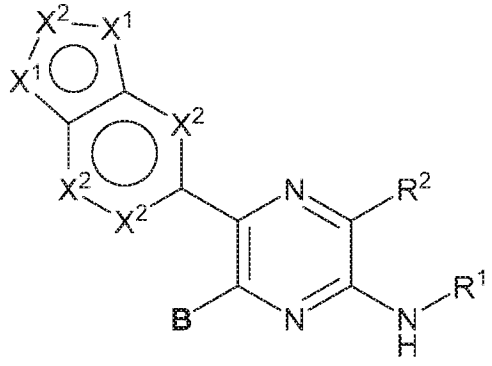
R^6 and R^7 are each independently hydrogen, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl;

or R^6 and R^7 are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl,

provided the compound is other than a compound selected from Table 1 or a salt thereof.

[0090] In some embodiments, provided is a compound of formula (IIIb), or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

[0091] In some embodiments, the compound of formula (I) is a compound of formula (IIIc):



(IIIc),

or a salt thereof, wherein R^1, R^2 and B are as defined for formula (I);

each X^1 is independently O, S, NH, NR^{4a}, CH_2, CHR^{4b}, $CR^{4b}R^{4b}$, N, CH or CR^{4b};

each X^2 is independently CH, CR^{4b} or N;

R^{4a} is C_1-C_6 alkyl;

each R^{4b} is independently halogen, -CN, -OR^5, -SR^5, -NR^6R^7, -NO_2, -C(O)R^5, -C(O)OR^5, -C(O)NR^6R^7, -C(O)$NR^5S(O)_2R^6$, -OC(O)R^5, -OC(O)NR^6R^7, -$NR^5C(O)R^6$, -$NR^5C(O)NR^6R^7$, -S(O)R^5, -$S(O)_2R^5$, C_3-C_6 cycloalkyl, or C_1-C_6 alkyl optionally substituted by halogen;

where each R^5 is independently hydrogen, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl; and

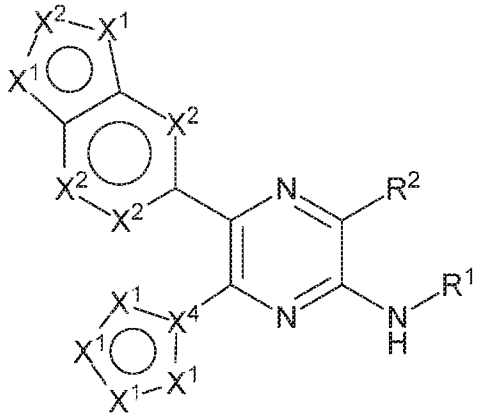
R^6 and R^7 are each independently hydrogen, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl;

or R^6 and R^7 are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl,

provided the compound is other than a compound selected from Table 1 or a salt thereof.

[0092] In some embodiments, provided is a compound of formula (IIIc), or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

[0093] In some embodiments, the compound of formula (I) is a compound of formula (IIIc-1):



(IIIc-1),

or a salt thereof, wherein R^1 and R^2 are as defined for formula (I);

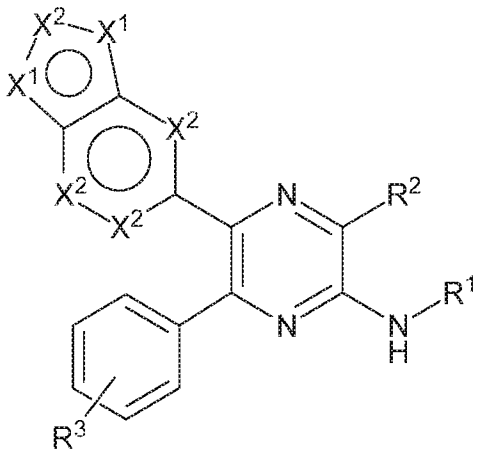
each X^1 and X^2 are as defined for formula (IIIc);

X^4 is C or N;

provided the compound is other than a compound selected from Table 1 or a salt thereof.

[0094] In some embodiments, provided is a compound of formula (IIIc-1), or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

[0095] In some embodiments, the compound of formula (I) is a compound of formula (IIIc-2):



(IIIc-2),

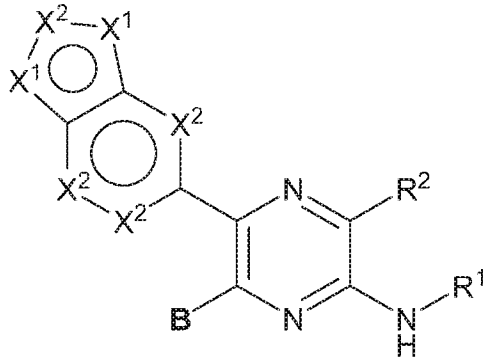
or a salt thereof, wherein R^1, R^2 and R^3 are as defined for formula (I);

each X^1 and X^2 are as defined for formula (IIIc);

provided the compound is other than a compound selected from Table 1 or a salt thereof.

[0096] In some embodiments, provided is a compound of formula (IIIc-2), or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

[0097] In some embodiments, the compound of formula (I) is a compound of formula (IIId):



(IIId),

or a salt thereof, wherein R^1, R^2 and B are as defined for formula (I);

each X^1 is independently O, S, NH, CH_2, CHR^{4b}, $CR^{4b}R^{4b}$, N, CH or CR^{4b};

each X^2 is independently CH, CR^{4b} or N;

each R^{4b} is independently halogen, -CN, $-OR^5$, $-SR^5$, $-NR^6R^7$, $-NO_2$, $-C(O)R^5$, $-C(O)OR^5$, $-C(O)NR^6R^7$, $-C(O)NR^5S(O)_2R^6$, $-OC(O)R^5$, $-OC(O)NR^6R^7$, $-NR^5C(O)R^6$, $-NR^5C(O)NR^6R^7$, $-S(O)R^5$, $-S(O)_2R^5$, C_3-C_6 cycloalkyl, or C_1-C_6 alkyl optionally substituted by halogen;

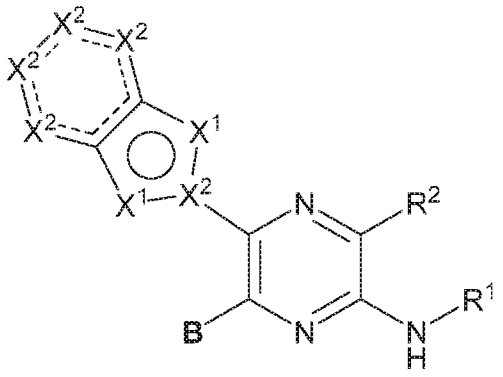
where each R^5 is independently hydrogen, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl; and

R^6 and R^7 are each independently hydrogen, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl;

or R^6 and R^7 are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl.

[0098] In some embodiments, provided is a compound of formula (IIId), or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

[0099] In some embodiments, the compound of formula (I) is a compound of formula (IIIe):



(IIIe),

or a salt thereof, wherein R^1, R^2 and B are as defined for formula (I);

each X^1 is independently O, S, NH, NR^{4a}, CH_2, CHR^{4b}, $CR^{4b}R^{4b}$, N, CH or CR^{4b};

each X^2 is independently O, CH_2, CHR^{4b}, $CR^{4b}R^{4b}$, CH, CR^{4b} or N;

each $\overline{--}$ is a single or double bond;

R^{4a} is C_1-C_6 alkyl;

each R^{4b} is independently halogen, -CN, $-OR^5$, $-SR^5$, $-NR^6R^7$, $-NO_2$, $-C(O)R^5$, $-C(O)OR^5$, $-C(O)NR^6R^7$, $-C(O)NR^5S(O)_2R^6$, $-OC(O)R^5$, $-OC(O)NR^6R^7$, $-NR^5C(O)R^6$, $-NR^5C(O)NR^6R^7$, $-S(O)R^5$, $-S(O)_2R^5$, C_3-C_6 cycloalkyl, or C_1-C_6 alkyl optionally substituted by halogen;

where each R^5 is independently hydrogen, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl; and

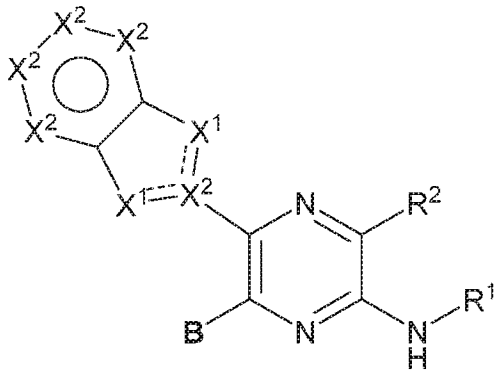
R^6 and R^7 are each independently hydrogen, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl;

or R^6 and R^7 are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl,

provided the compound is other than a compound selected from Table 1 or a salt thereof.

[0100] In some embodiments, provided is a compound of formula (IIIe), or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

[0101] In some embodiments, the compound of formula (I) is a compound of formula (IIIf):



(IIIf),

or a salt thereof, wherein R^1, R^2 and B are as defined for formula (I);

each X^1 is independently O, S, NH, NR^{4a}, CH_2, CHR^{4b}, $CR^{4b}R^{4b}$, N, CH or CR^{4b};

each X^2 is independently C, CH, CR^{4b} or N;

each $\overline{\overline{\quad}}$ is a single or double bond, provided that when $X^1\overline{\overline{\quad}}X^2$ is a double bond, $X^2\overline{\overline{\quad}}X^1$ is a single bond and when $X^2\overline{\overline{\quad}}X^1$ is a double bond, $X^1\overline{\overline{\quad}}X^2$ is a single bond;

R^{4a} is C_1-C_6 alkyl;

each R^{4b} is independently halogen, -CN, $-OR^5$, $-SR^5$, $-NR^6R^7$, $-NO_2$, $-C(O)R^5$, $-C(O)OR^5$, $-C(O)NR^6R^7$, $-C(O)NR^5S(O)_2R^6$, $-OC(O)R^5$, $-OC(O)NR^6R^7$, $-NR^5C(O)R^6$, $-NR^5C(O)NR^6R^7$, $-S(O)R^5$, $-S(O)_2R^5$, C_3-C_6 cycloalkyl, or C_1-C_6 alkyl optionally substituted by halogen;

where each R^5 is independently hydrogen, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl; and

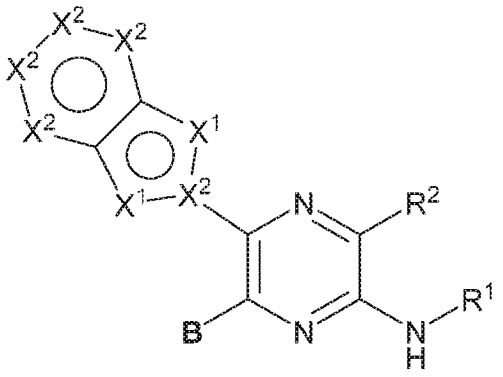
R^6 and R^7 are each independently hydrogen, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl;

or R^6 and R^7 are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl,

provided the compound is other than a compound selected from Table 1 or a salt thereof.

[0102] In some embodiments, provided is a compound of formula (IIIf), or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

[0103] In some embodiments, the compound of formula (I) is a compound of formula (IIIg):



(IIIg),

or a salt thereof, wherein R^1, R^2 and B are as defined for formula (I);

each X^1 is independently O, S, NH, NR^{4a}, N, CH or CR^{4b};

each X^2 is independently C, CH, CR^{4b} or N;

R^{4a} is C_1-C_6 alkyl;

each R^{4b} is independently halogen, -CN, $-OR^5$, $-SR^5$, $-NR^6R^7$, $-NO_2$, $-C(O)R^5$, $-C(O)OR^5$, $-C(O)NR^6R^7$, $-C(O)NR^5S(O)_2R^6$, $-OC(O)R^5$, $-OC(O)NR^6R^7$, $-NR^5C(O)R^6$, $-NR^5C(O)NR^6R^7$, $-S(O)R^5$, $-S(O)_2R^5$, C_3-C_6 cycloalkyl, or C_1-C_6 alkyl optionally substituted by halogen;

where each R^5 is independently hydrogen, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl; and

R^6 and R^7 are each independently hydrogen, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl;

or R^6 and R^7 are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl,

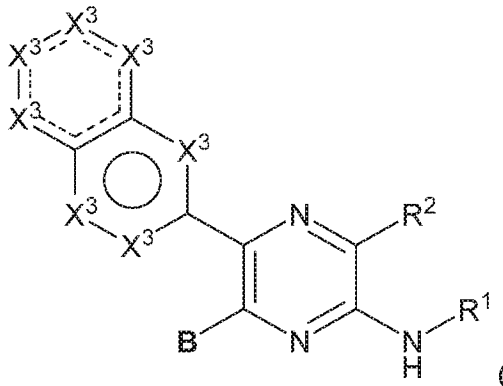
provided the compound is other than a compound selected from Table 1 or a salt thereof.

[0104] In some embodiments, provided is a compound of formula (IIIg), or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

[0105] In some embodiments of the compound of formula (III), R^{4b} is selected from the group consisting of halogen, $-OR^5$ and C_1-C_6 alkyl optionally substituted by halogen.

[0106] In some embodiments of the compound of formula (III), one of X^1 is N, and the other one of X^1 is NR^{4a}, and each X^2 is CH or CR^{4b}. In other embodiments of the compound of formula (III), one of X^1 is N, and the other one of X^1 is O or S, and each X^2 is CH or CR^{4b}.

[0107] In some embodiments, the compound of formula (I) is a compound of formula (IVa):



(IVa)

or a salt thereof, wherein R^1, R^2 and **B** are as defined for formula (I);

each X^3 is independently NH, NR^4, CH_2, CHR^4, CR^4R^4, CR^4, CH, C=O, O or N;

each $\overline{\quad}$ is a single or double bond;

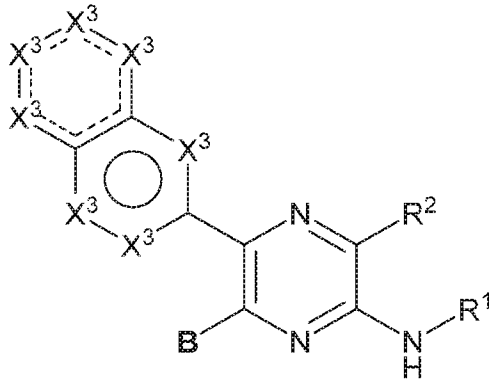
each R^4 is independently halogen, -CN, $-OR^5$, $-SR^5$, $-NR^6R^7$, $-NO_2$, $-C(O)R^5$, $-C(O)OR^5$, $-C(O)NR^6R^7$, $-C(O)NR^5S(O)_2R^6$, $-OC(O)R^5$, $-OC(O)NR^6R^7$, $-NR^5C(O)R^6$, $-NR^5C(O)NR^6R^7$, $-S(O)R^5$, $-S(O)_2R^5$, C_3-C_6 cycloalkyl, -(C_1-C_3 alkylene)(6-membered aryl) optionally substituted by halogen or C_1-C_6 alkyl optionally substituted by halogen;

where each R^5 is independently hydrogen, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl; and

R^6 and R^7 are each independently hydrogen, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl;

or R^6 and R^7 are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl.

[0108] In some embodiments, the compound of formula (I) is a compound of formula (IVa):



(IVa)

or a salt thereof, wherein R^1, R^2 and **B** are as defined for formula (I);

each X^3 is independently NH, NR^4, CH_2, CHR^4, CR^4R^4, CR^4, CH or N;

each $\overline{\quad}$ is a single or double bond;

each R^4 is independently halogen, -CN, -OR^5, -SR^5, -NR^6R^7, -NO_2, -$C(O)R^5$, -$C(O)OR^5$, -$C(O)NR^6R^7$, -$C(O)NR^5S(O)_2R^6$, -$OC(O)R^5$, -$OC(O)NR^6R^7$, -$NR^5C(O)R^6$, -$NR^5C(O)NR^6R^7$, -$S(O)R^5$, -$S(O)_2R^5$, C_3-C_6 cycloalkyl, or C_1-C_6 alkyl optionally substituted by halogen;

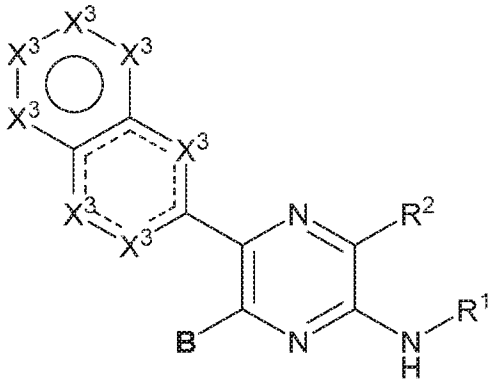
where each R^5 is independently hydrogen, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl; and

R^6 and R^7 are each independently hydrogen, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl;

or R^6 and R^7 are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl.

[0109] In some embodiments, provided is a compound of formula (IVa), or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

[0110] In some embodiments, the compound of formula (I) is a compound of formula (IVb):



(IVb)

or a salt thereof, wherein R^1, R^2 and **B** are as defined for formula (I);

each X^3 is independently NH, NR^4, CH_2, CHR^4, CR^4R^4, CR^4, CH or N;

each $\overline{--}$ is a single or double bond;

each R^4 is independently halogen, -CN, -OR^5, -SR^5, -NR^6R^7, -NO_2, -$C(O)R^5$, -$C(O)OR^5$, -$C(O)NR^6R^7$, -$C(O)NR^5S(O)_2R^6$, -$OC(O)R^5$, -$OC(O)NR^6R^7$, -$NR^5C(O)R^6$, -$NR^5C(O)NR^6R^7$, -$S(O)R^5$, -$S(O)_2R^5$, C_3-C_6 cycloalkyl, or C_1-C_6 alkyl optionally substituted by halogen;

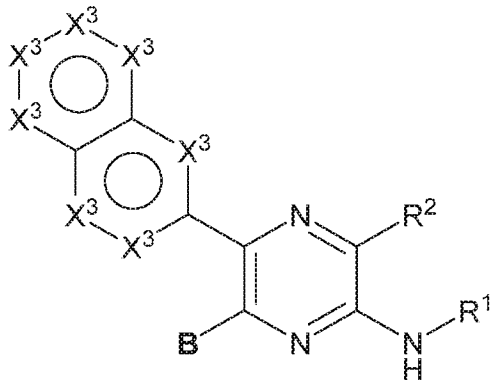
where each R^5 is independently hydrogen, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl; and

R^6 and R^7 are each independently hydrogen, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl;

or R^6 and R^7 are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl.

[0111] In some embodiments, provided is a compound of formula (IVb), or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

[0112] In some embodiments, the compound of formula (I) is a compound of formula (IVc):



(IVc),

or a salt thereof, wherein R^1, R^2 and **B** are as defined for formula (I);

each X^3 is independently CR^4, CH or N;

each R^4 is independently halogen, -CN, -OR^5, -SR^5, -NR^6R^7, -NO_2, -$C(O)R^5$, -$C(O)OR^5$, -$C(O)NR^6R^7$, -$C(O)NR^5S(O)_2R^6$, -$OC(O)R^5$, -$OC(O)NR^6R^7$, -$NR^5C(O)R^6$, -$NR^5C(O)NR^6R^7$, -$S(O)R^5$, -$S(O)_2R^5$, C_3-C_6 cycloalkyl, or C_1-C_6 alkyl optionally substituted by halogen;

where each R^5 is independently hydrogen, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl; and

R^6 and R^7 are each independently hydrogen, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl;

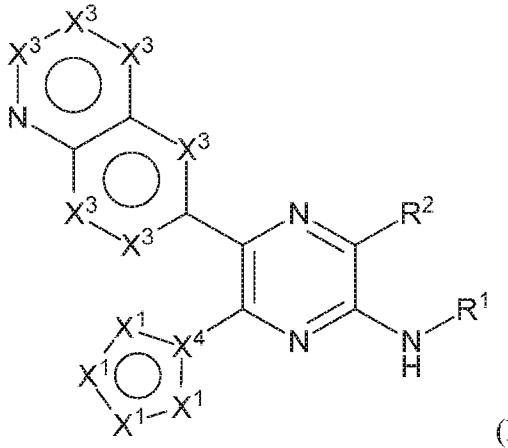
or R^6 and R^7 are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl.

[0113] In some embodiments, provided is a compound of formula (IVc), or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

[0114] In some embodiments of formula (IV), R^4 is selected from the group consisting of halogen, –OR^5 and C_1-C_6 alkyl optionally substituted by halogen.

[0115] In some embodiments, one X^3 is N, and the remaining X^3 are each CR^4. In some embodiments, two of the X^3 are N, and the remaining X^3 are each CR^4.

[0116] In some embodiments, the compound of formula (I) is a compound of formula (IVc-1):



(IVc-1),

or a salt thereof, wherein R^1 and R^2 are as defined for formula (I);

each X^1 is independently O, S, NH, NR^{4a}, N, CH or CR^{4b};

X^4 is C or N;

each X^3 is as defined for formula (IVc)

R^{4a} is C_1-C_6 alkyl;

each R^{4b} is independently halogen, -CN, $-OR^5$, $-SR^5$, $-NR^6R^7$, $-NO_2$, $-C(O)R^5$, $-C(O)OR^5$, $-C(O)NR^6R^7$, $-C(O)NR^5S(O)_2R^6$, $-OC(O)R^5$, $-OC(O)NR^6R^7$, $-NR^5C(O)R^6$, $-NR^5C(O)NR^6R^7$, $-S(O)R^5$, $-S(O)_2R^5$, C_3-C_6 cycloalkyl, or C_1-C_6 alkyl optionally substituted by halogen;

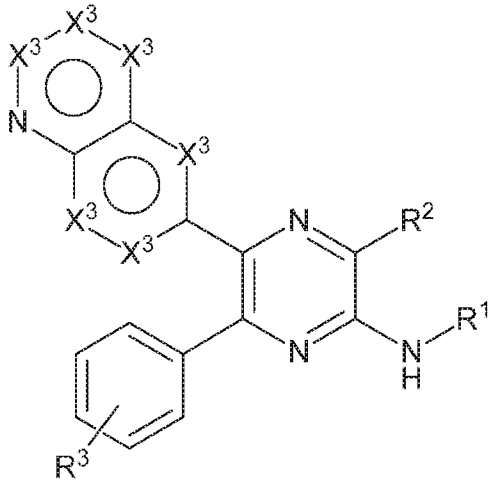
where each R^5 is independently hydrogen, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl; and

R^6 and R^7 are each independently hydrogen, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl;

or R^6 and R^7 are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl.

[0117] In some embodiments, provided is a compound of formula (IVc-1), or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

[0118] In some embodiments, the compound of formula (I) is a compound of formula (IVc-2):



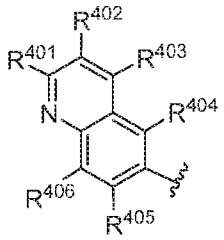
(IVc-2),

or a salt thereof, wherein R^1, R^2 and R^3 are as defined for formula (I);

each X_3 is as defined for formula (IVc);

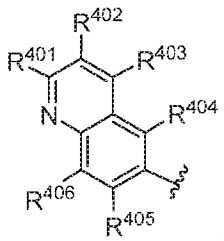
[0119] In some embodiments, provided is a compound of formula (IVc-2), or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

[0120] In some embodiments of a compound of formula (I), (IVa), (IVb), or (IVc), A is



, wherein R^{401}, R^{402}, R^{403}, R^{404}, R^{405}, and R^{406} are each independently R^4. In some embodiments, R^{401}, R^{402}, R^{403}, R^{404}, R^{405}, and R^{406} are each independently halogen, -CN, $-OR^5$, $-SR^5$, $-NR^6R^7$, $-NO_2$, $-C(O)R^5$, $-C(O)OR^5$, $-C(O)NR^6R^7$, $-C(O)NR^5S(O)_2R^6$, $-OC(O)R^5$, $-OC(O)NR^6R^7$, $-NR^5C(O)R^6$, $-NR^5C(O)NR^6R^7$, $-S(O)R^5$, $-S(O)_2R^5$, C_3-C_6 cycloalkyl, or C_1-C_6 alkyl optionally substituted by halogen.

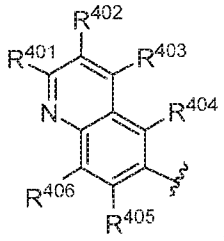
[0121] In some embodiments of a compound of formula (I), (IVa), (IVb), or (IVc), A is



, wherein R^{401}, R^{402}, R^{403}, R^{404}, R^{405}, and R^{406} are each independently halogen, -CN, $-OR^5$, $-SR^5$, $-NR^6R^7$, $-NO_2$, $-C(O)R^5$, $-C(O)OR^5$, $-C(O)NR^6R^7$, $-C(O)NR^5S(O)_2R^6$,

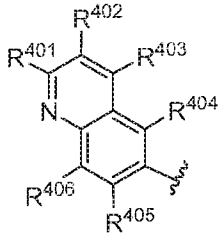
-OC(O)R^5, -OC(O)NR^6R^7, -NR^5C(O)R^6, -NR^5C(O)NR^6R^7, -S(O)R^5, -$S(O)_2R^5$, C_3-C_6 cycloalkyl, or C_1-C_6 alkyl optionally substituted by halogen; and **B** is phenyl, optionally substituted with R^3.

[0122] In some embodiments of a compound of formula (I), (IVa), (IVb), or (IVc), A is



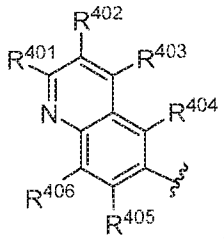
, wherein R^{401}, R^{402}, R^{403}, R^{404}, R^{405}, and R^{406} are each independently halogen, -CN, -OR^5, -SR^5, -NR^6R^7, -NO_2, -C(O)R^5, -C(O)OR^5, -C(O)NR^6R^7, -C(O)$NR^5S(O)_2R^6$, -OC(O)R^5, -OC(O)NR^6R^7, -NR^5C(O)R^6, -NR^5C(O)NR^6R^7, -S(O)R^5, -$S(O)_2R^5$, C_3-C_6 cycloalkyl, or C_1-C_6 alkyl optionally substituted by halogen; and **B** is 5- to 6-membered heteroaryl, optionally substituted with R^4.

[0123] In some embodiments of a compound of formula (I), (IVa), (IVb), or (IVc), A is



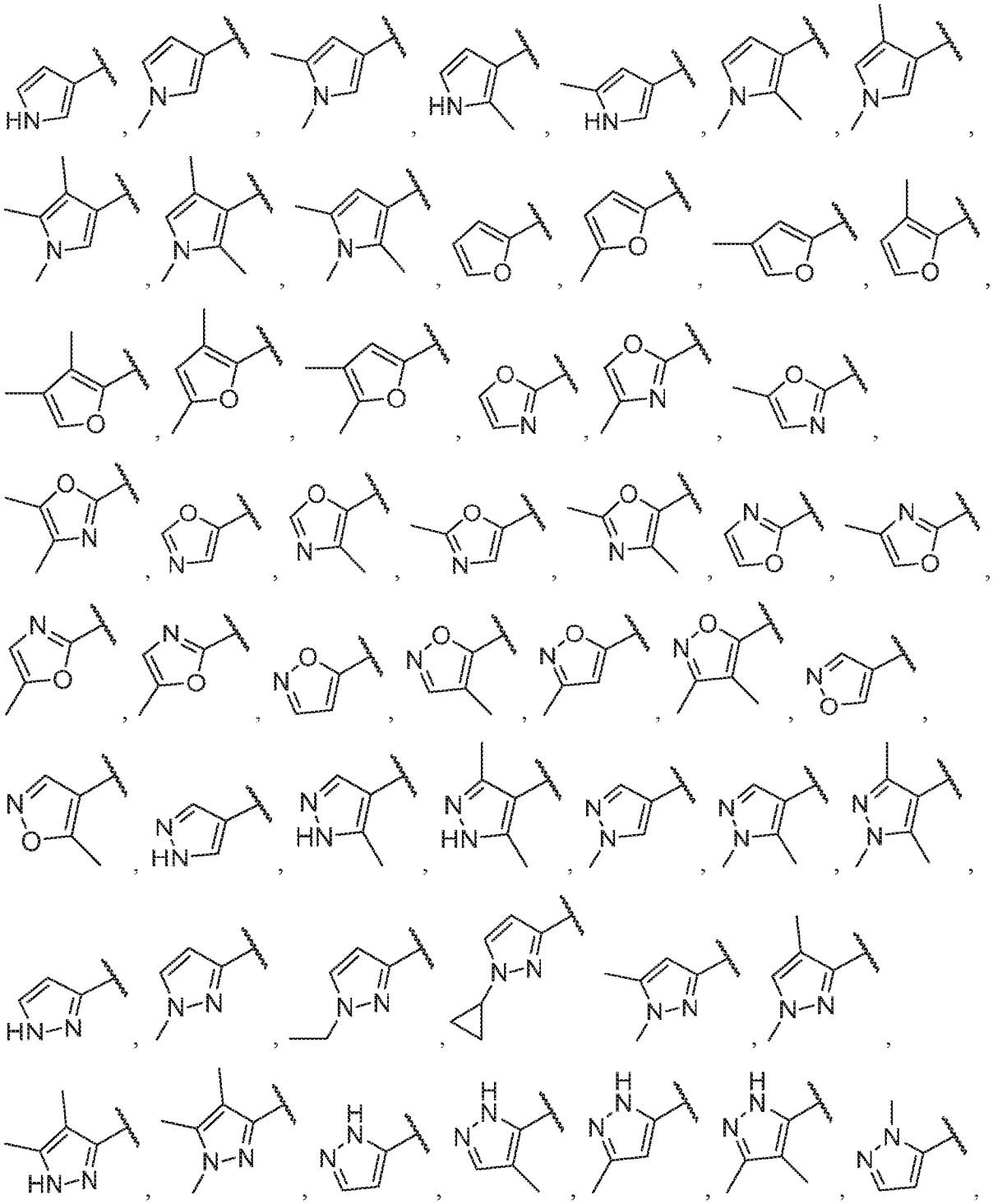
, wherein R^{401}, R^{402}, R^{403}, R^{404}, R^{405}, and R^{406} are each independently halogen, -CN, -OR^5, -SR^5, -NR^6R^7, -NO_2, -C(O)R^5, -C(O)OR^5, -C(O)NR^6R^7, -C(O)$NR^5S(O)_2R^6$, -OC(O)R^5, -OC(O)NR^6R^7, -NR^5C(O)R^6, -NR^5C(O)NR^6R^7, -S(O)R^5, -$S(O)_2R^5$, C_3-C_6 cycloalkyl, or C_1-C_6 alkyl optionally substituted by halogen; and **B** is 5-membered heteroaryl such as furanyl, oxazolyl, thiophenyl, pyrazolyl, isoxazolyl, 1,3,4-oxadiazolyl, imidazolyl, thiazolyl, isothiazolyl, triazolyl, 1,3,4-thiadiazolyl and tetrazolyl, each of which optionally substituted with R^4.

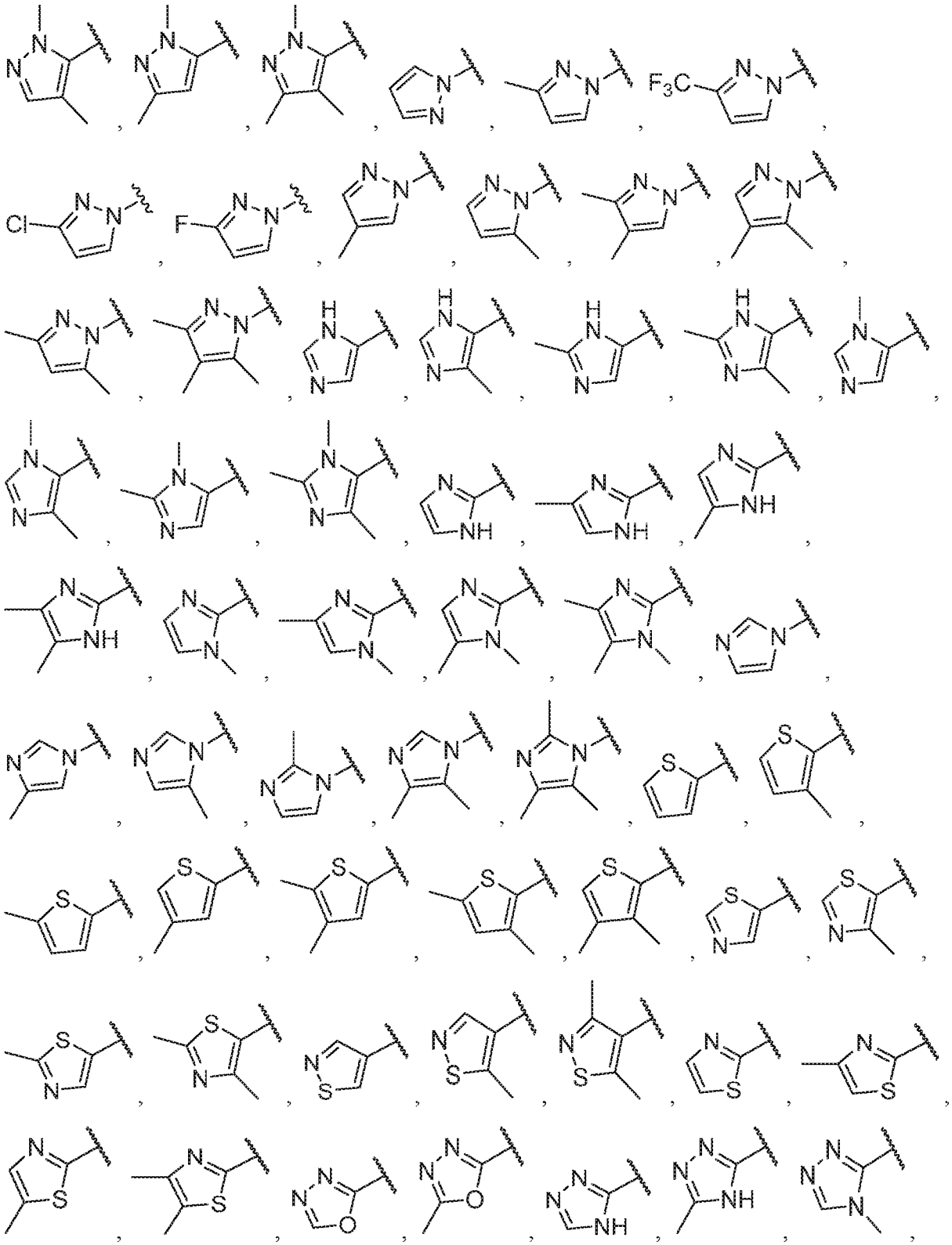
[0124] In some embodiments of a compound of formula (I), (IVa), (IVb), or (IVc), A is

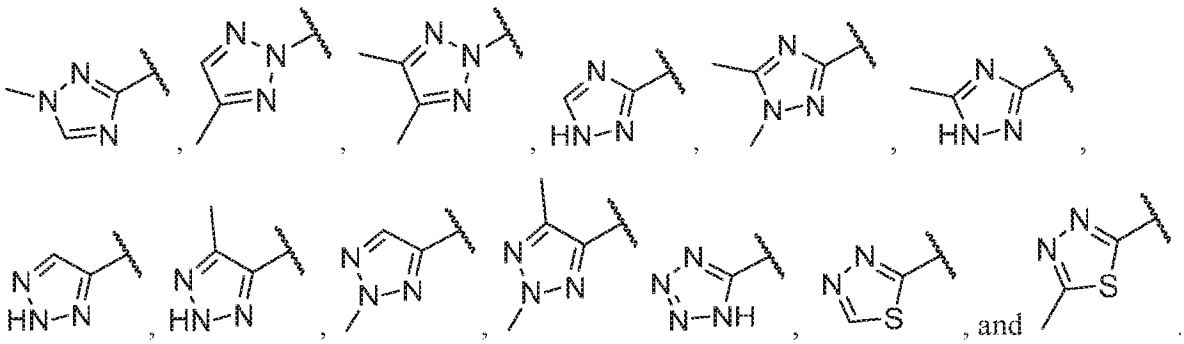


, wherein R^{401}, R^{402}, R^{403}, R^{404}, R^{405}, and R^{406} are each independently halogen, -CN, -OR^5, -SR^5, -NR^6R^7, -NO_2, -C(O)R^5, -C(O)OR^5, -C(O)NR^6R^7, -C(O)$NR^5S(O)_2R^6$,

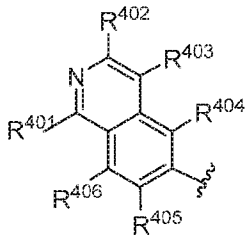
-OC(O)R^5, -OC(O)NR^6R^7, -NR^5C(O)R^6, -NR^5C(O)NR^6R^7, -S(O)R^5, -S(O)$_2R^5$, C_3-C_6 cycloalkyl, or C_1-C_6 alkyl optionally substituted by halogen; and **B** is selected from the group consisting of:





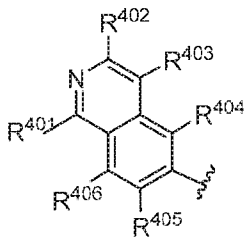


[0125] In some embodiments of a compound of formula (I), (IVa), (IVb), or (IVc), A is



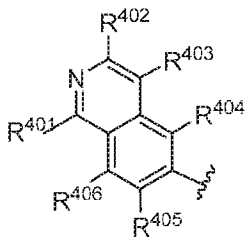
, wherein R^{401}, R^{402}, R^{403}, R^{404}, R^{405}, and R^{406} are each independently R^4. In some embodiments, R^{401}, R^{402}, R^{403}, R^{404}, R^{405}, and R^{406} are each independently halogen, -CN, $-OR^5$, $-SR^5$, $-NR^6R^7$, $-NO_2$, $-C(O)R^5$, $-C(O)OR^5$, $-C(O)NR^6R^7$, $-C(O)NR^5S(O)_2R^6$, $-OC(O)R^5$, $-OC(O)NR^6R^7$, $-NR^5C(O)R^6$, $-NR^5C(O)NR^6R^7$, $-S(O)R^5$, $-S(O)_2R^5$, C_3-C_6 cycloalkyl, or C_1-C_6 alkyl optionally substituted by halogen.

[0126] In some embodiments of a compound of formula (I), (IVa), (IVb), or (IVc), A is



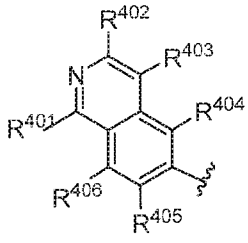
, wherein R^{401}, R^{402}, R^{403}, R^{404}, R^{405}, and R^{406} are each independently halogen, -CN, $-OR^5$, $-SR^5$, $-NR^6R^7$, $-NO_2$, $-C(O)R^5$, $-C(O)OR^5$, $-C(O)NR^6R^7$, $-C(O)NR^5S(O)_2R^6$, $-OC(O)R^5$, $-OC(O)NR^6R^7$, $-NR^5C(O)R^6$, $-NR^5C(O)NR^6R^7$, $-S(O)R^5$, $-S(O)_2R^5$, C_3-C_6 cycloalkyl, or C_1-C_6 alkyl optionally substituted by halogen; and **B** is phenyl, optionally substituted with R^3.

[0127] In some embodiments of a compound of formula (I), (IVa), (IVb), or (IVc), A is



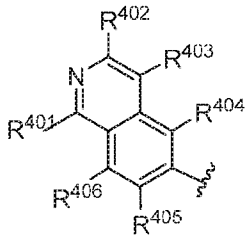
, wherein R^{401}, R^{402}, R^{403}, R^{404}, R^{405}, and R^{406} are each independently halogen, -CN, -OR^5, -SR^5, -NR^6R^7, -NO_2, -$C(O)R^5$, -$C(O)OR^5$, -$C(O)NR^6R^7$, -$C(O)NR^5S(O)_2R^6$, -$OC(O)R^5$, -$OC(O)NR^6R^7$, -$NR^5C(O)R^6$, -$NR^5C(O)NR^6R^7$, -$S(O)R^5$, -$S(O)_2R^5$, C_3-C_6 cycloalkyl, or C_1-C_6 alkyl optionally substituted by halogen; and **B** is 5- to 6-membered heteroaryl, optionally substituted with R^4.

[0128] In some embodiments of a compound of formula (I), (IVa), (IVb), or (IVc), A is

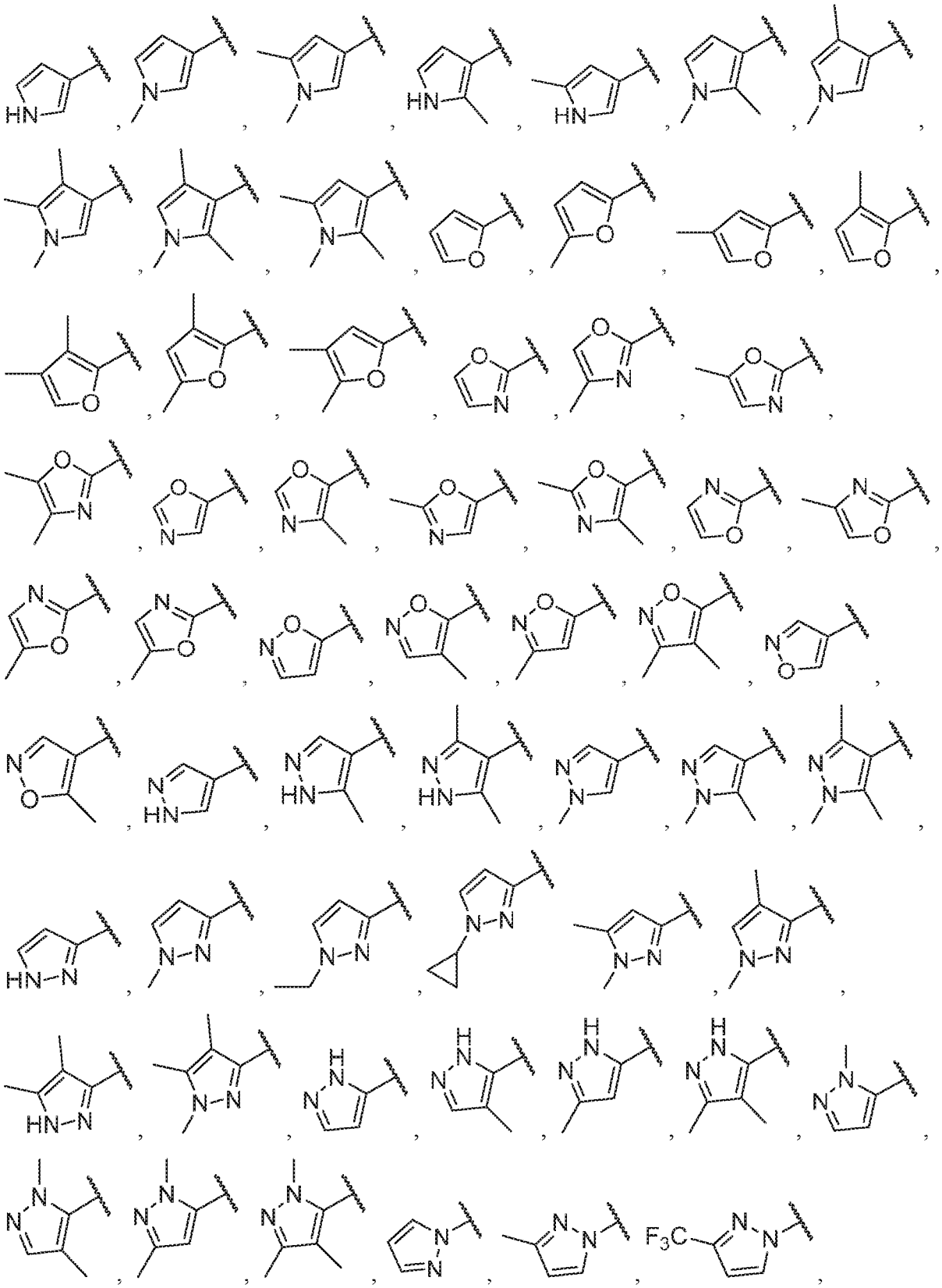


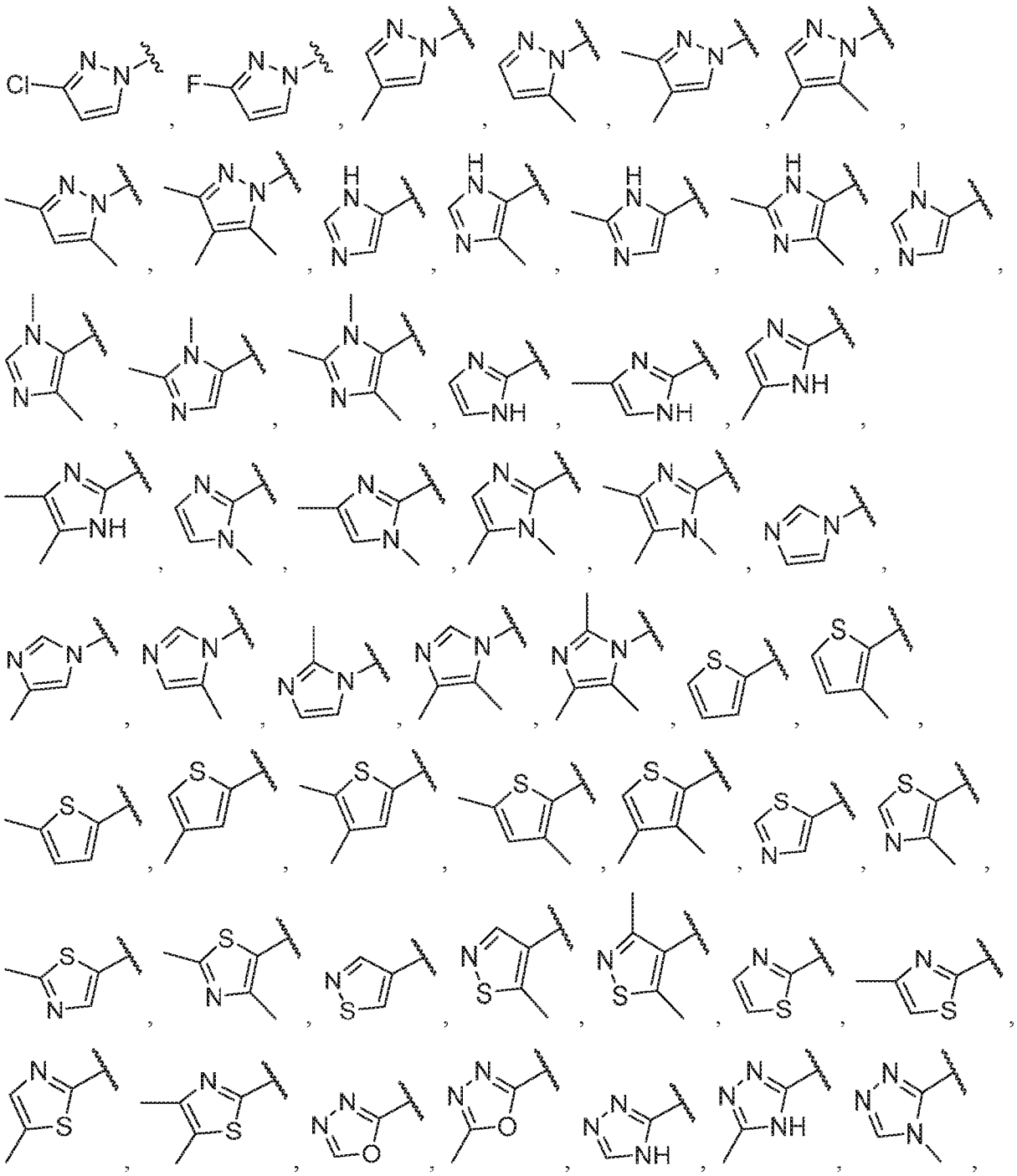
, wherein R^{401}, R^{402}, R^{403}, R^{404}, R^{405}, and R^{406} are each independently halogen, -CN, -OR^5, -SR^5, -NR^6R^7, -NO_2, -$C(O)R^5$, -$C(O)OR^5$, -$C(O)NR^6R^7$, -$C(O)NR^5S(O)_2R^6$, -$OC(O)R^5$, -$OC(O)NR^6R^7$, -$NR^5C(O)R^6$, -$NR^5C(O)NR^6R^7$, -$S(O)R^5$, -$S(O)_2R^5$, C_3-C_6 cycloalkyl, or C_1-C_6 alkyl optionally substituted by halogen; and **B** is 5-membered heteroaryl such as furanyl, oxazolyl, thiophenyl, pyrazolyl, isoxazolyl, 1,3,4-oxadiazolyl, imidazolyl, thiazolyl, isothiazolyl, triazolyl, 1,3,4-thiadiazolyl and tetrazolyl, each of which optionally substituted with R^4.

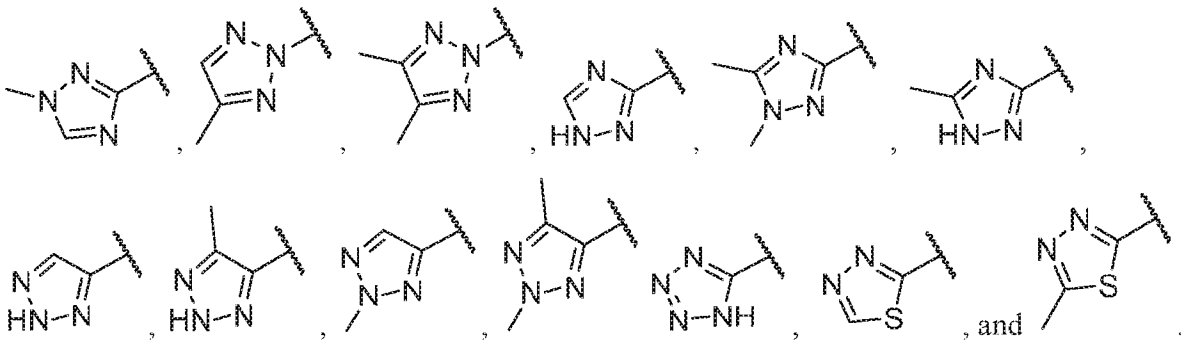
[0129] In some embodiments of a compound of formula (I), (IVa), (IVb), or (IVc), A is



, wherein R^{401}, R^{402}, R^{403}, R^{404}, R^{405}, and R^{406} are each independently halogen, -CN, -OR^5, -SR^5, -NR^6R^7, -NO_2, -$C(O)R^5$, -$C(O)OR^5$, -$C(O)NR^6R^7$, -$C(O)NR^5S(O)_2R^6$, -$OC(O)R^5$, -$OC(O)NR^6R^7$, -$NR^5C(O)R^6$, -$NR^5C(O)NR^6R^7$, -$S(O)R^5$, -$S(O)_2R^5$, C_3-C_6 cycloalkyl, or C_1-C_6 alkyl optionally substituted by halogen; and **B** is selected from the group consisting of:





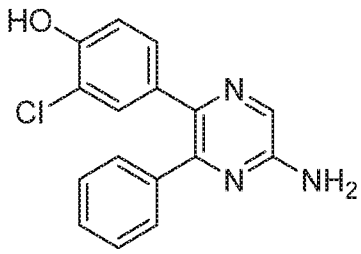
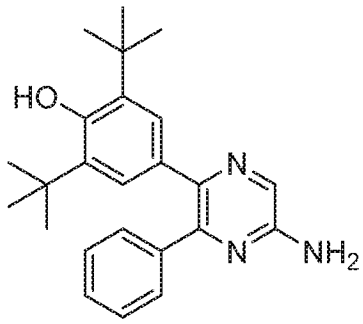
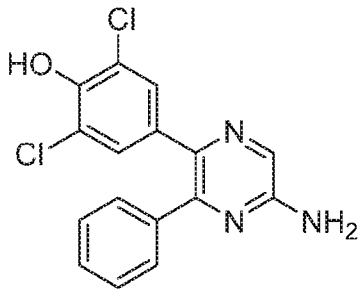
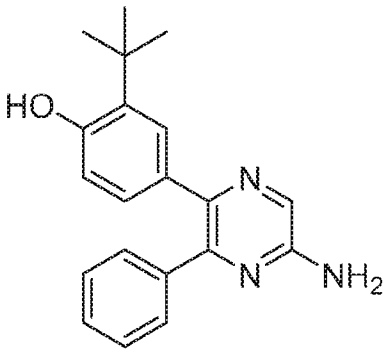
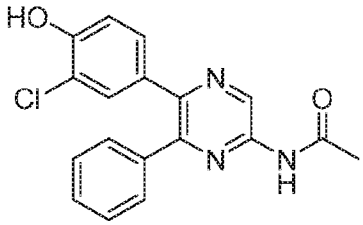
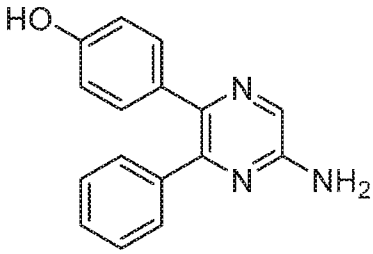
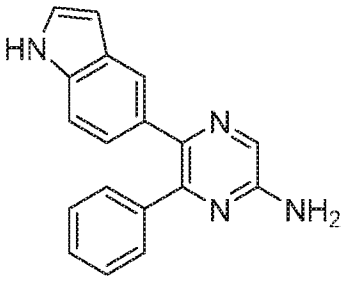
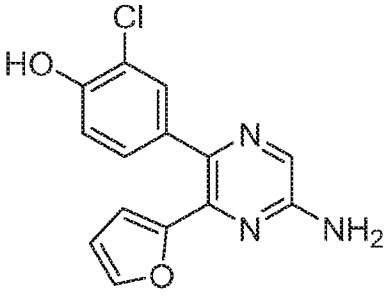


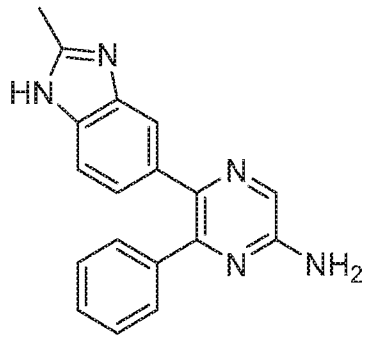
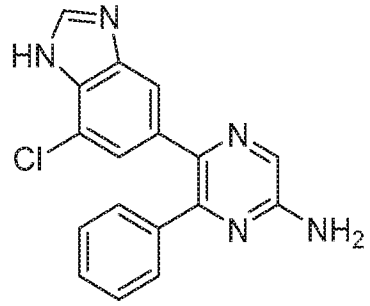
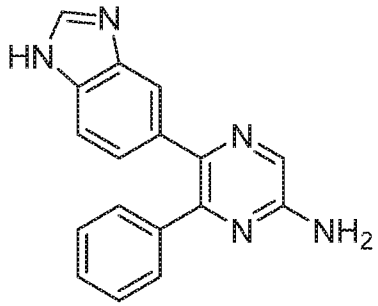
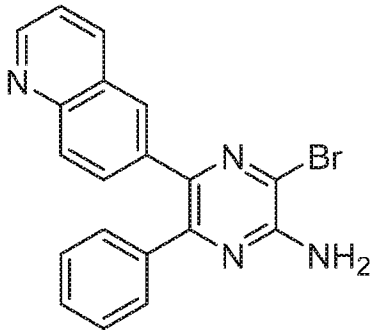
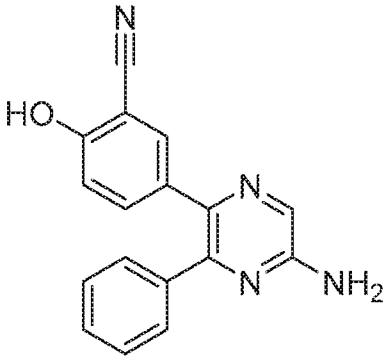
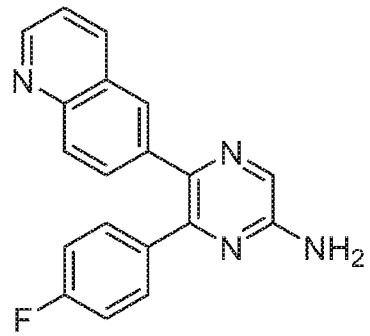
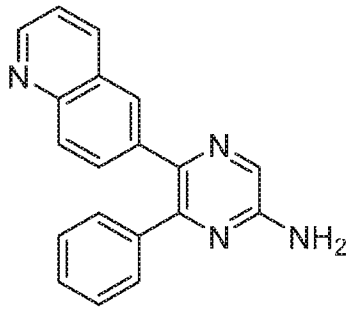
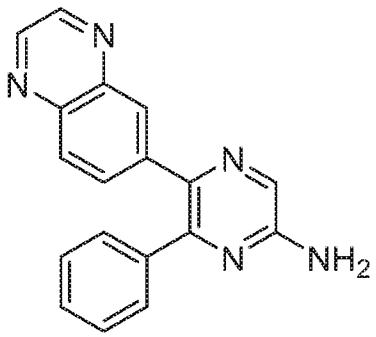
[0130] Also provided are salts of compounds referred to herein, such as pharmaceutically acceptable salts. The invention also includes any or all of the stereochemical forms, including any enantiomeric or diastereomeric forms, and any tautomers or other forms of the compounds described.

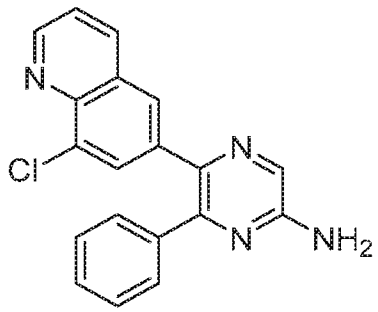
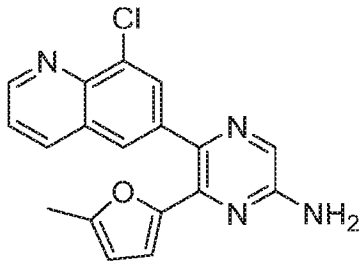
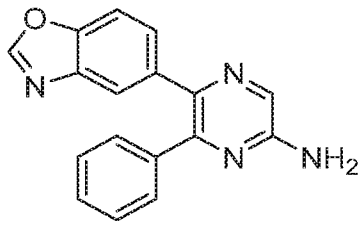
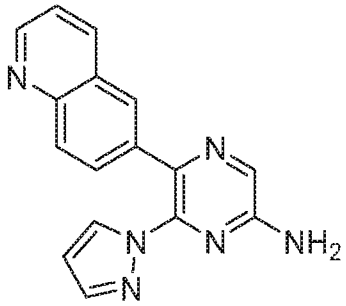
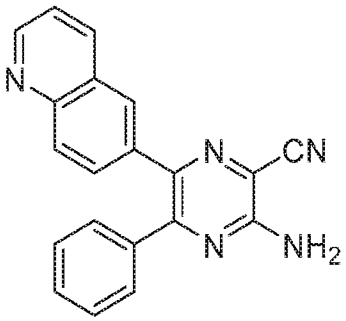
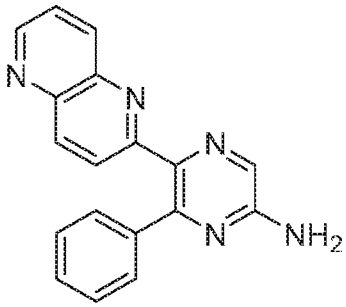
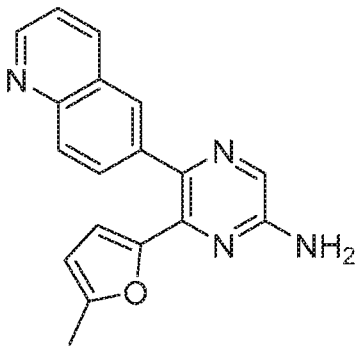
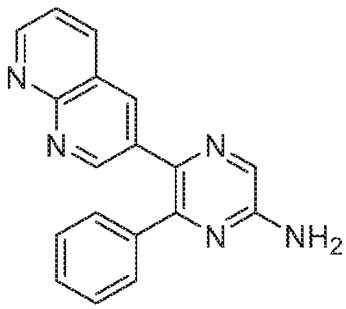
[0131] A compound as detailed herein may in one aspect be in a purified form and compositions comprising a compound in purified forms are detailed herein. Compositions comprising a compound as detailed herein or a salt thereof are provided, such as compositions of substantially pure compounds. In some embodiments, a composition containing a compound as detailed herein or a salt thereof 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 salt thereof. In some embodiments, a composition of substantially pure compound or a salt thereof 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 salt thereof is provided wherein the composition contains or no more than 3 %, 2%, 1% or 0.5% impurity.

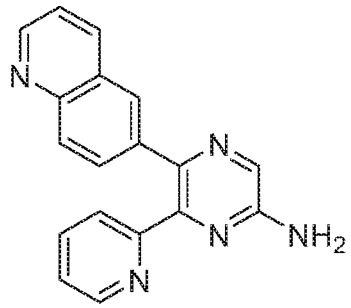
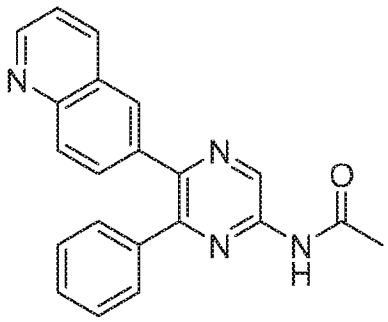
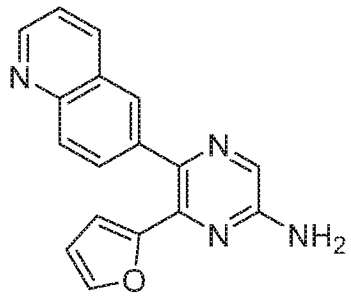
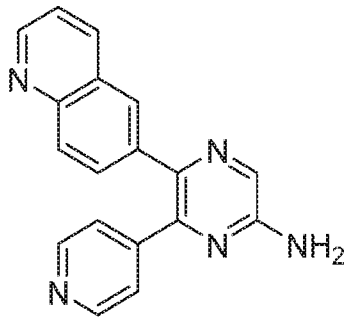
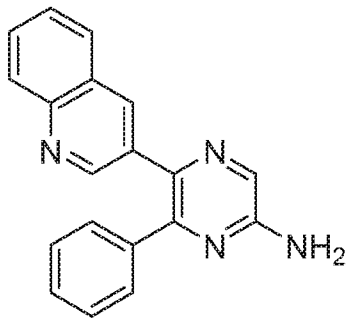
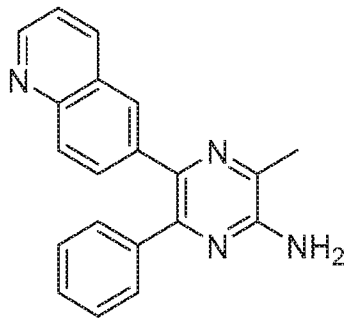
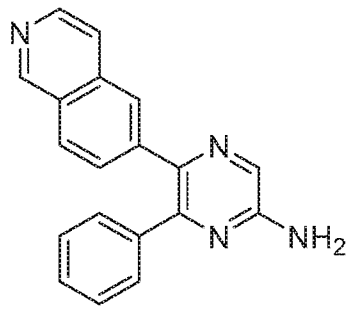
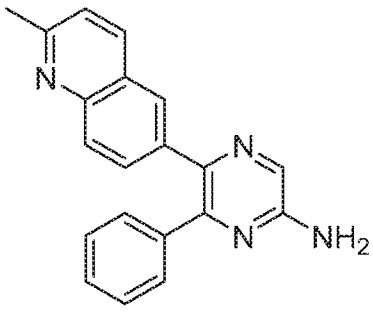
[0132] Representative compounds are listed in Table 2. It is understood that individual enantiomers and diastereomers if not depicted and their corresponding structures can be readily determined therefrom. Compounds 1.180-1.185 are provided as reference compounds.

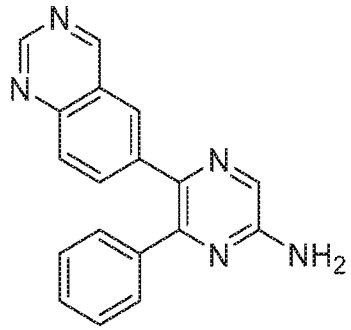
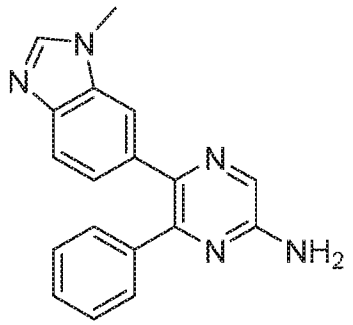
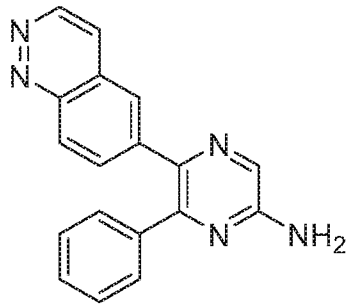
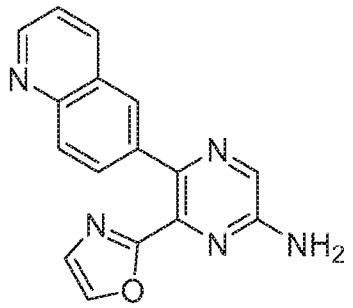
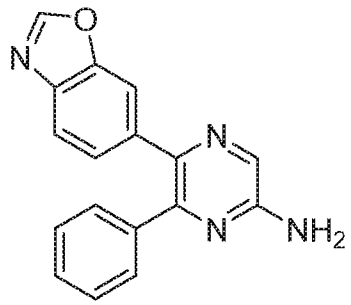
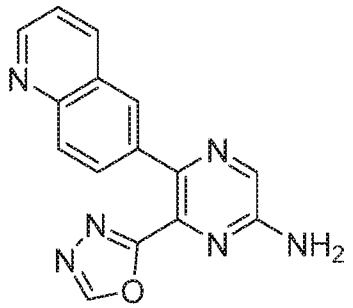
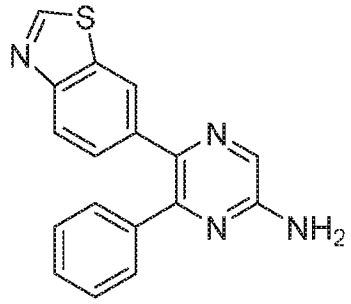
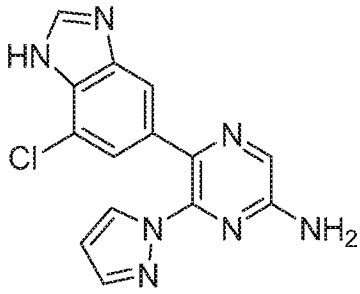
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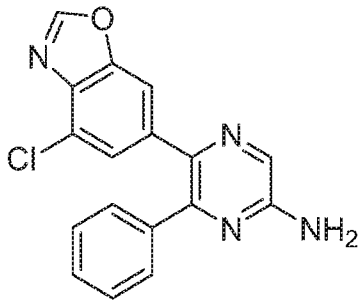
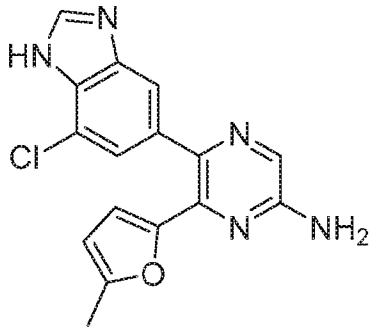
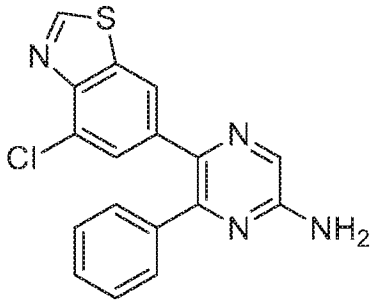
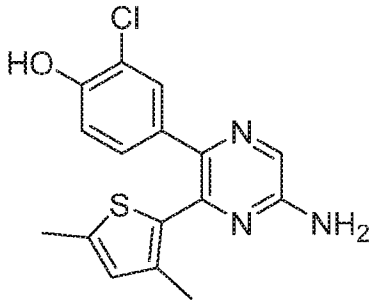
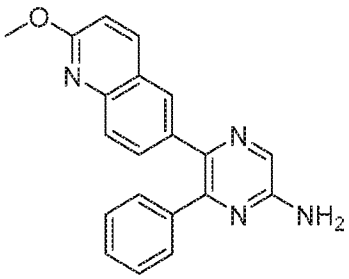
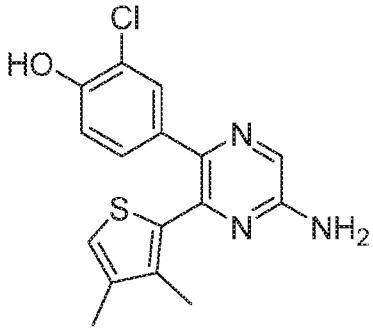
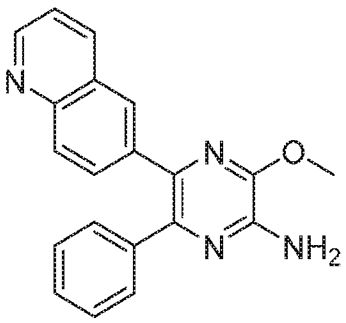
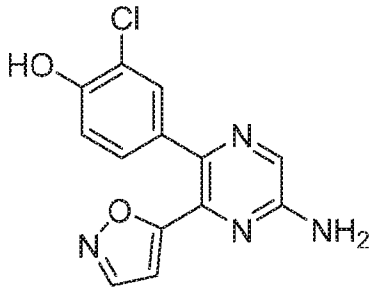
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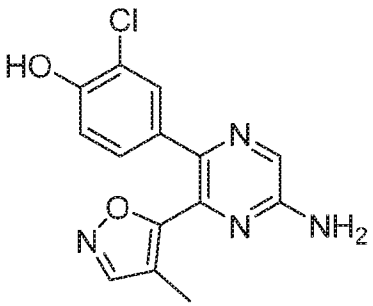
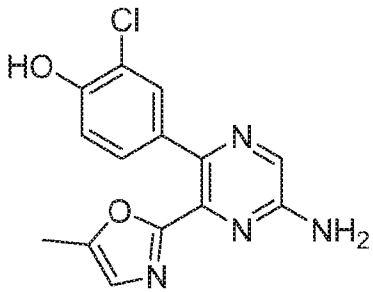
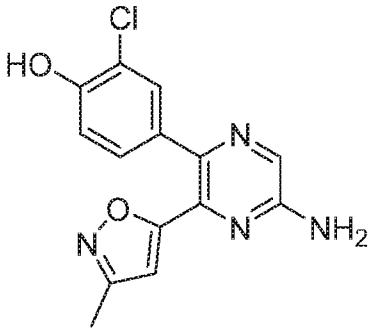
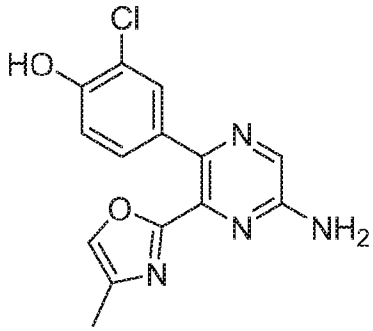
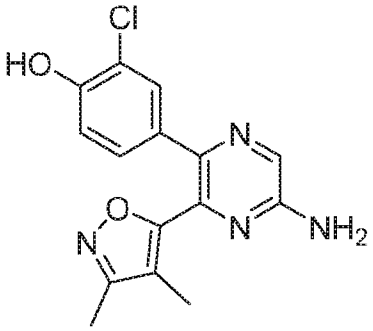
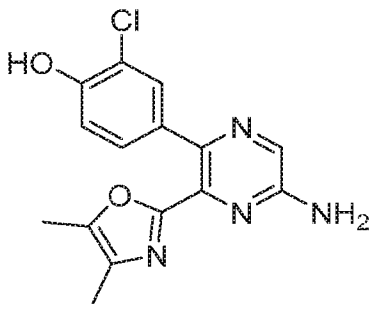
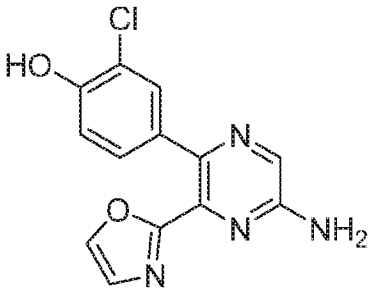
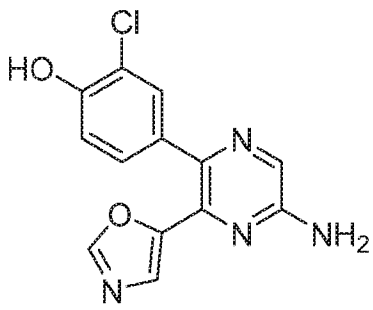
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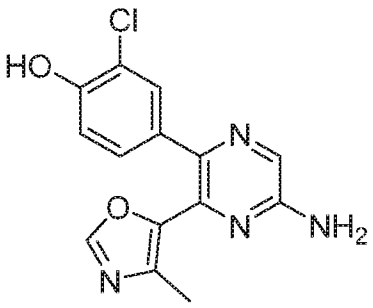
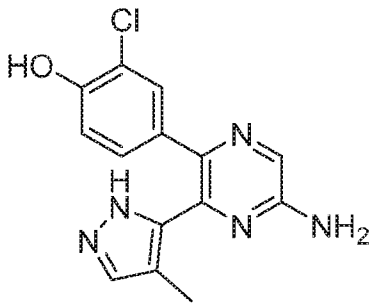
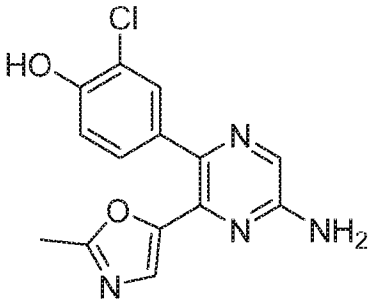
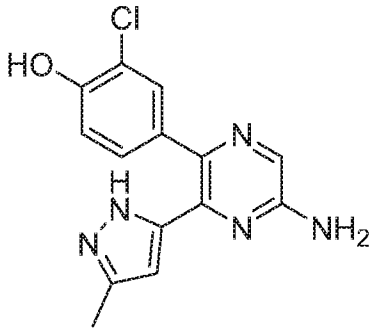
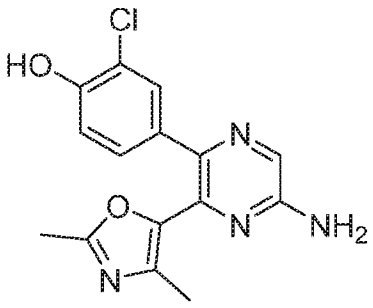
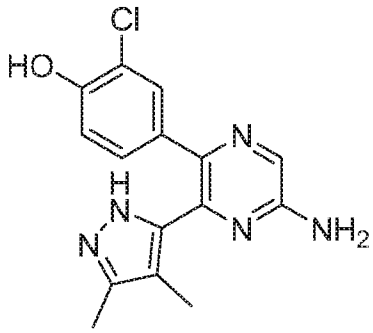
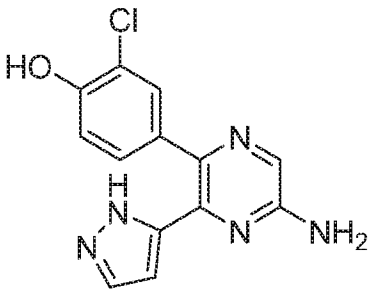
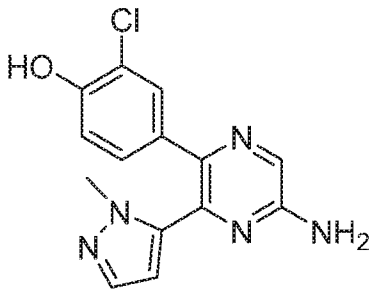
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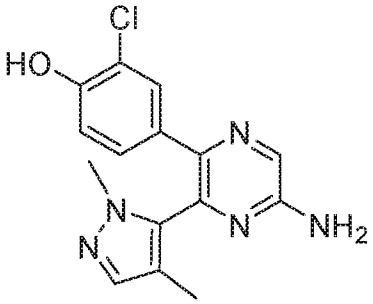
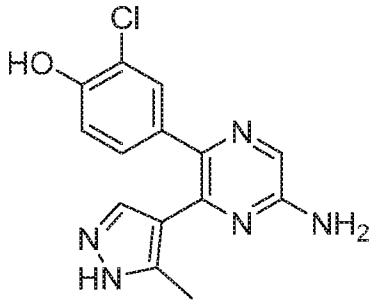
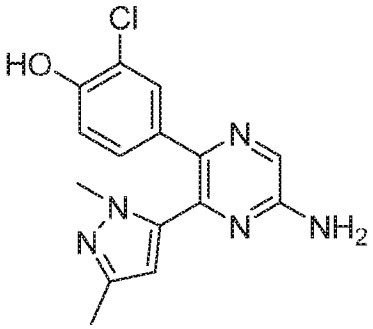
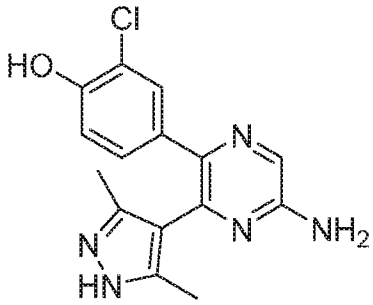
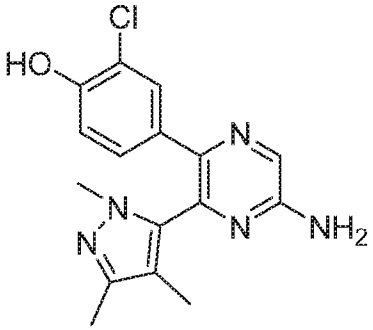
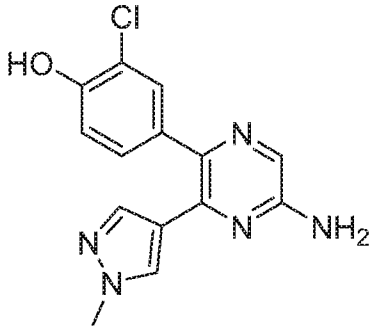
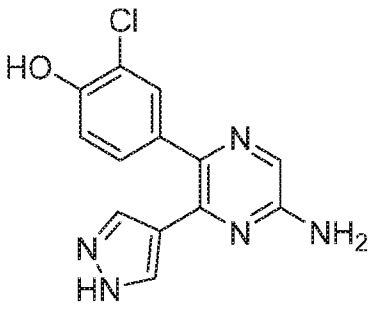
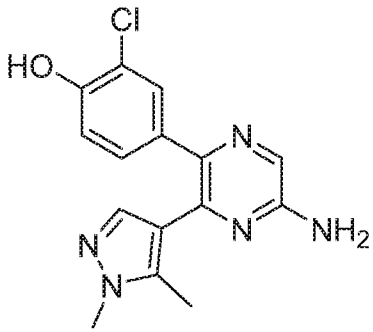
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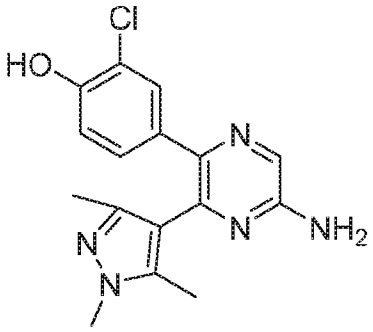
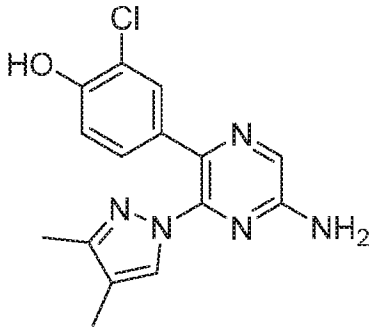
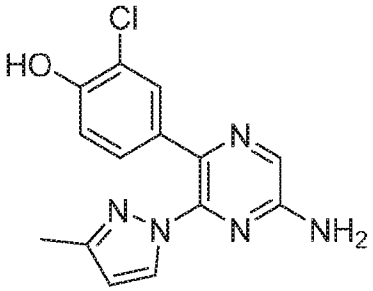
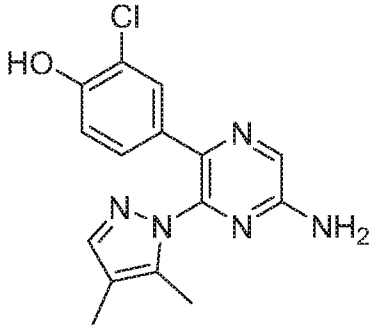
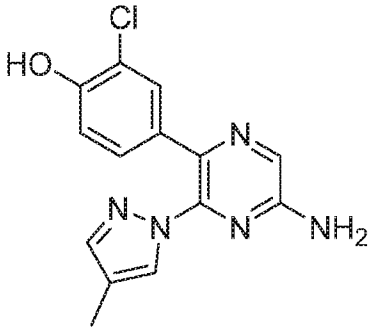
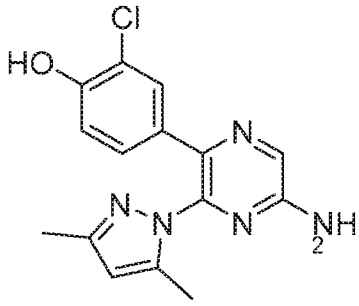
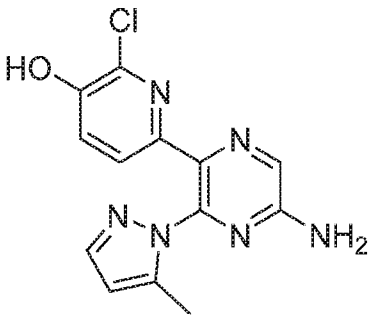
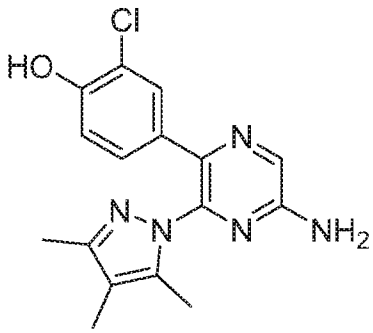
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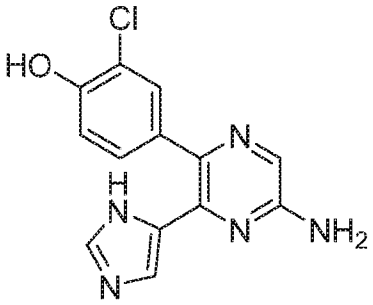
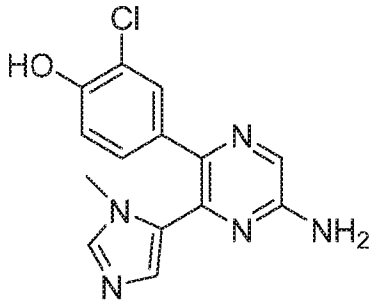
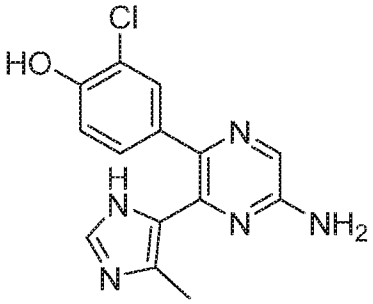
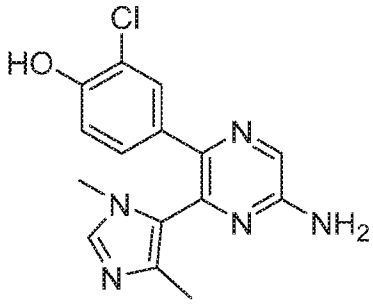
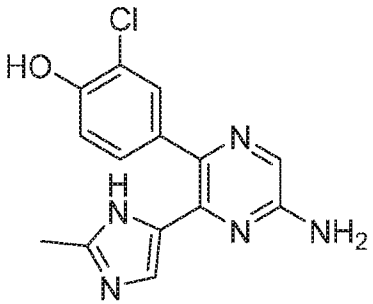
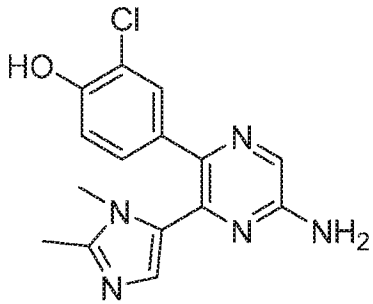
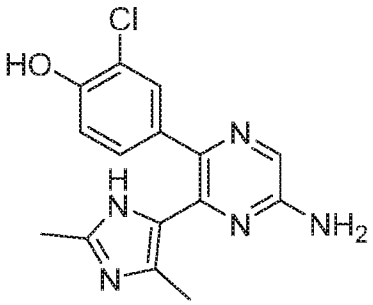
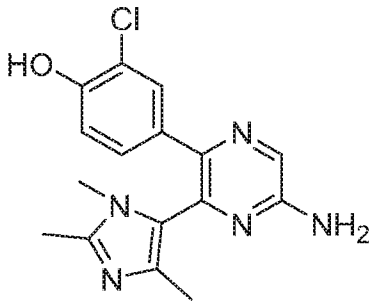
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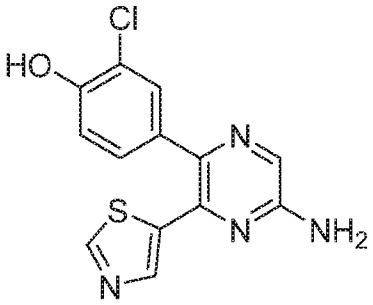
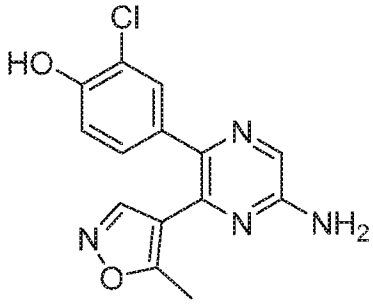
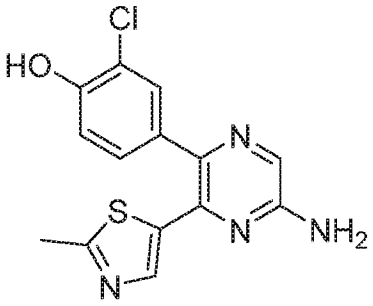
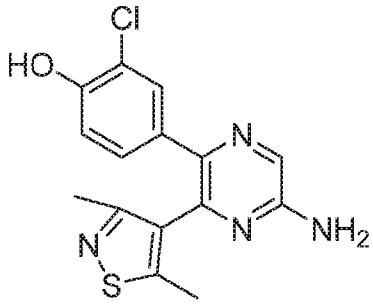
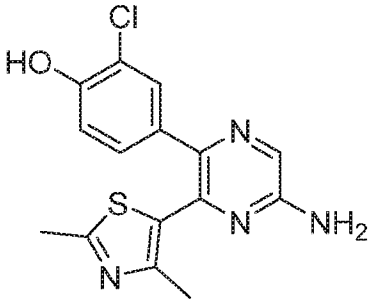
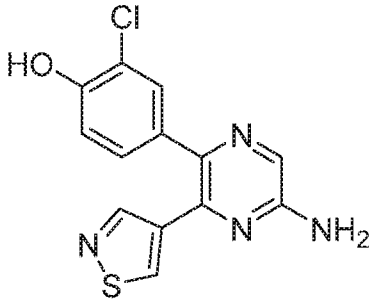
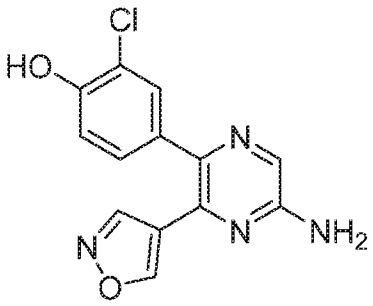
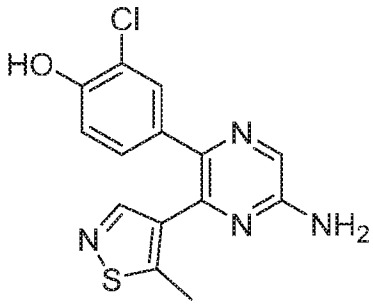
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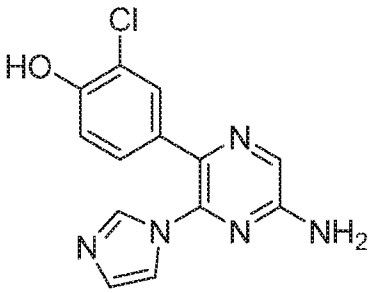
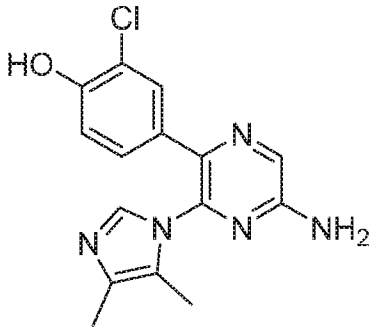
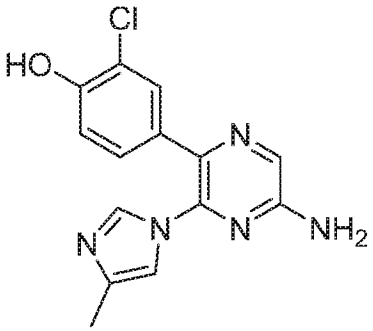
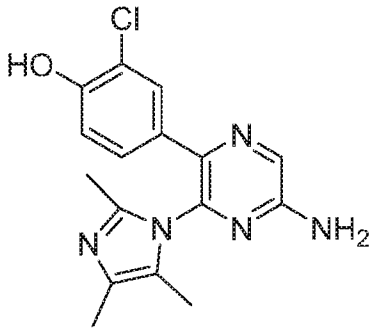
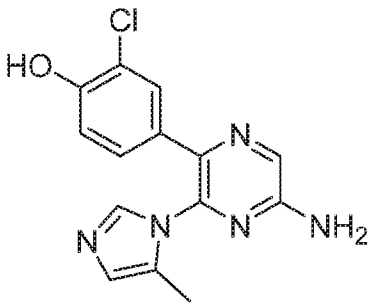
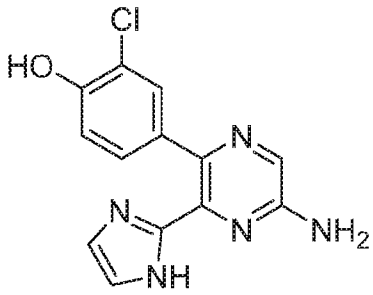
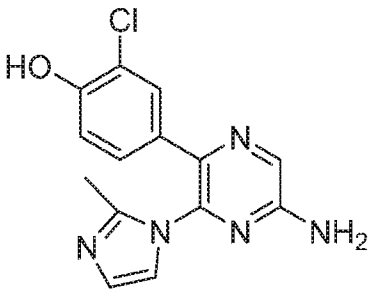
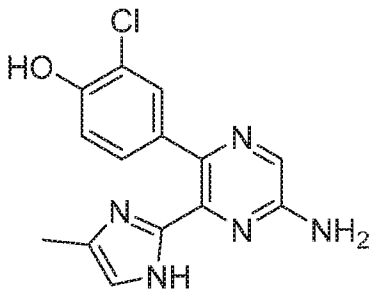
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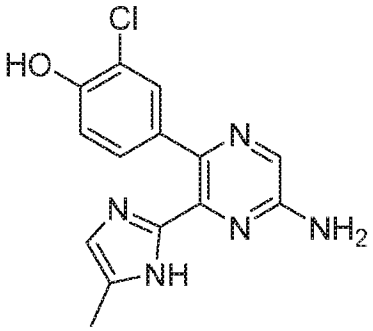
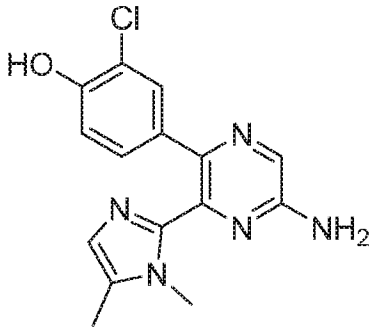
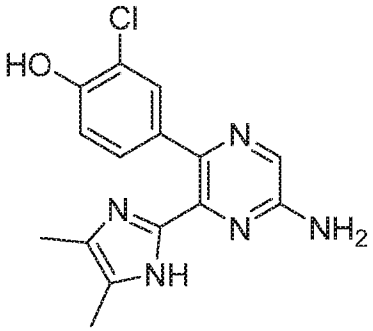
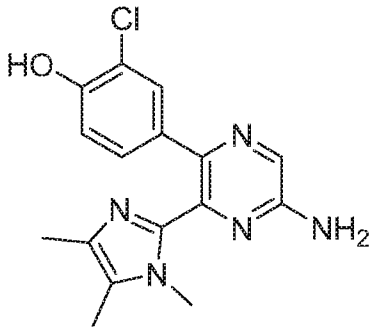
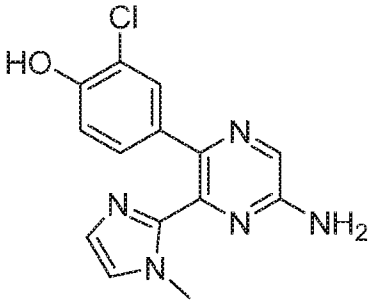
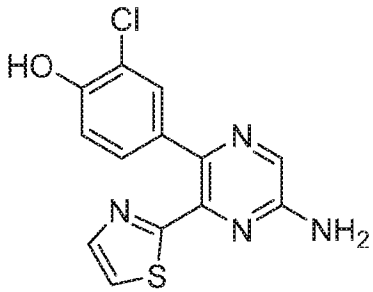
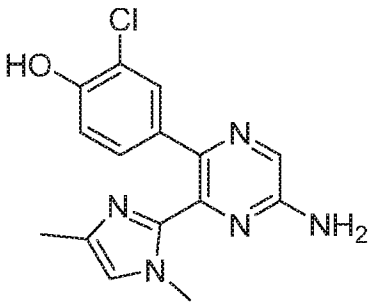
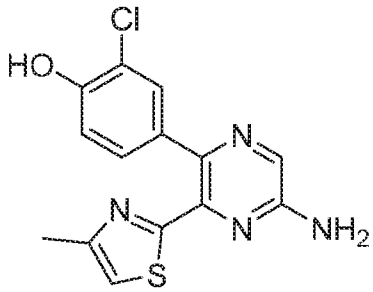
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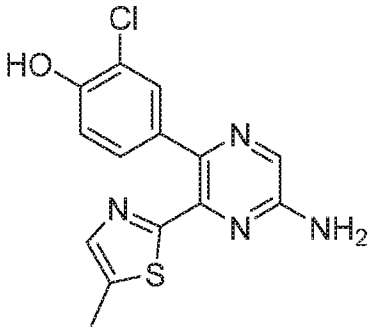
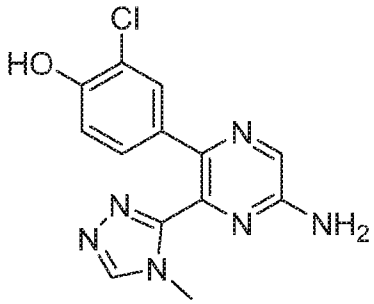
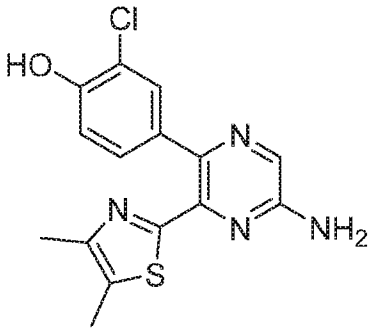
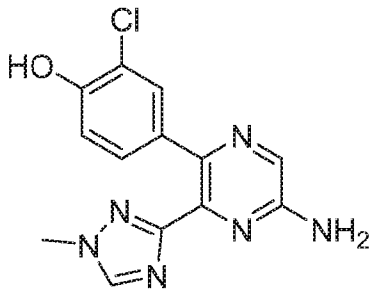
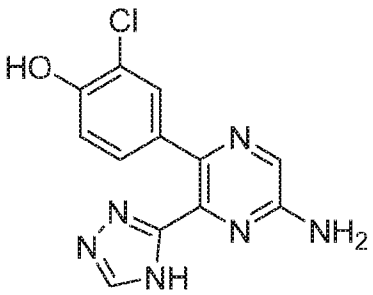
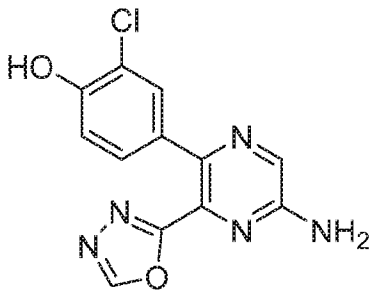
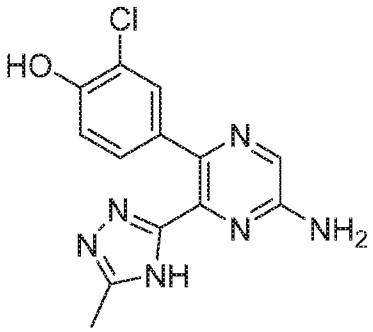
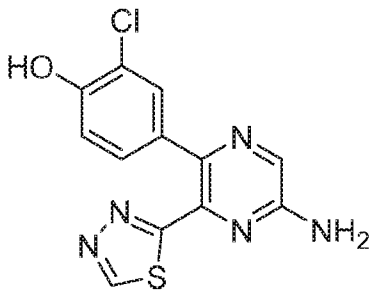
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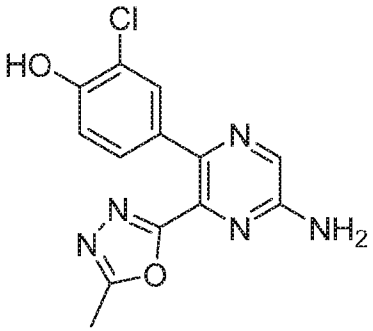
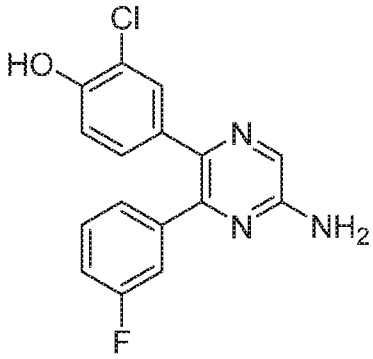
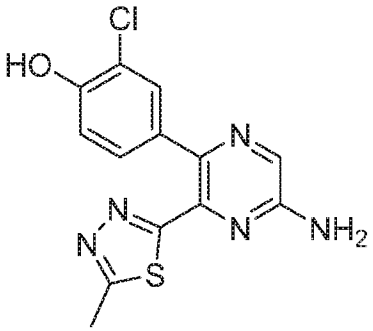
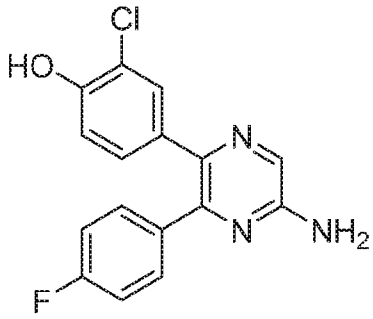
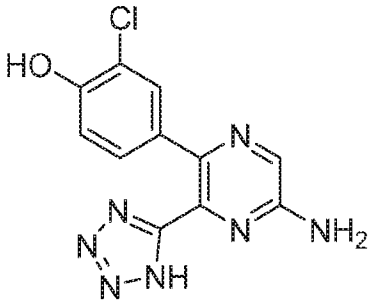
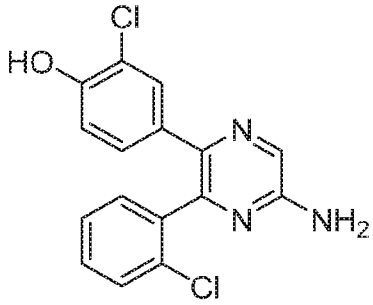
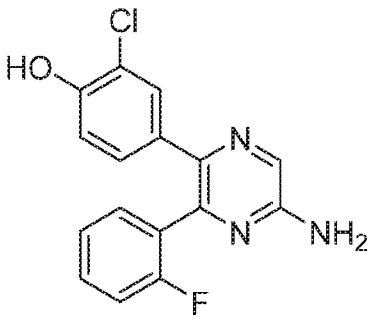
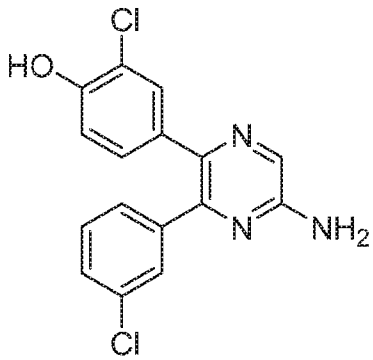
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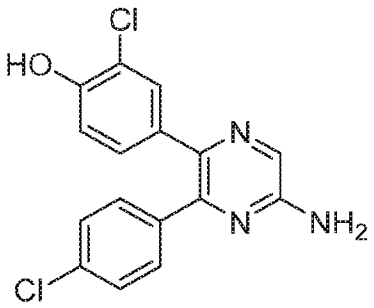
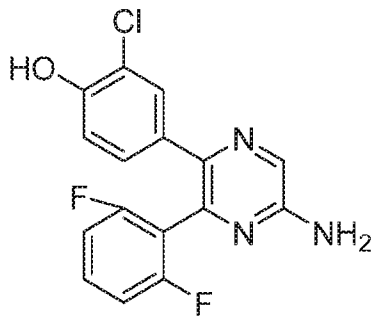
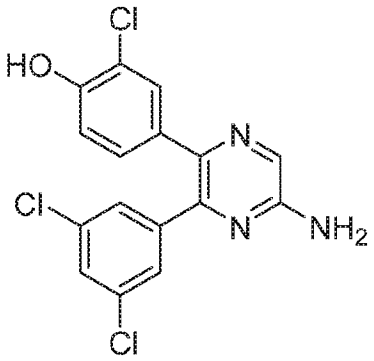
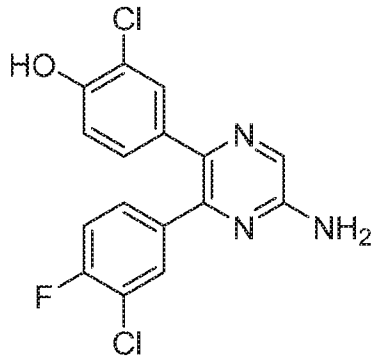
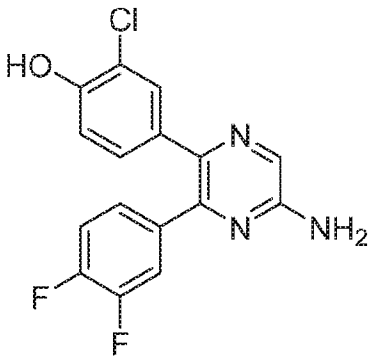
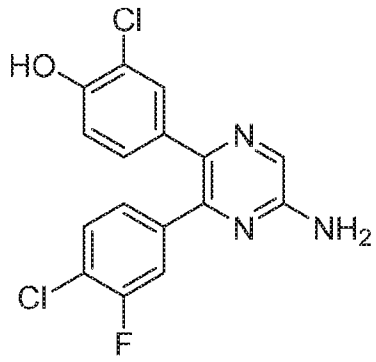
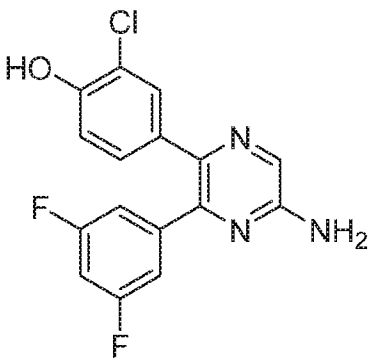
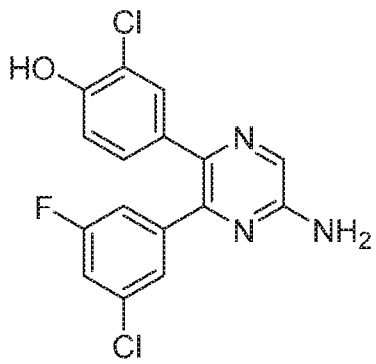
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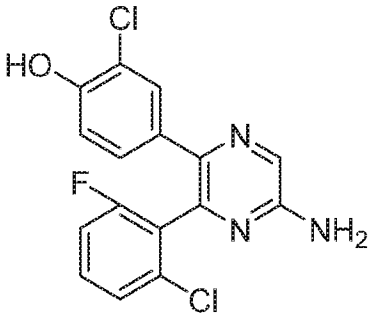
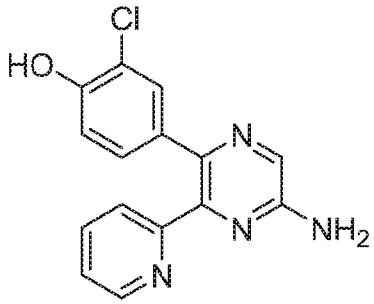
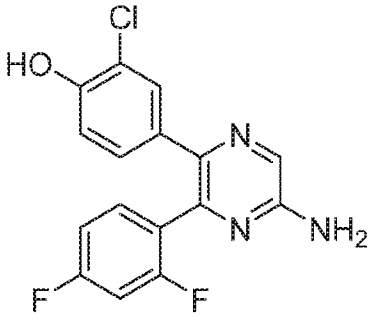
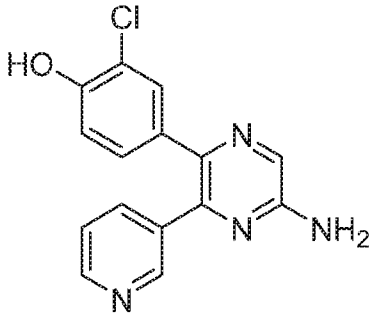
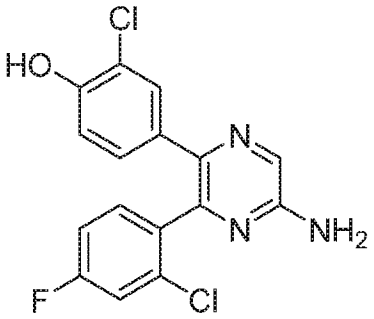
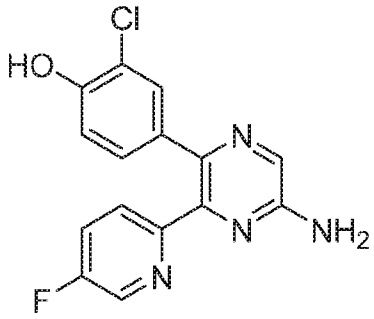
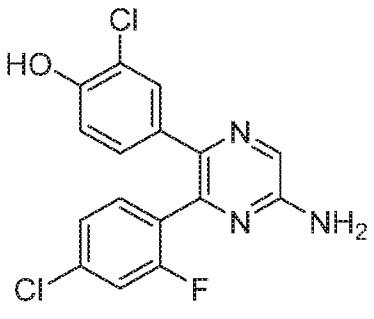
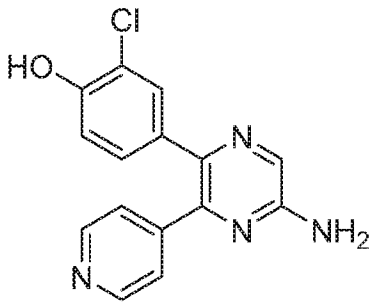
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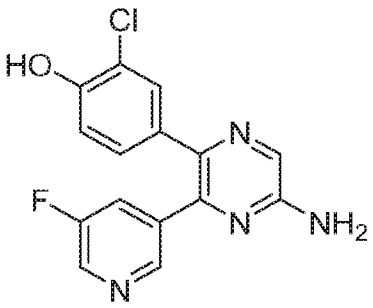
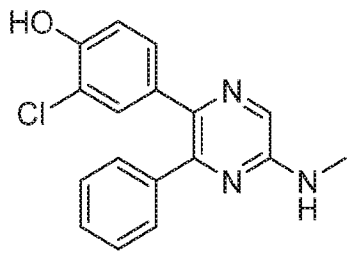
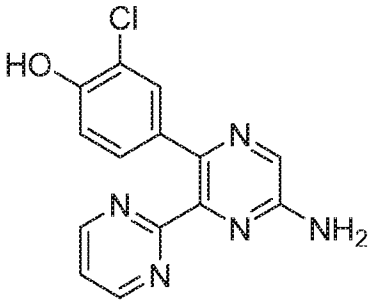
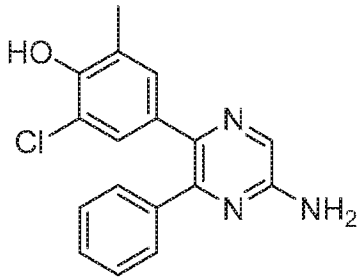
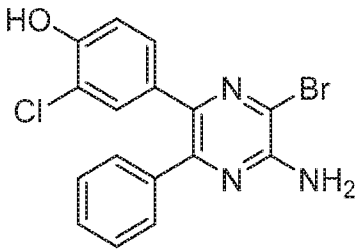
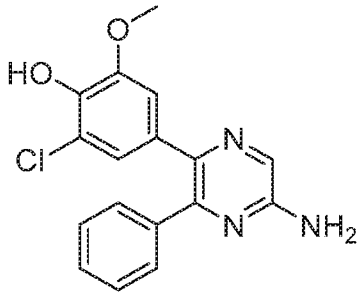
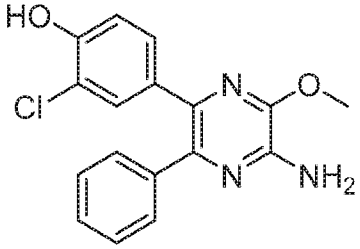
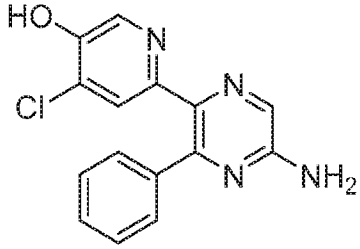
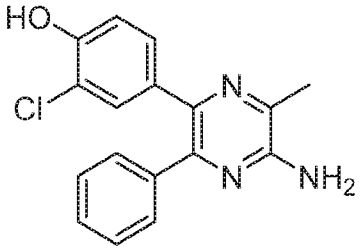
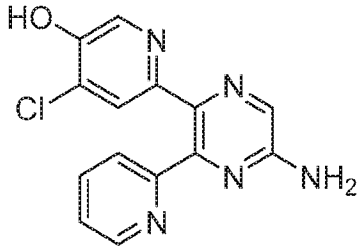
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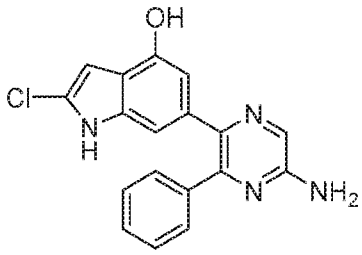
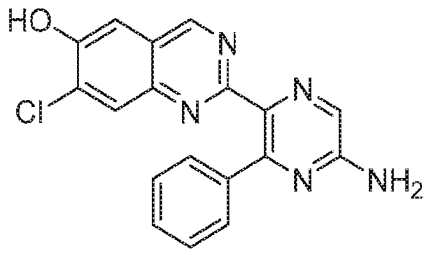
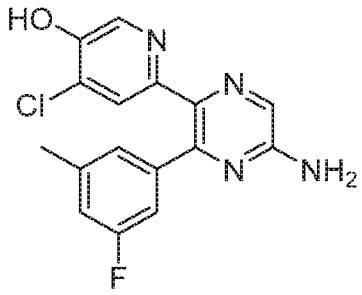
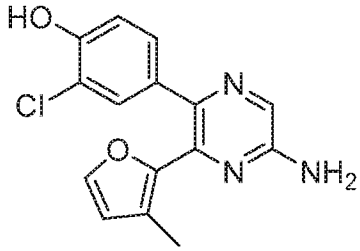
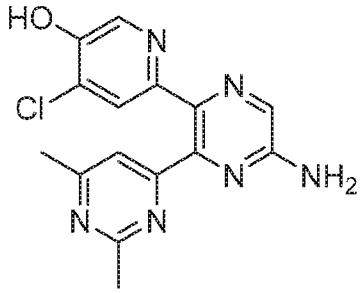
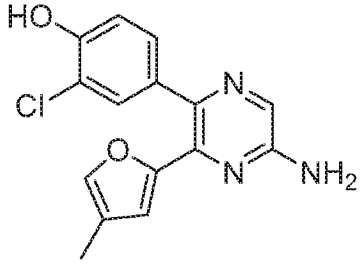
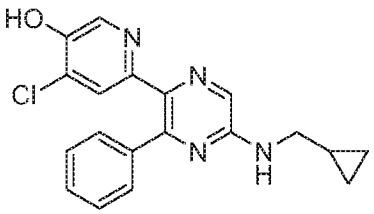
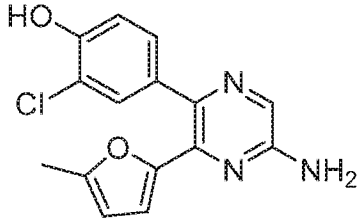
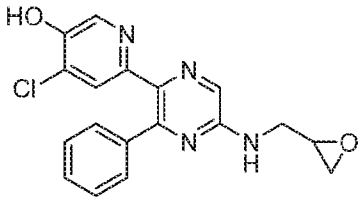
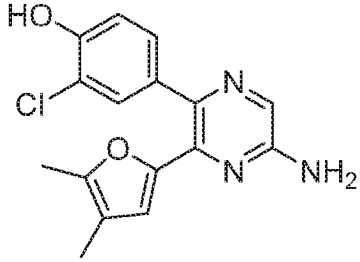
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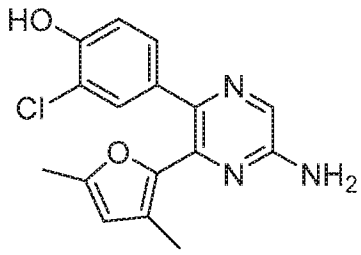
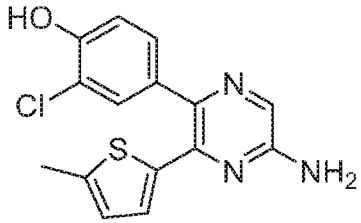
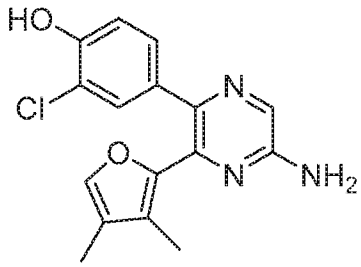
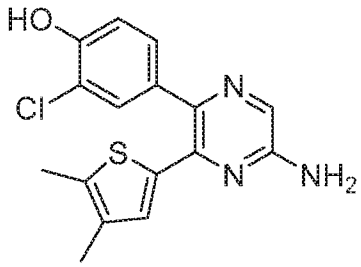
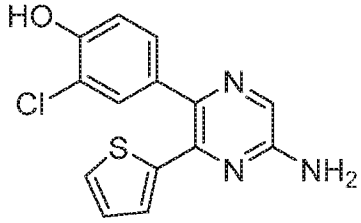
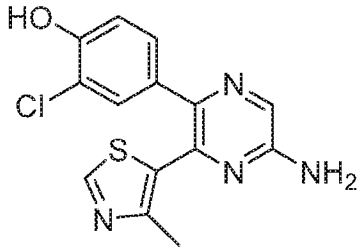
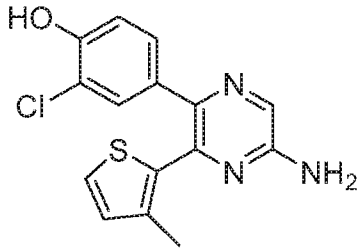
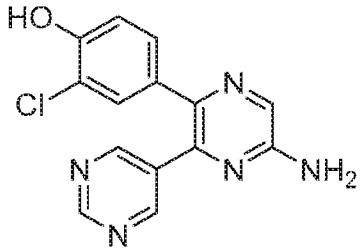
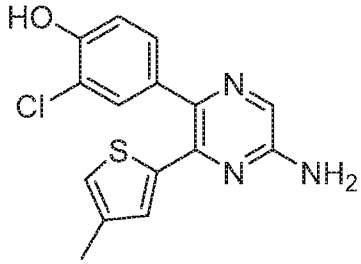
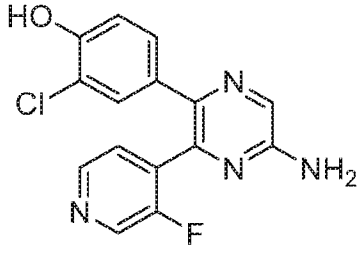
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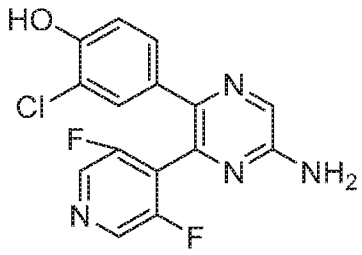
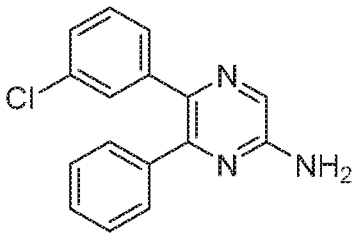
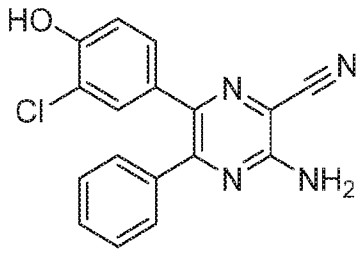
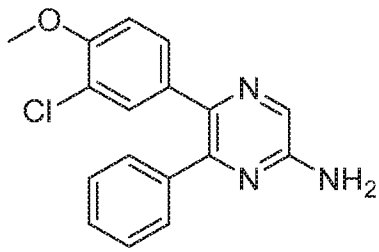
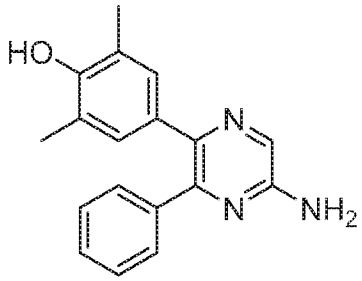
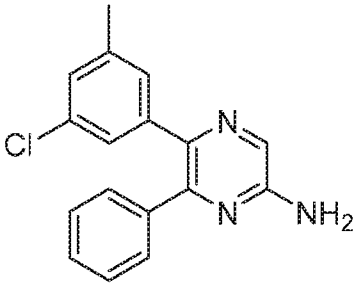
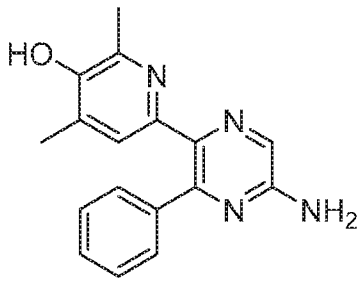
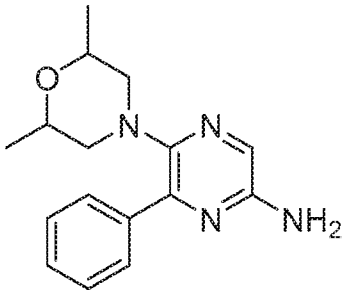
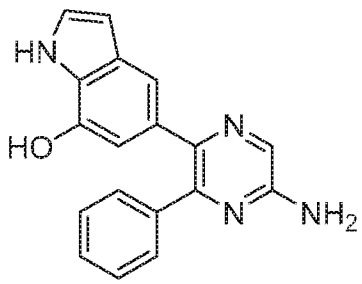
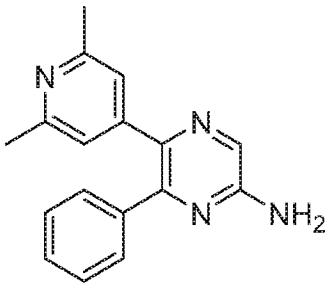
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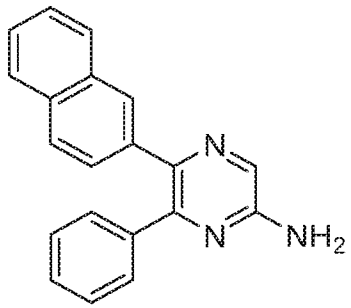
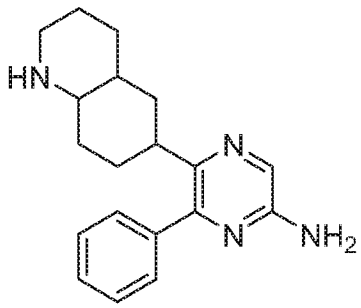
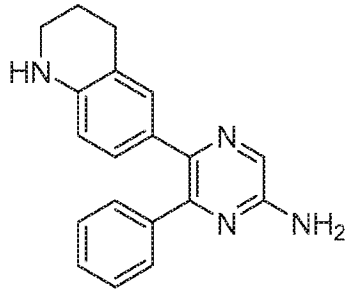
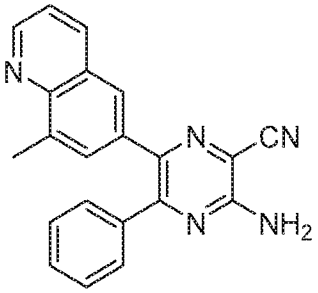
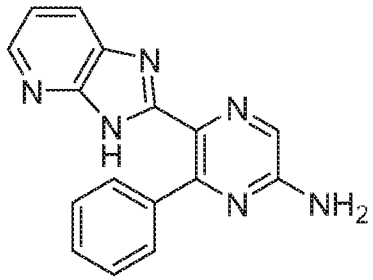
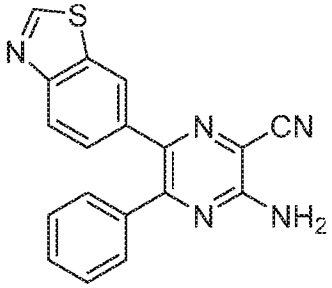
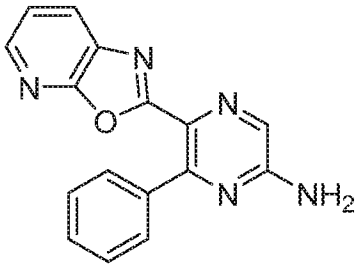
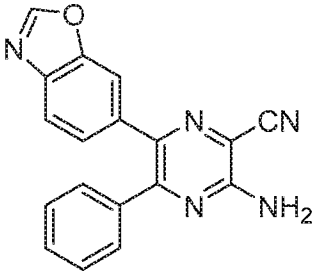
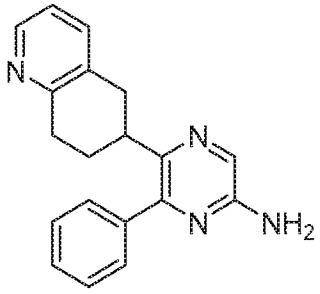
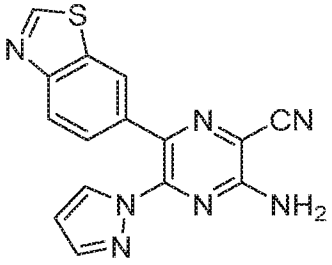
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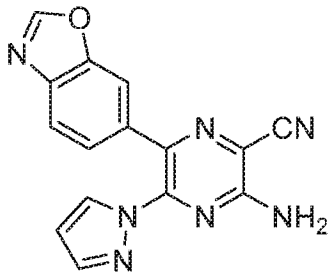
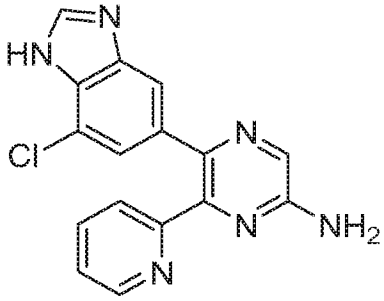
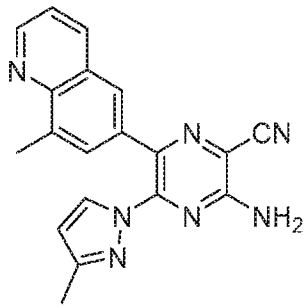
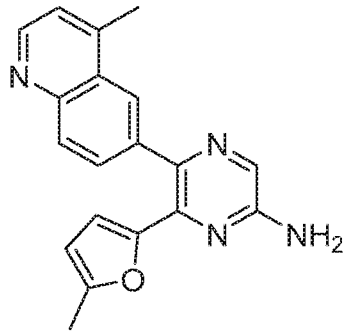
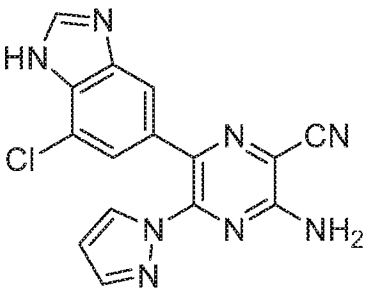
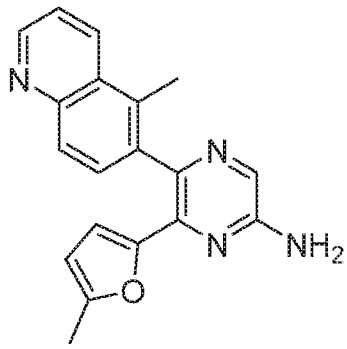
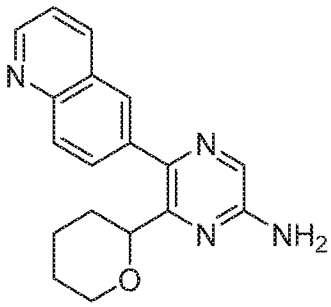
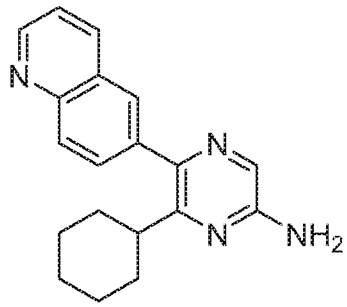
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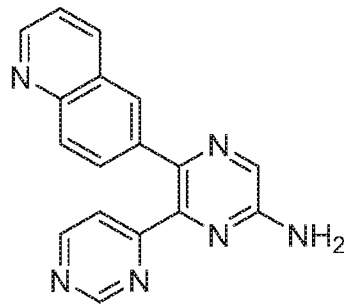
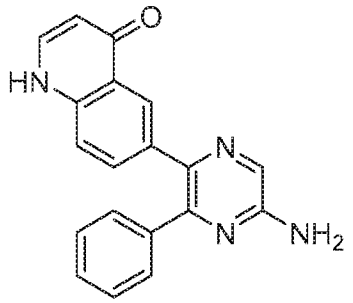
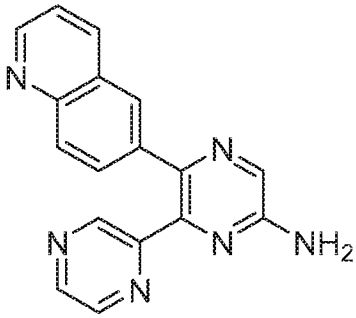
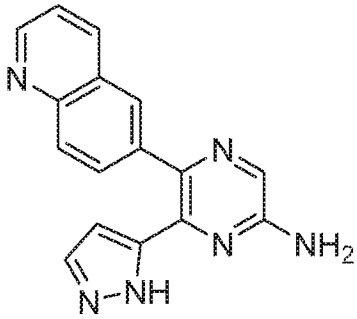
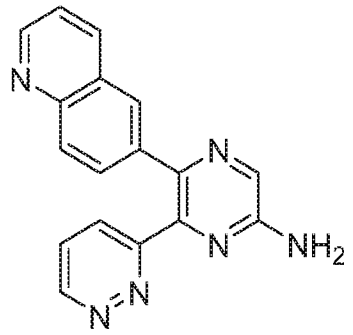
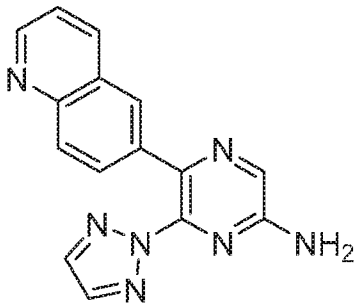
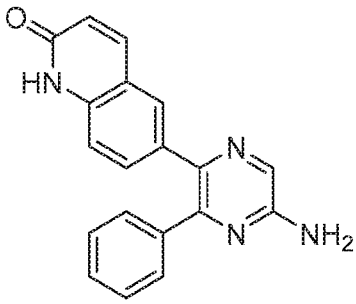
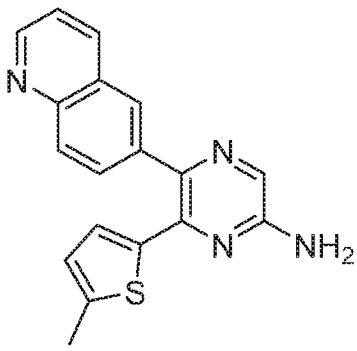
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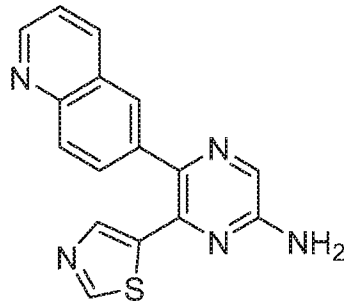
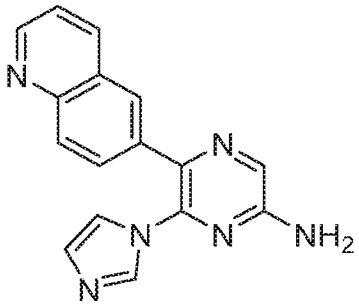
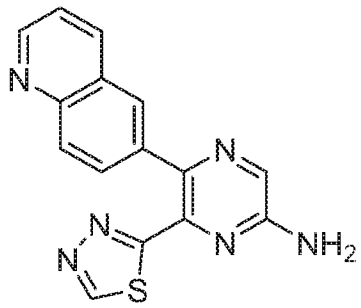
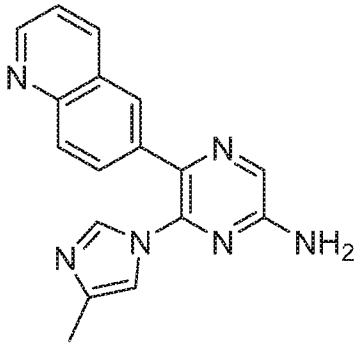
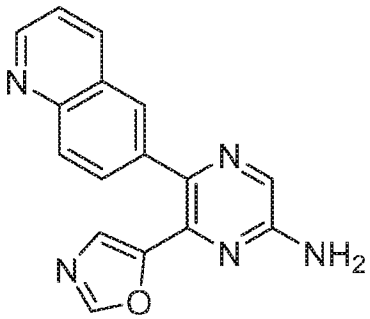
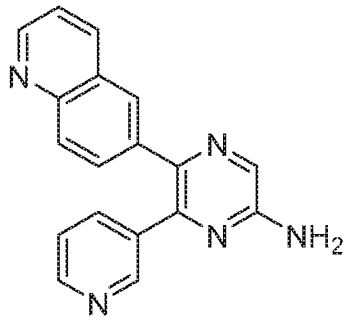
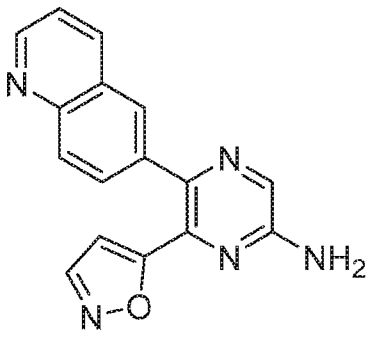
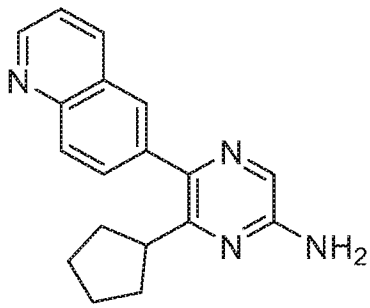
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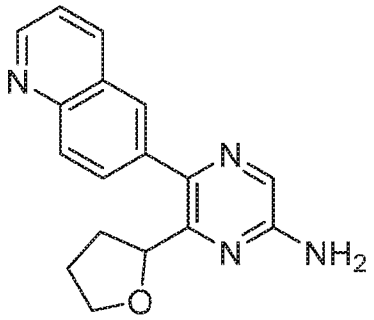
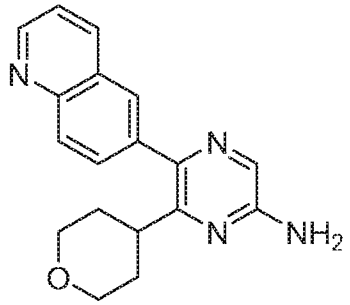
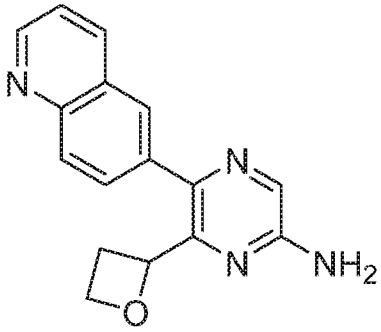
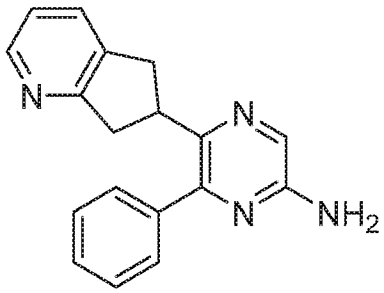
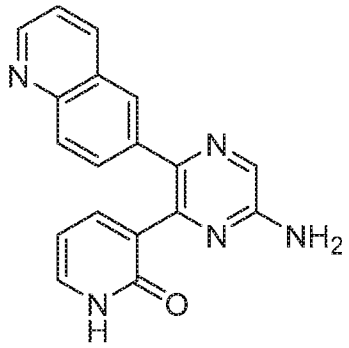
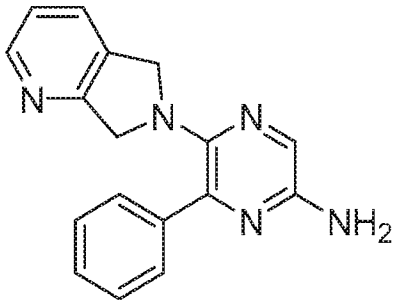
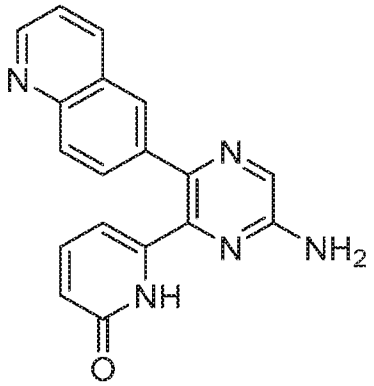
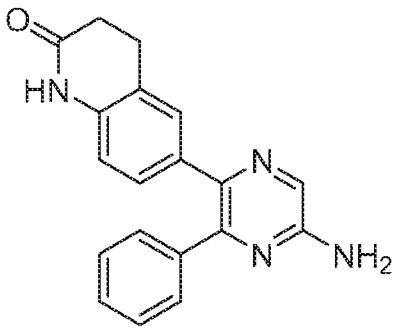
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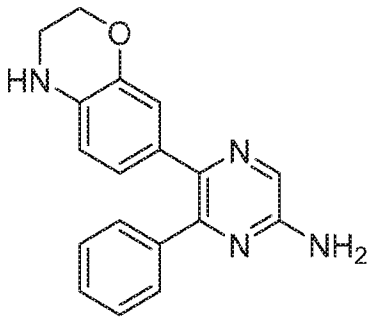
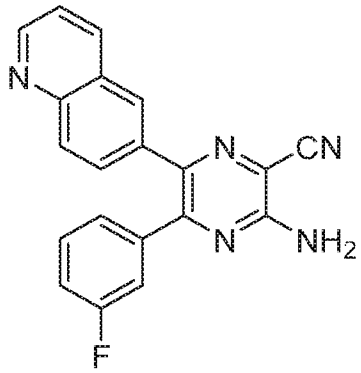
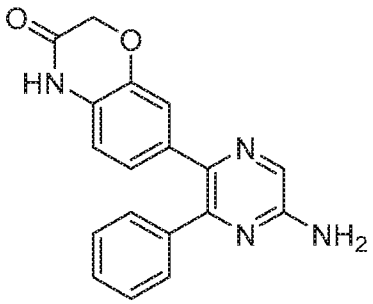
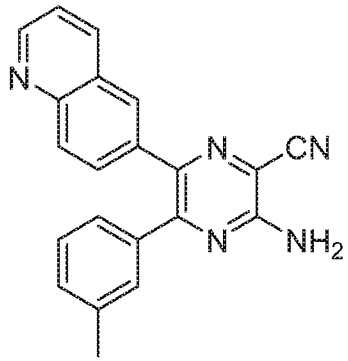
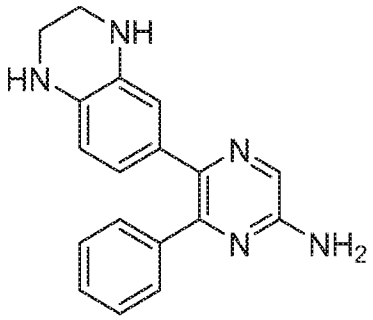
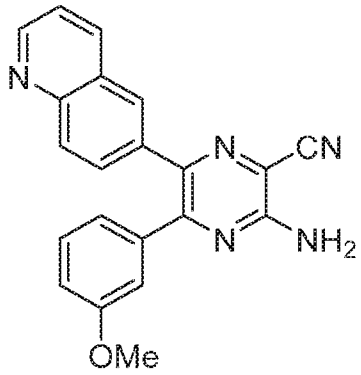
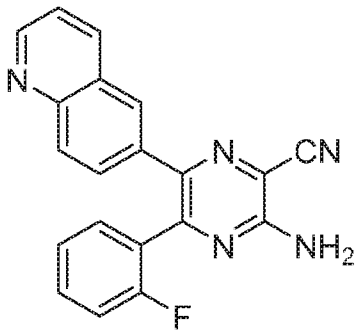
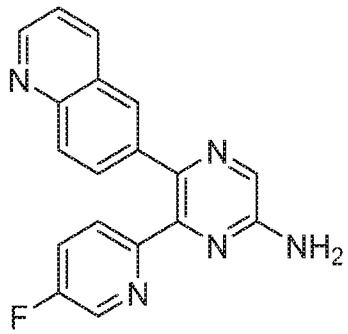
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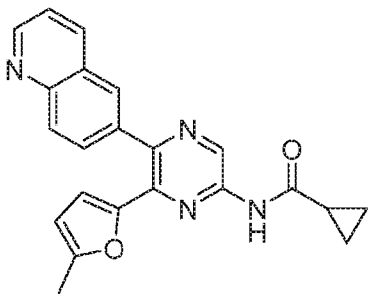
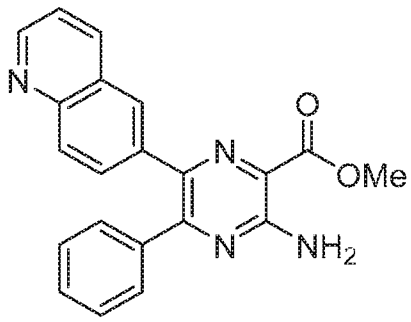
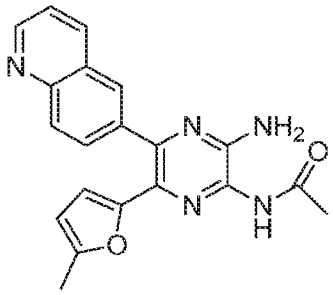
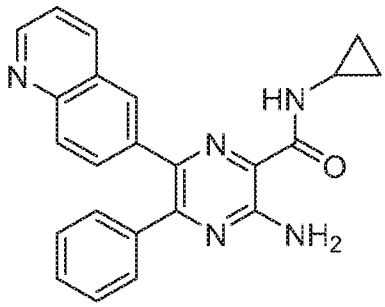
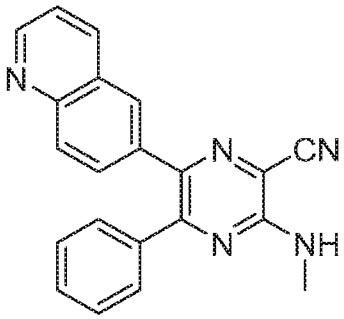
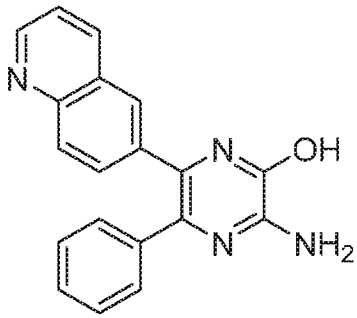
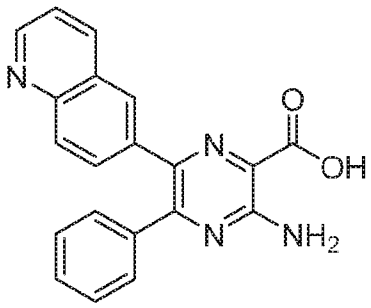
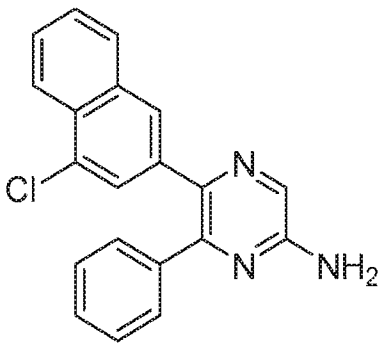
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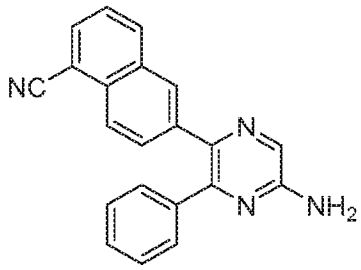
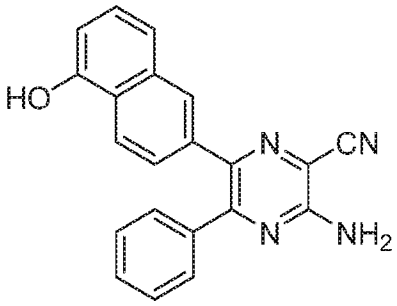
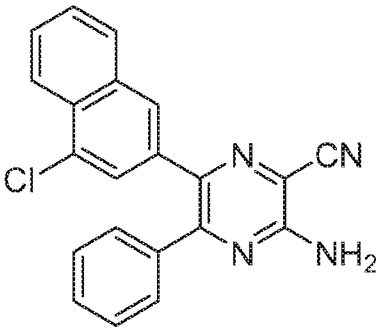
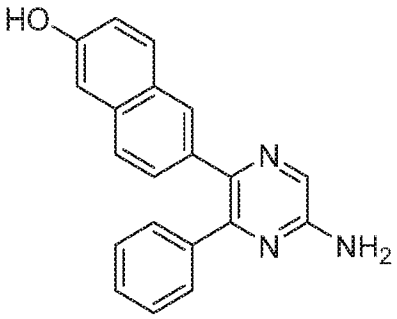
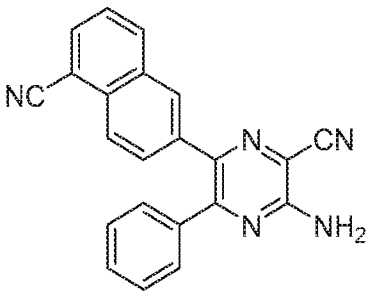
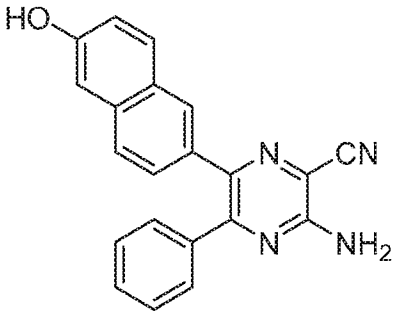
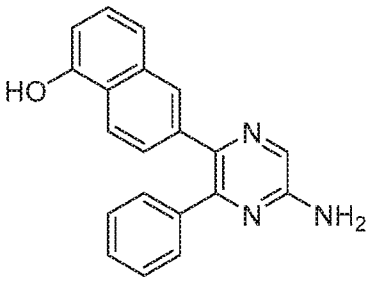
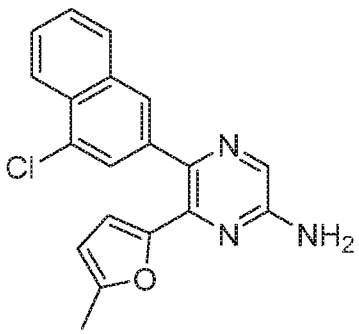
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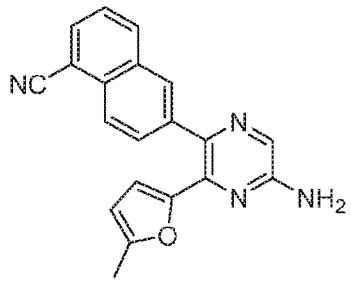
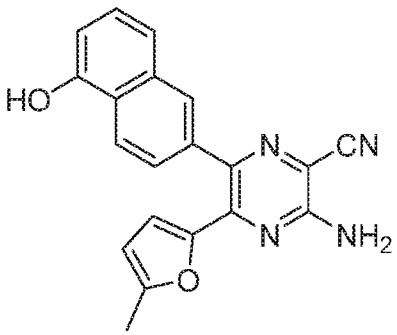
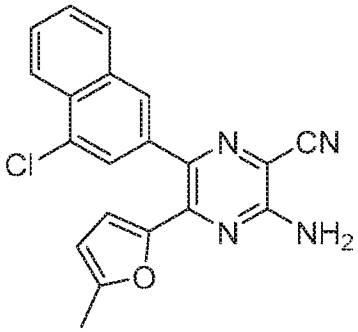
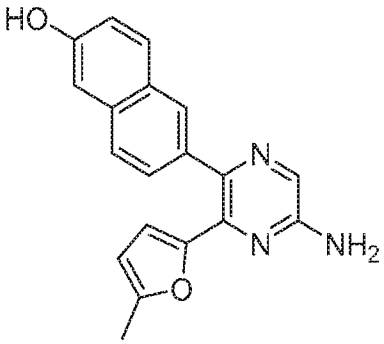
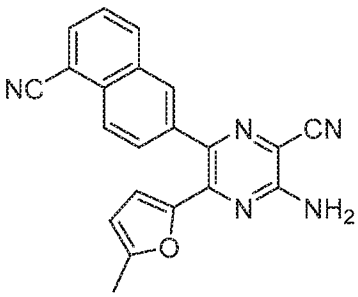
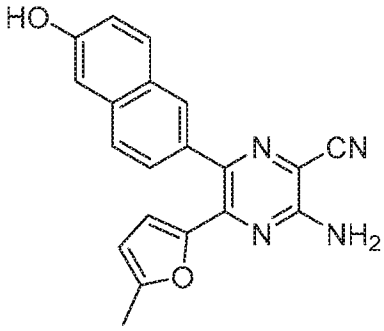
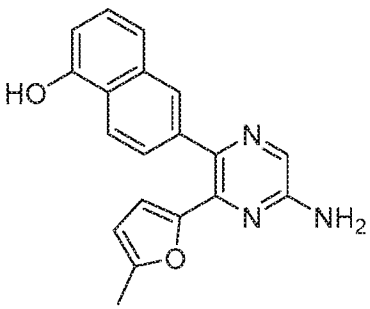
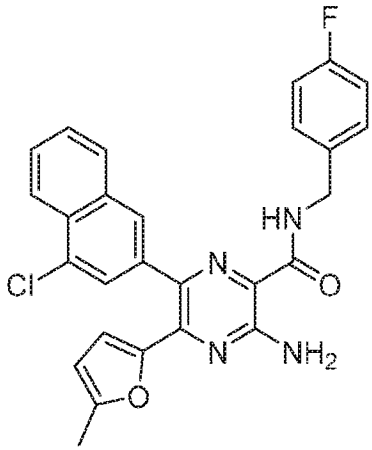
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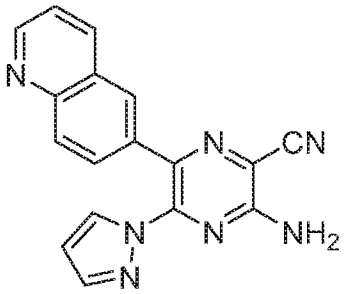
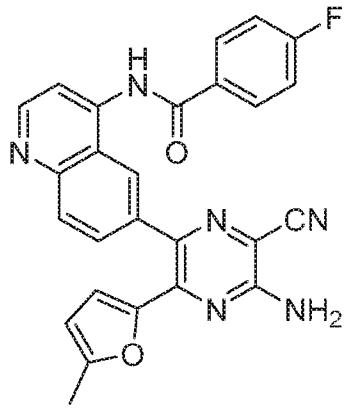
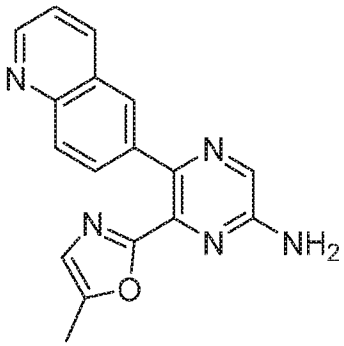
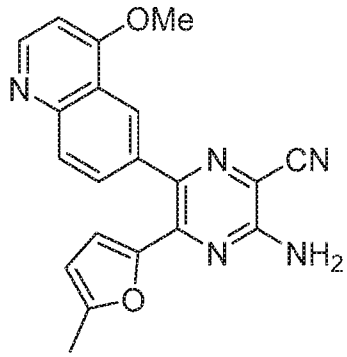
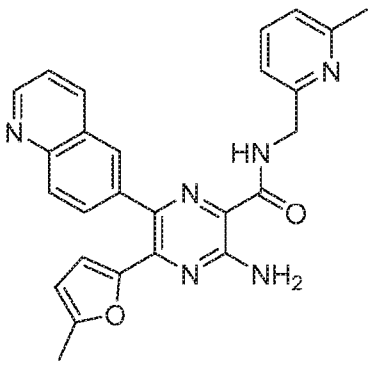
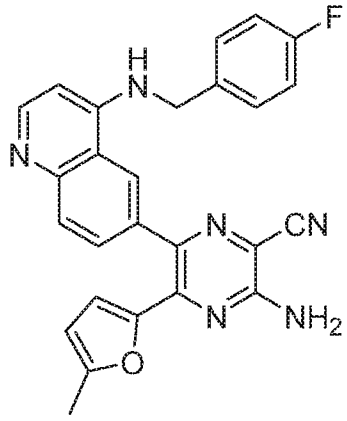
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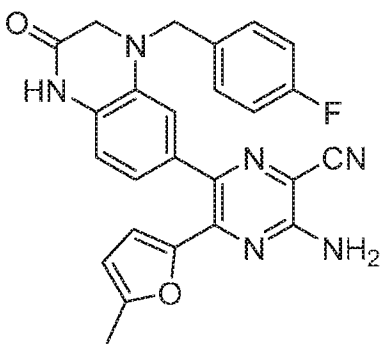
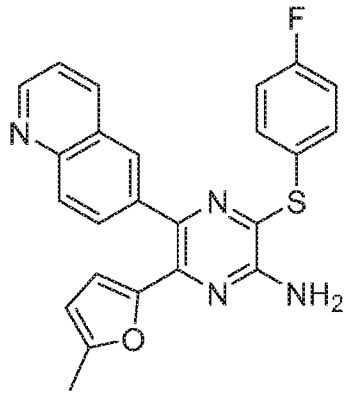
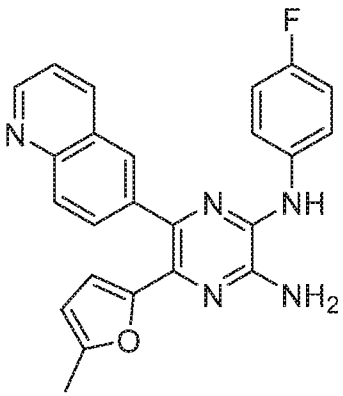
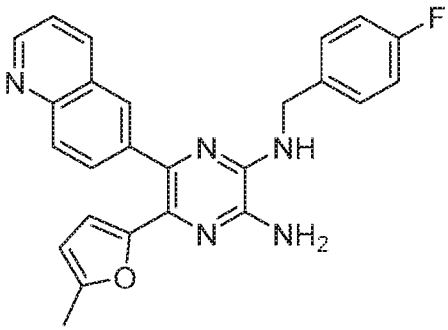
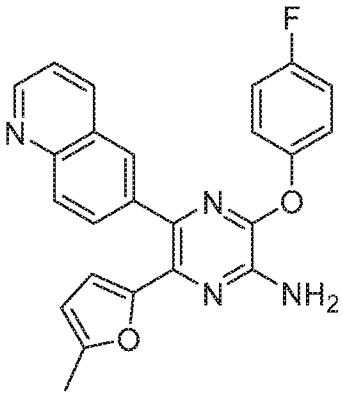
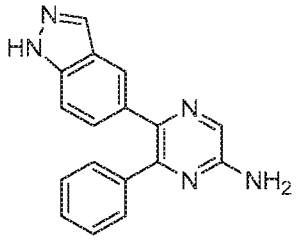
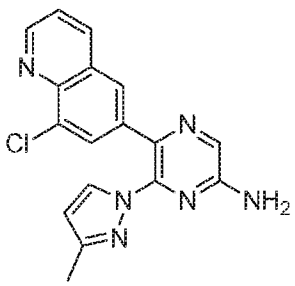
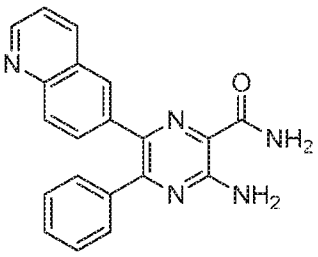
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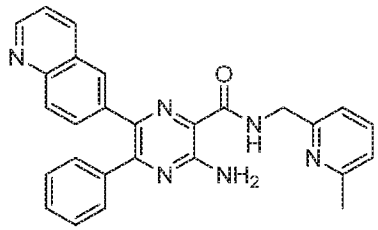
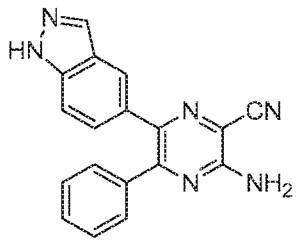
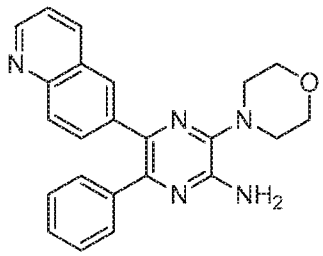
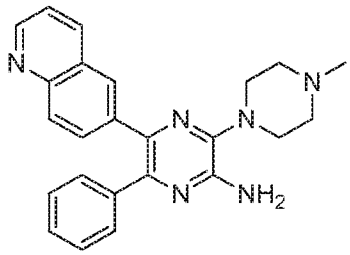
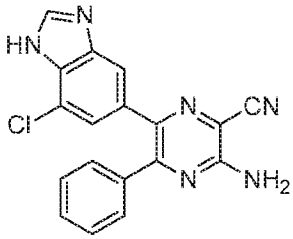
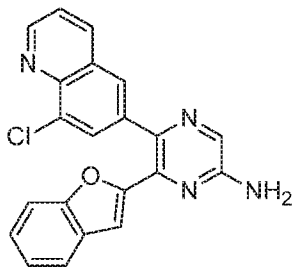
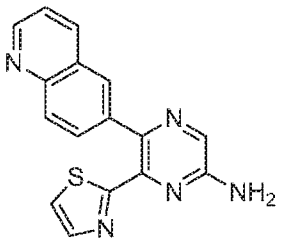
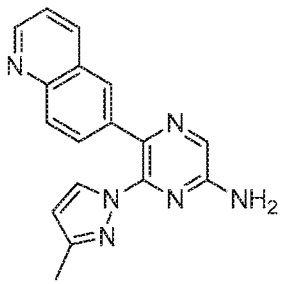
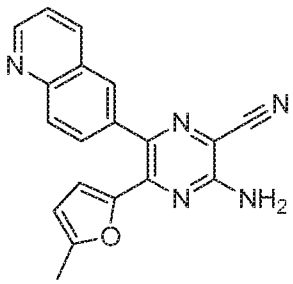
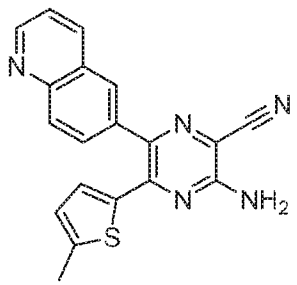
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1.238		1.242	

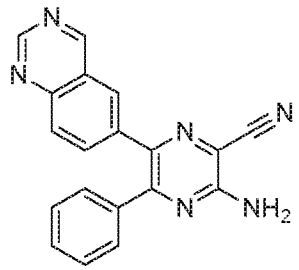
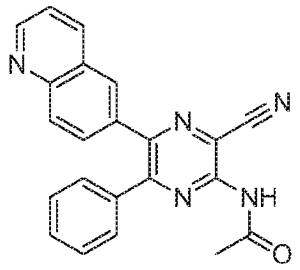
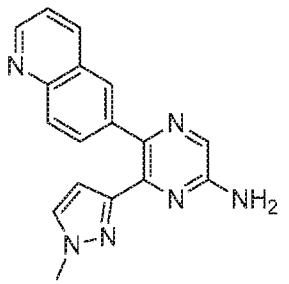
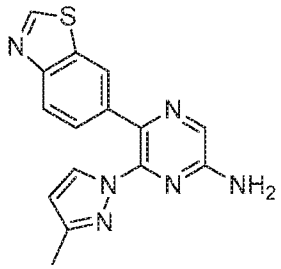
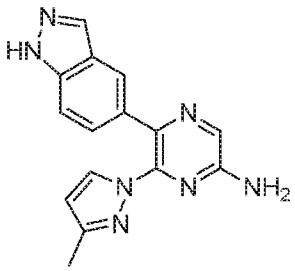
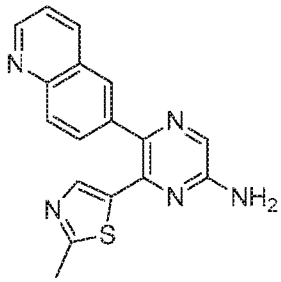
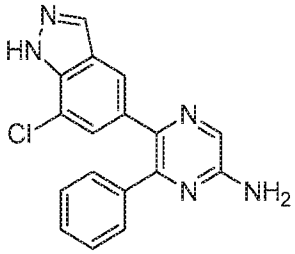
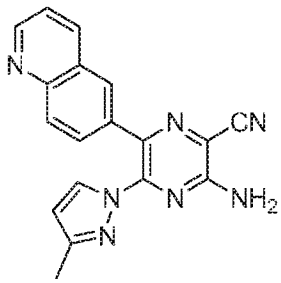
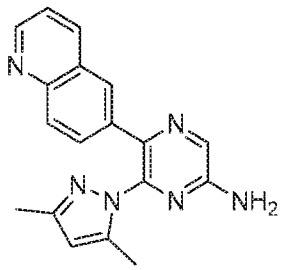
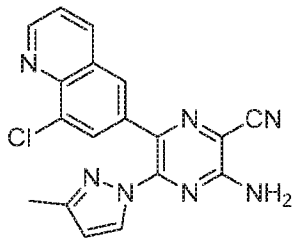
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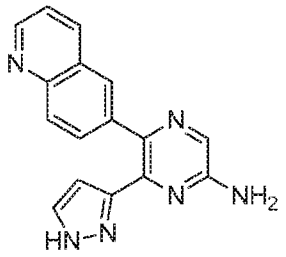
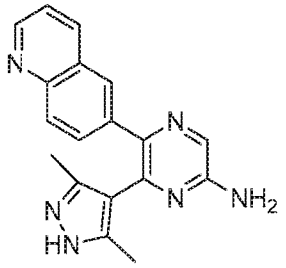
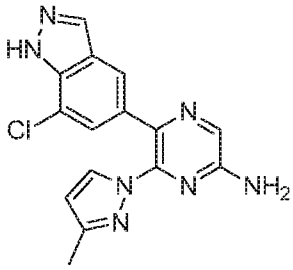
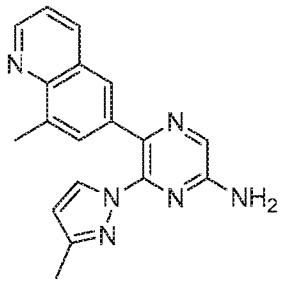
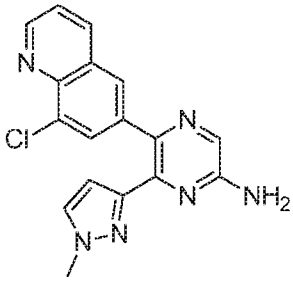
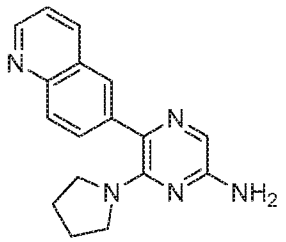
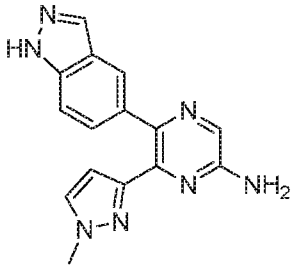
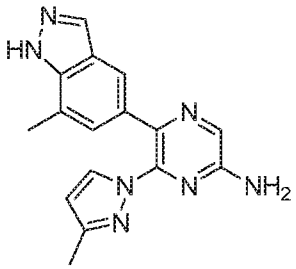
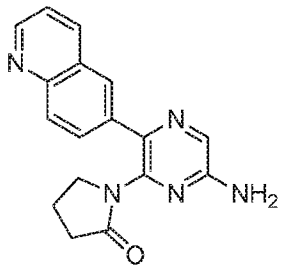
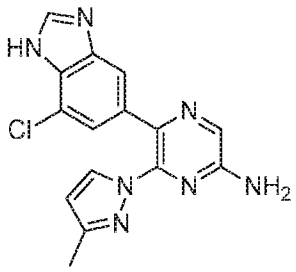
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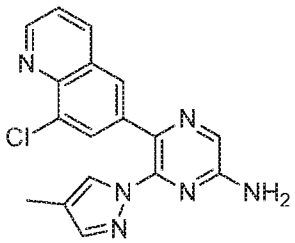
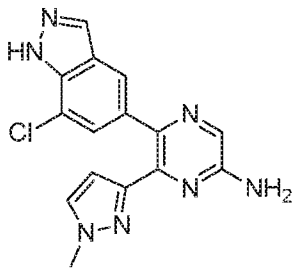
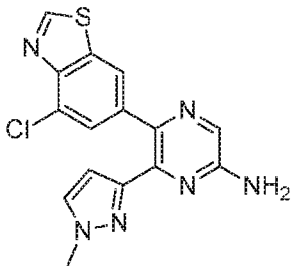
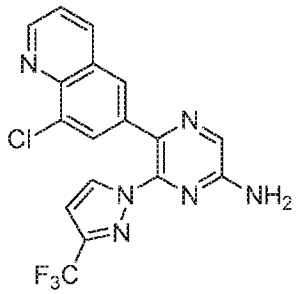
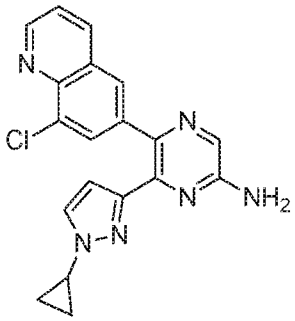
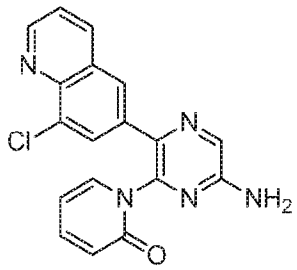
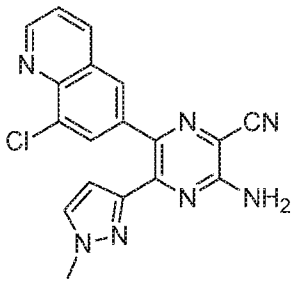
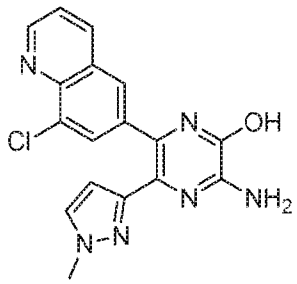
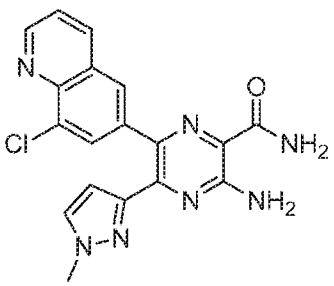
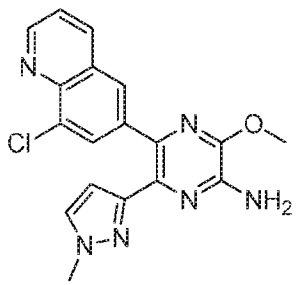
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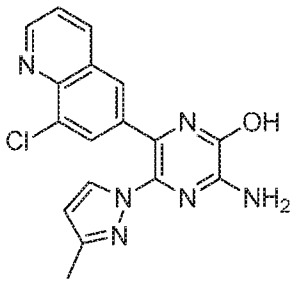
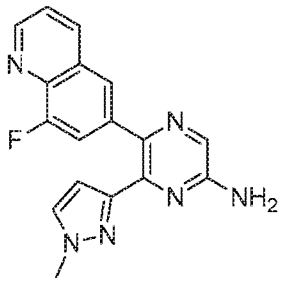
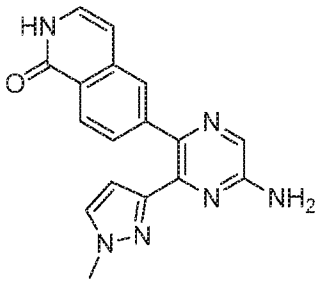
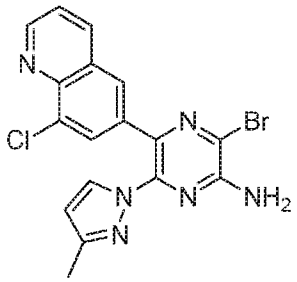
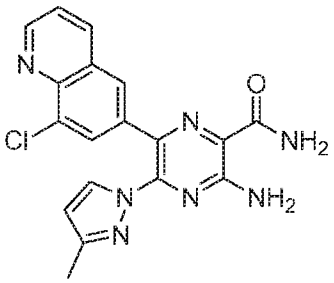
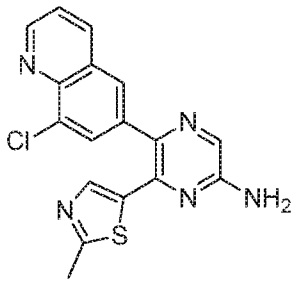
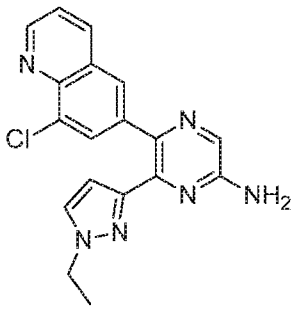
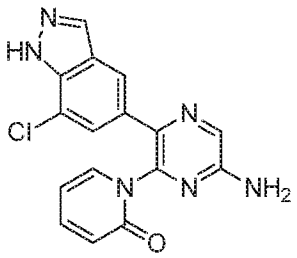
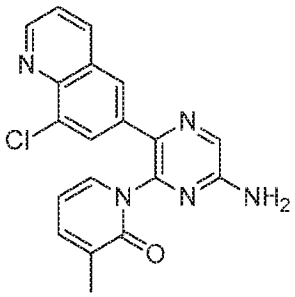
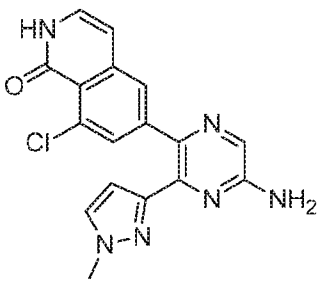
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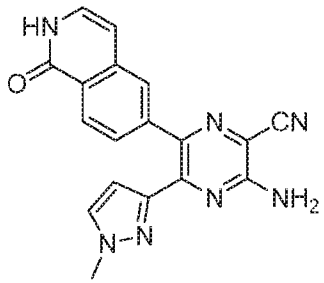
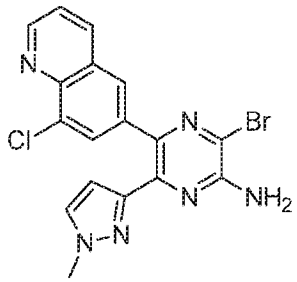
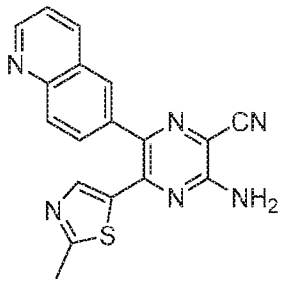
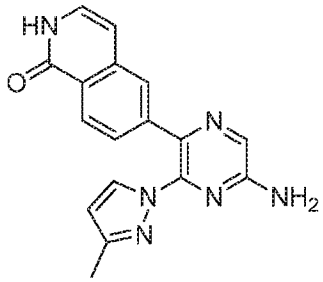
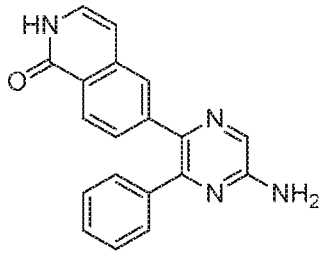
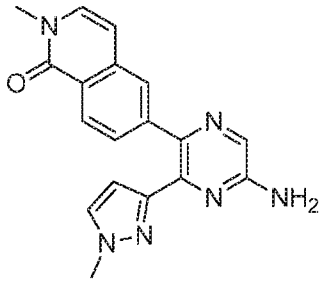
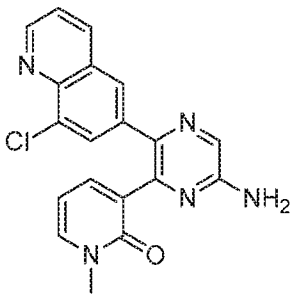
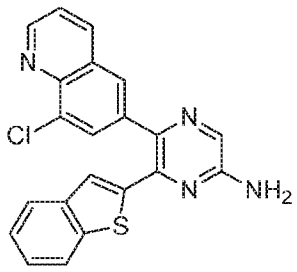
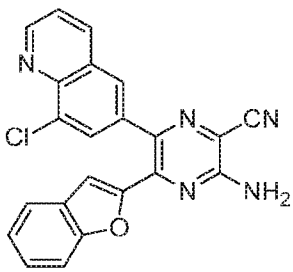
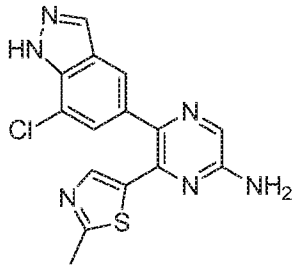
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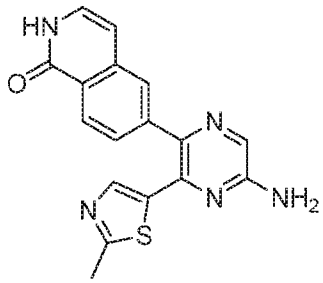
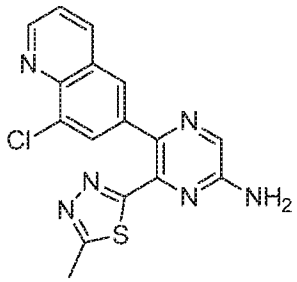
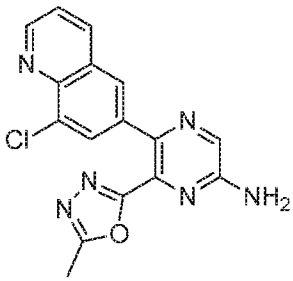
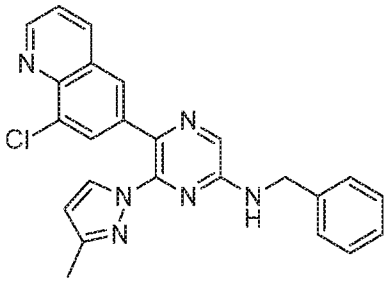
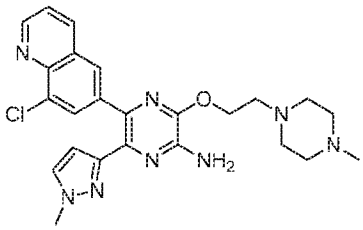
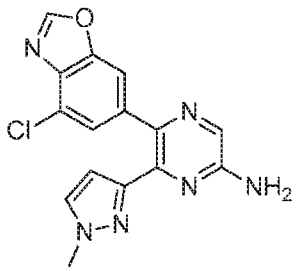
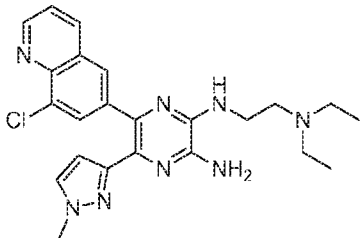
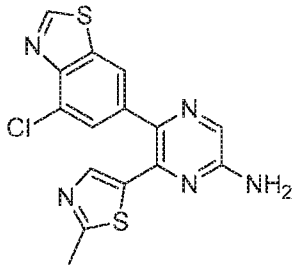
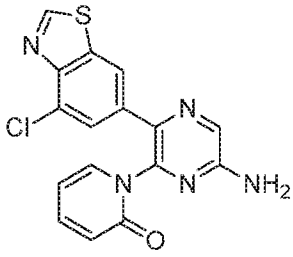
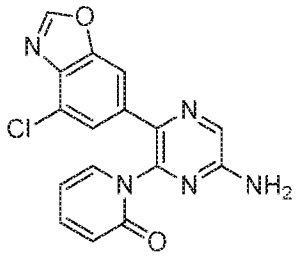
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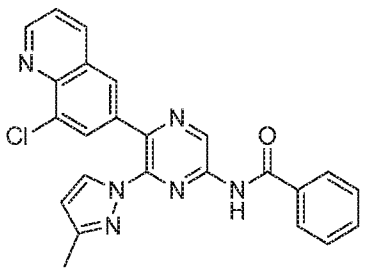
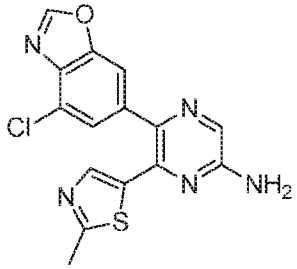
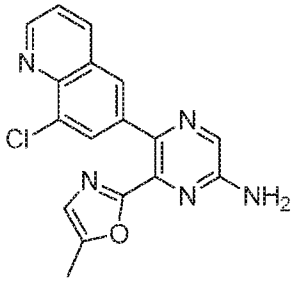
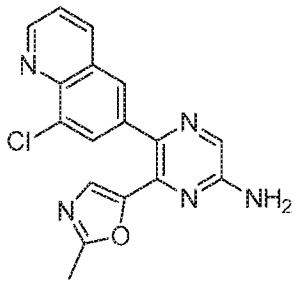
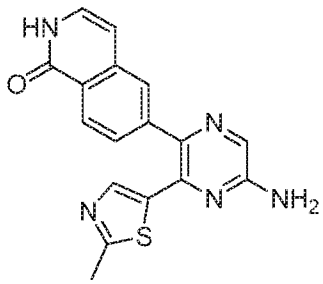
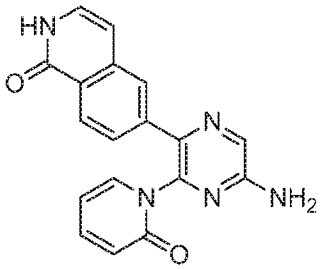
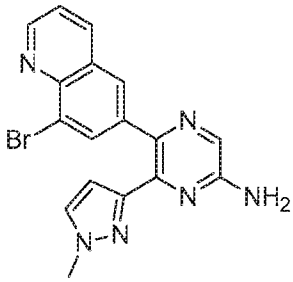
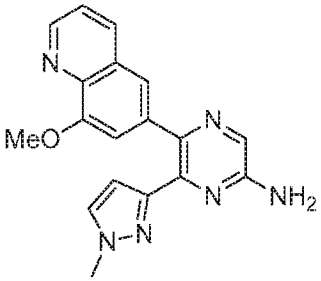
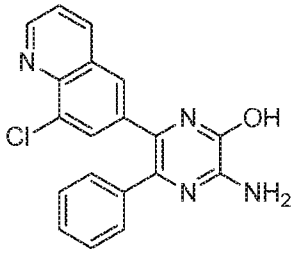
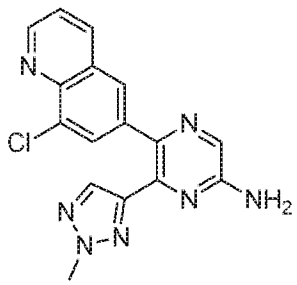
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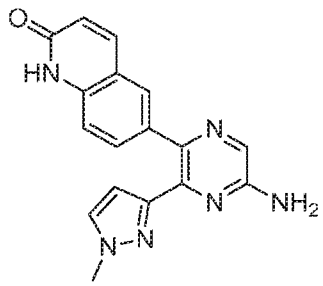
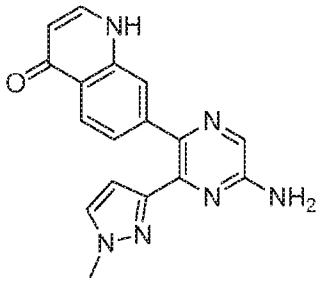
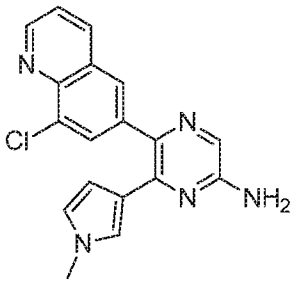
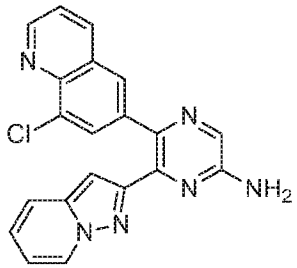
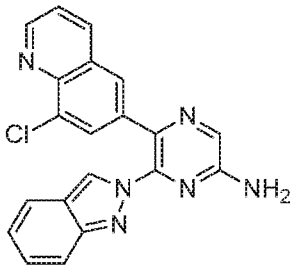
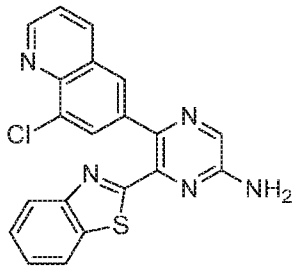
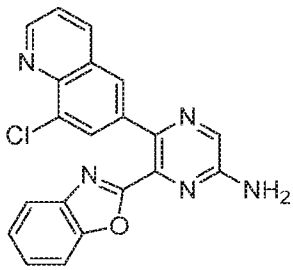
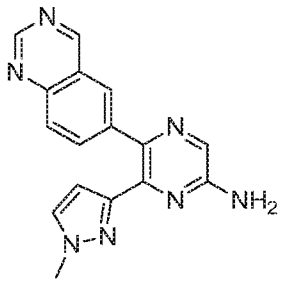
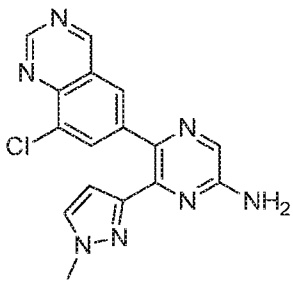
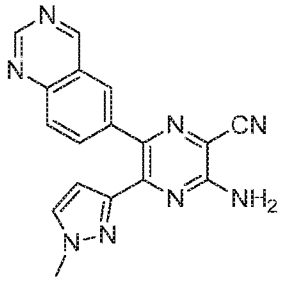
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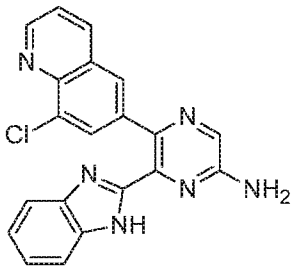
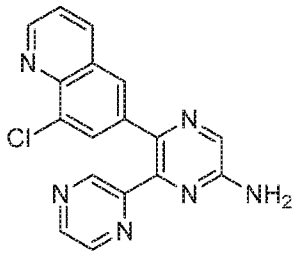
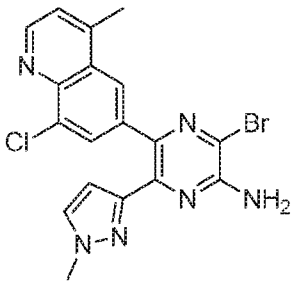
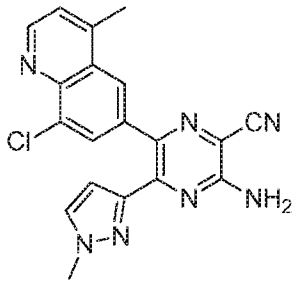
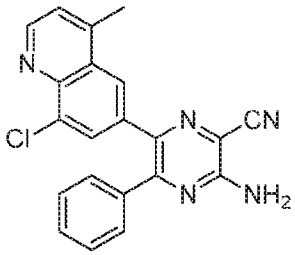
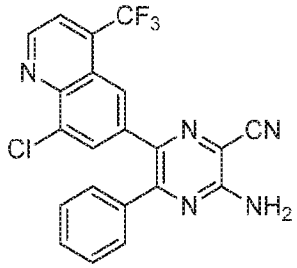
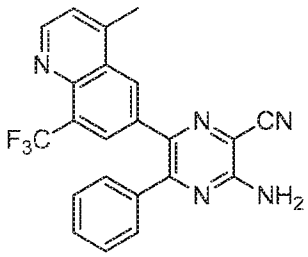
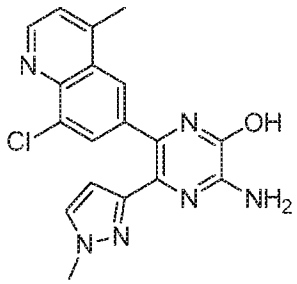
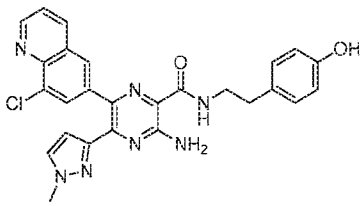
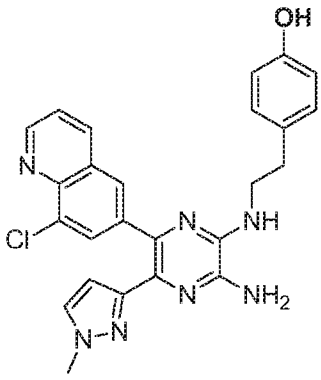
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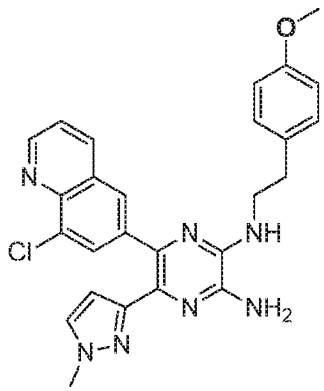
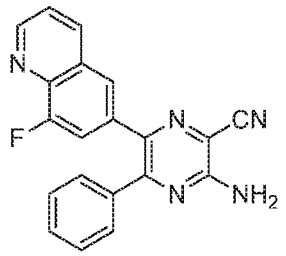
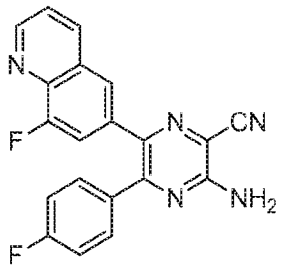
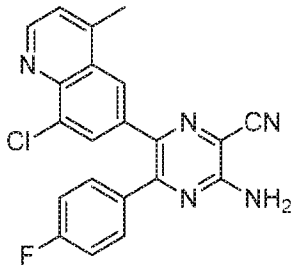
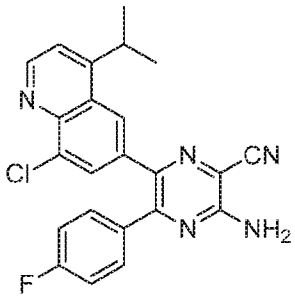
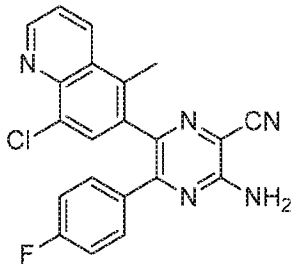
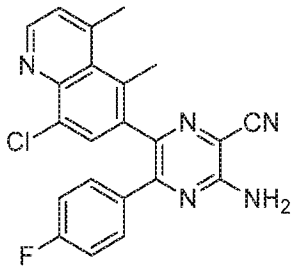
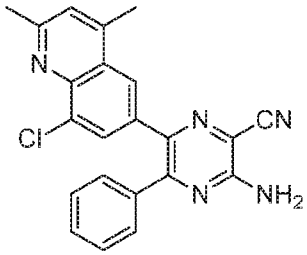
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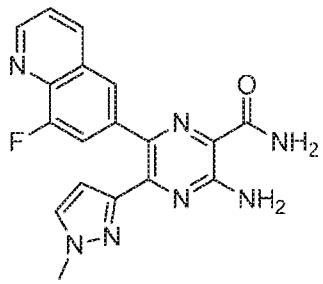
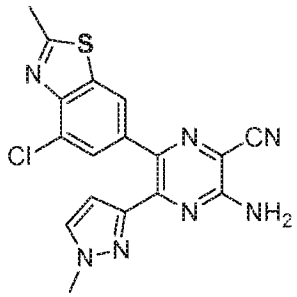
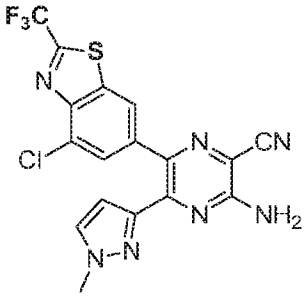
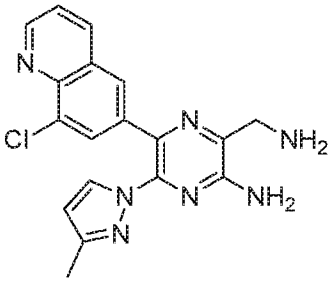
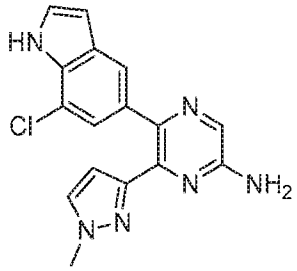
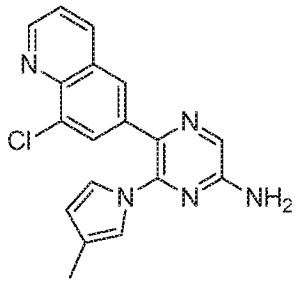
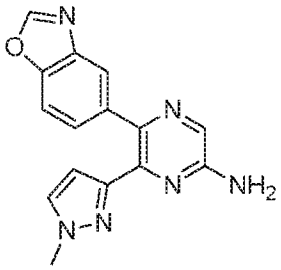
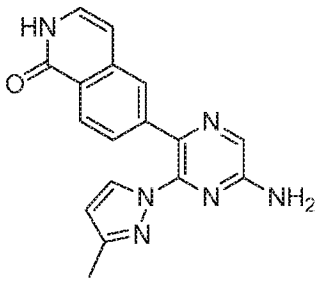
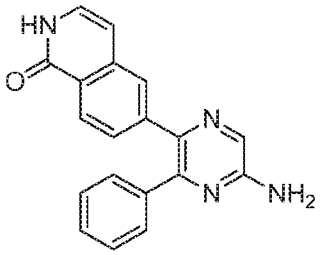
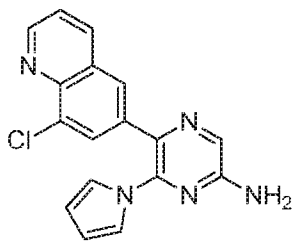
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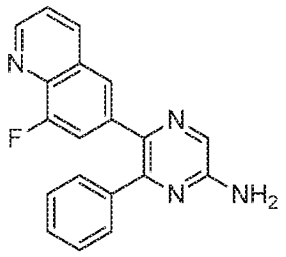
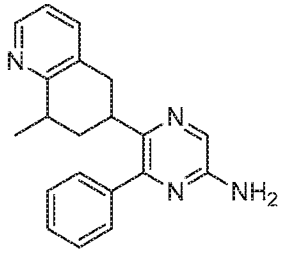
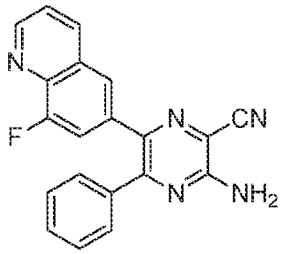
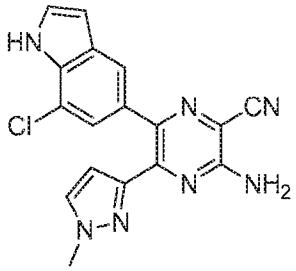
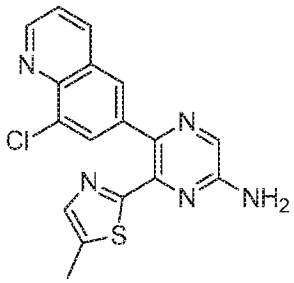
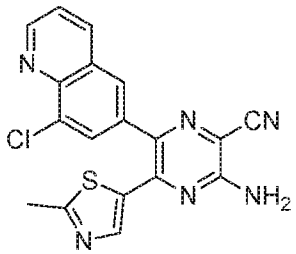
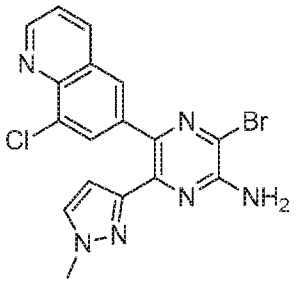
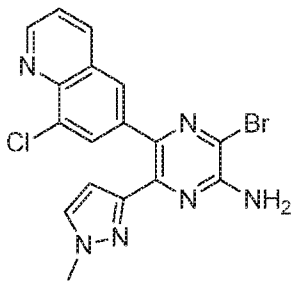
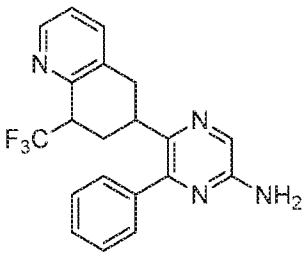
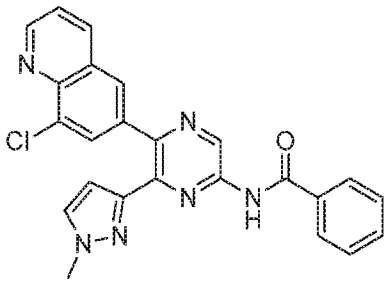
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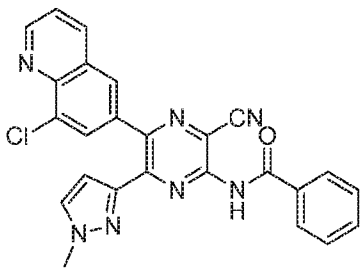
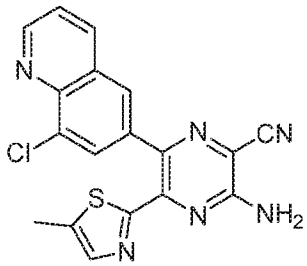
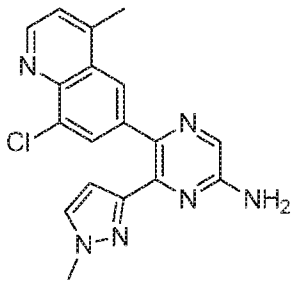
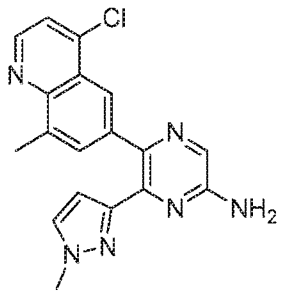
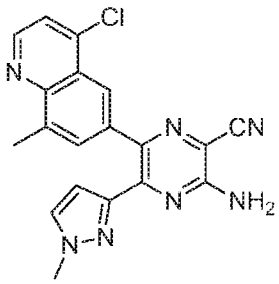
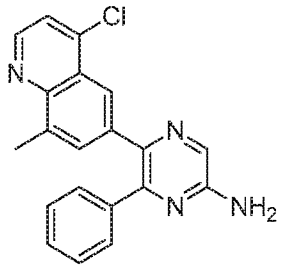
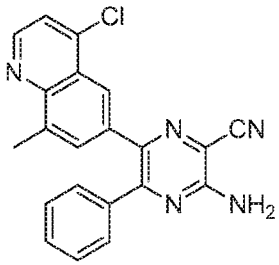
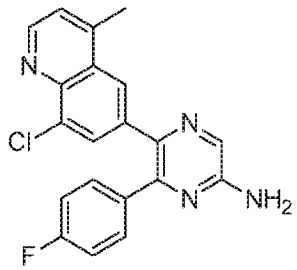
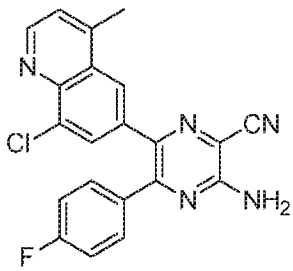
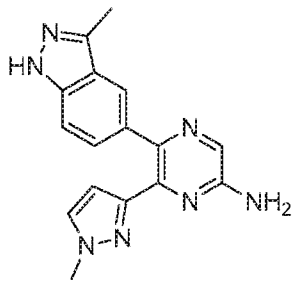
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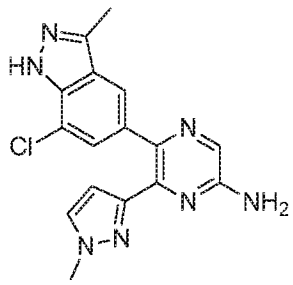
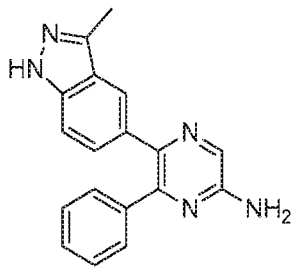
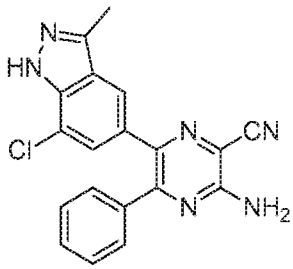
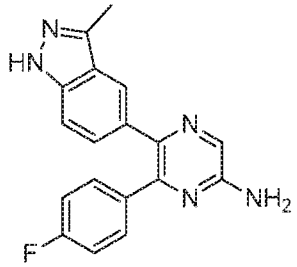
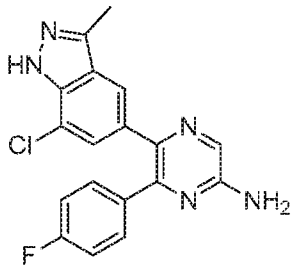
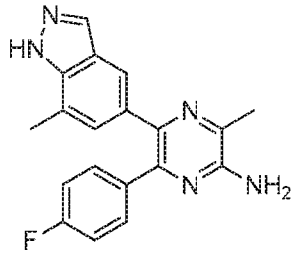
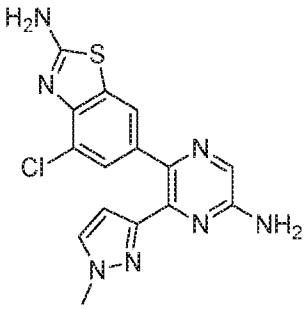
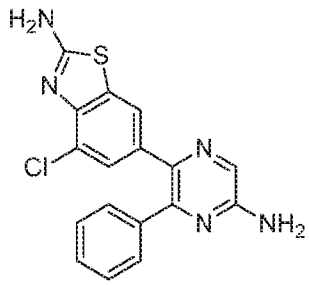
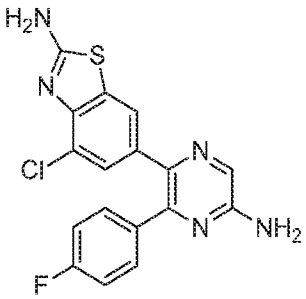
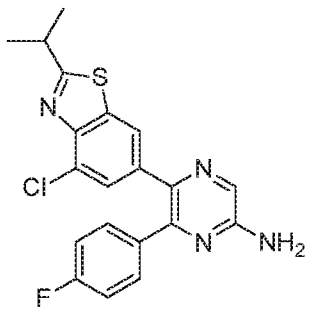
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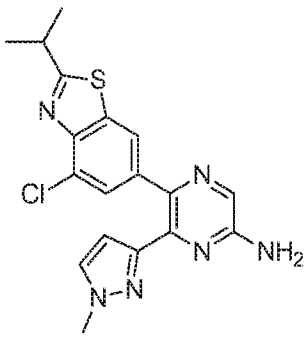
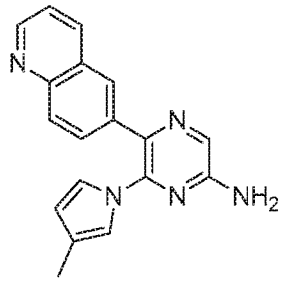
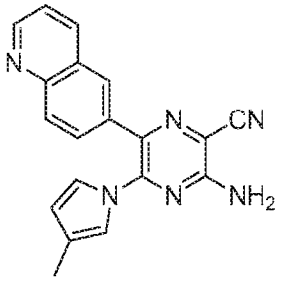
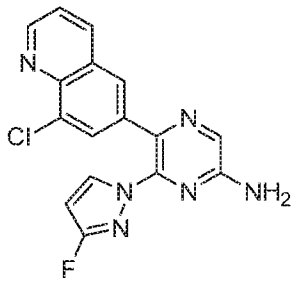
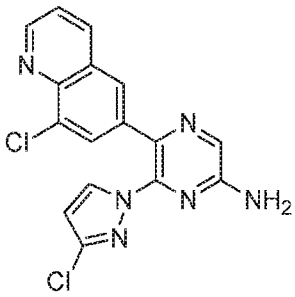
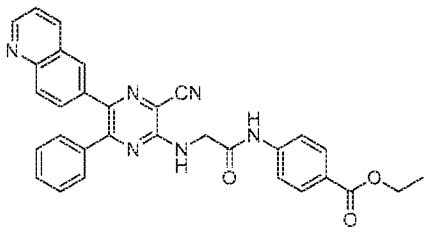
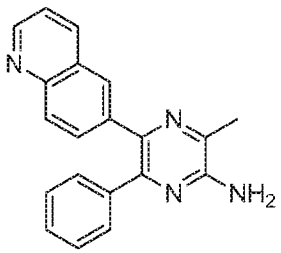
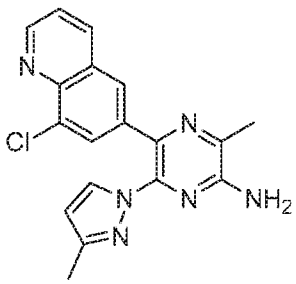
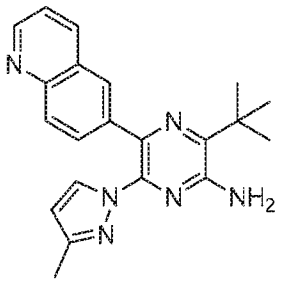
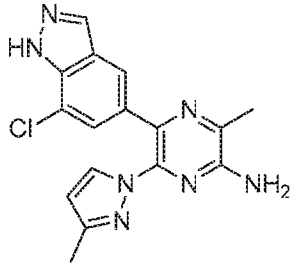
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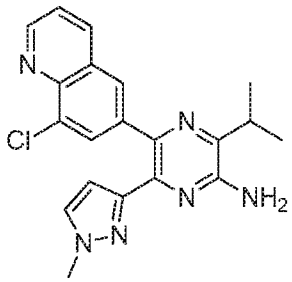
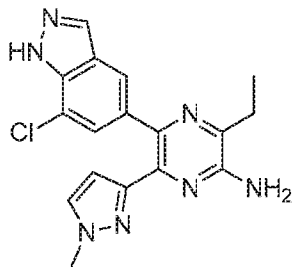
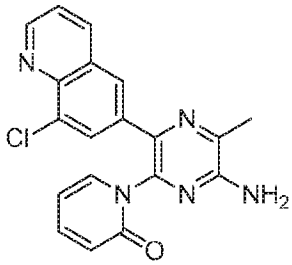
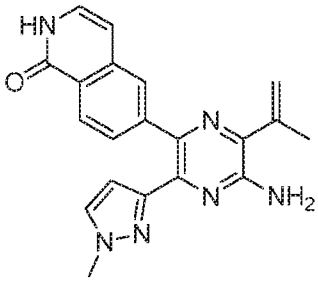
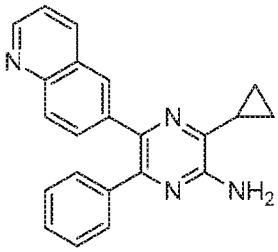
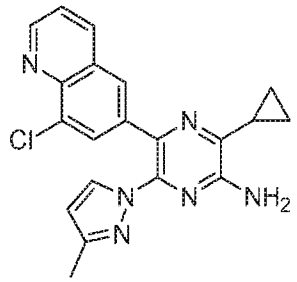
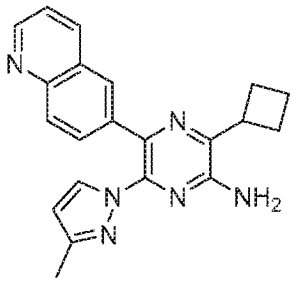
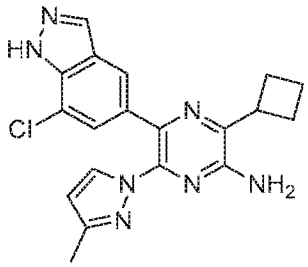
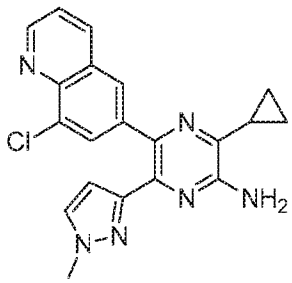
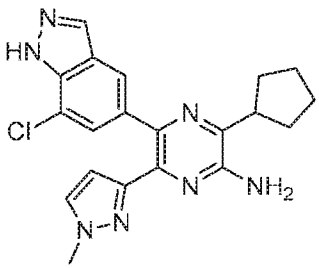
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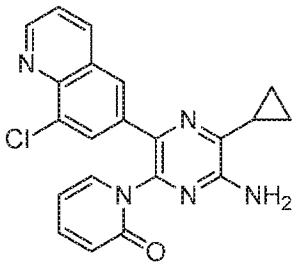
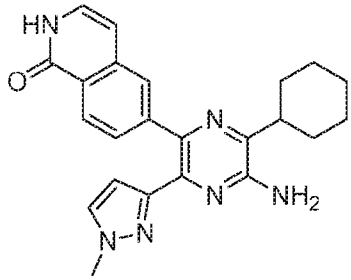
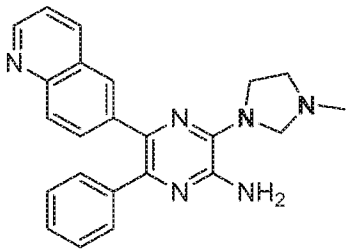
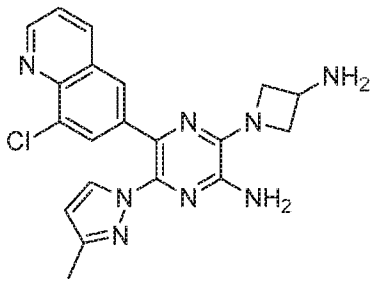
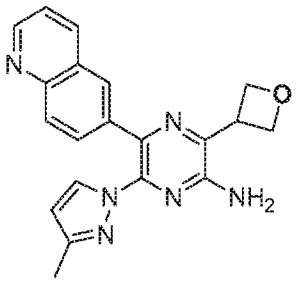
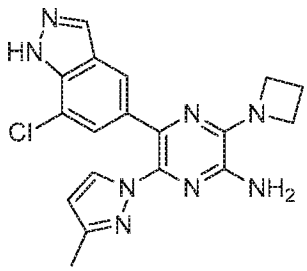
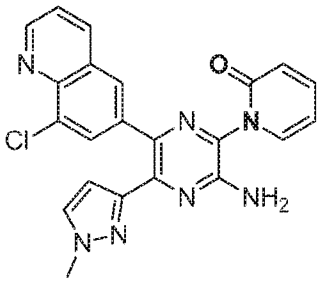
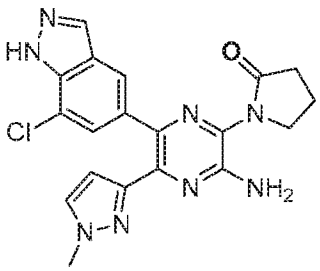
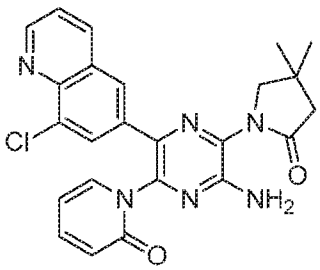
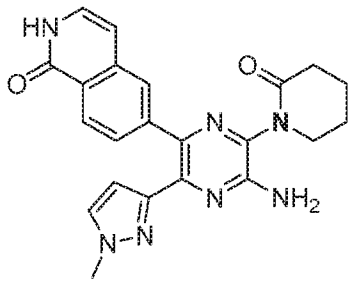
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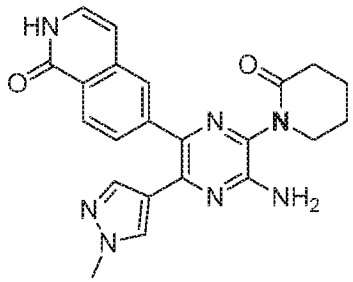
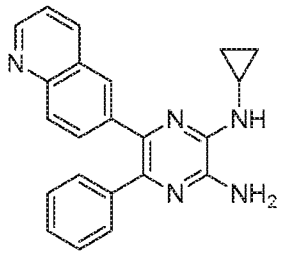
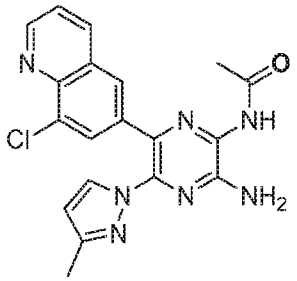
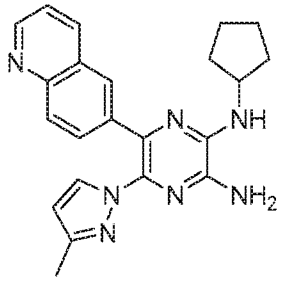
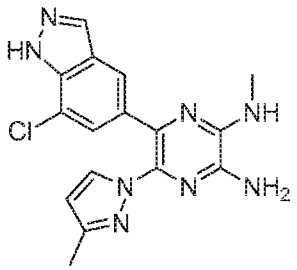
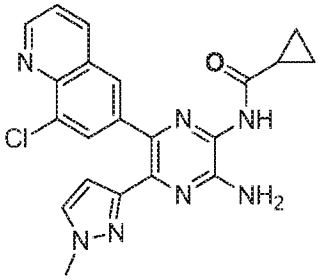
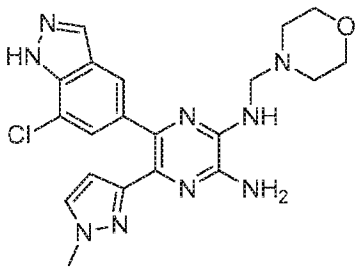
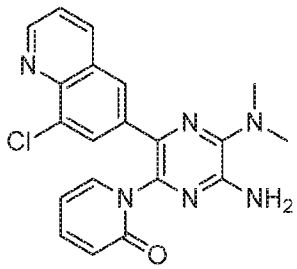
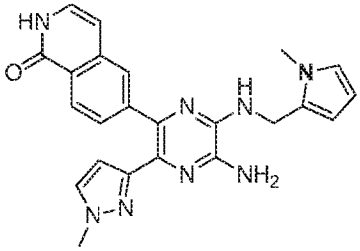
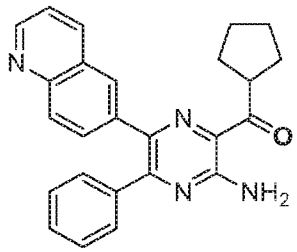
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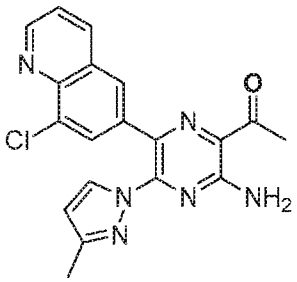
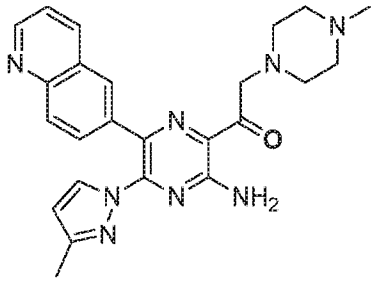
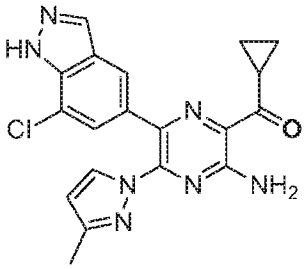
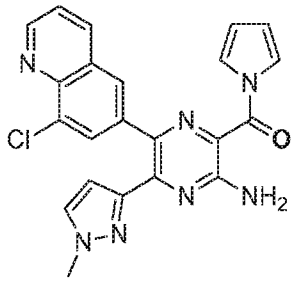
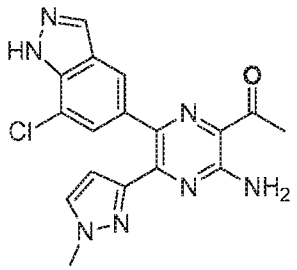
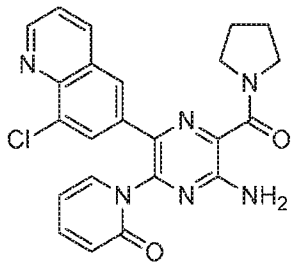
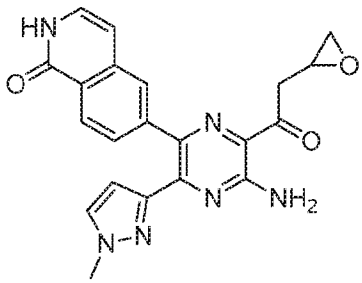
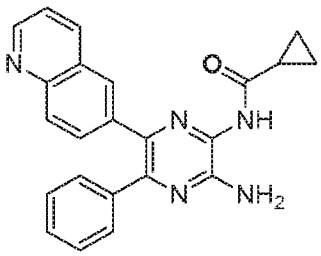
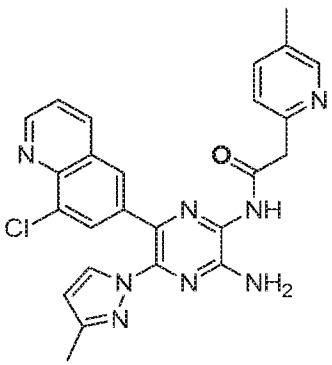
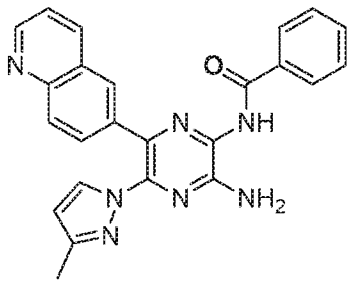
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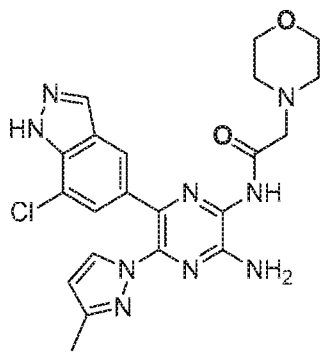
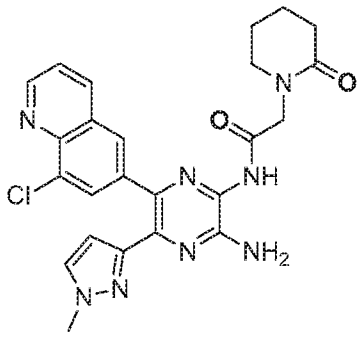
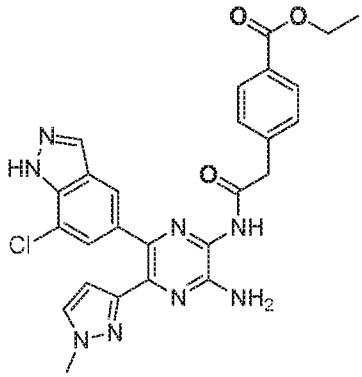
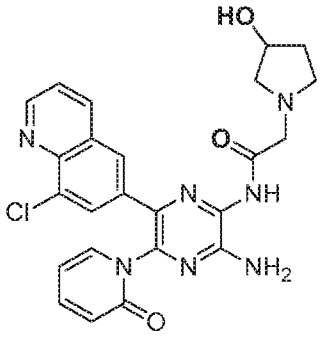
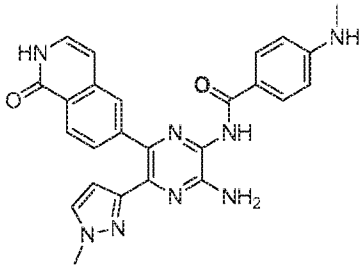
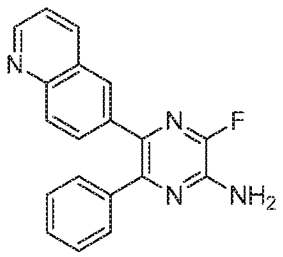
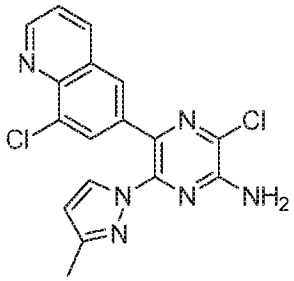
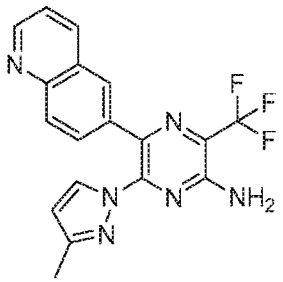
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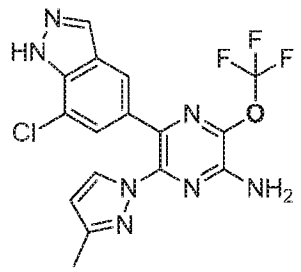
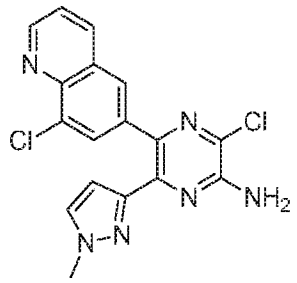
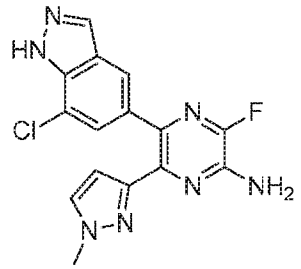
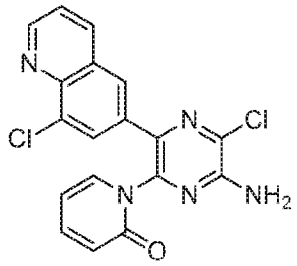
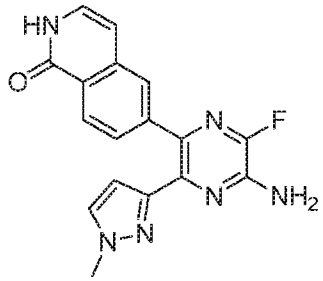
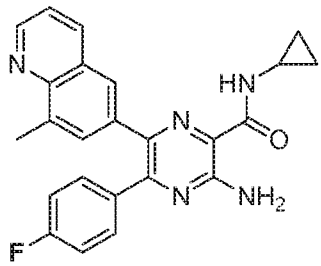
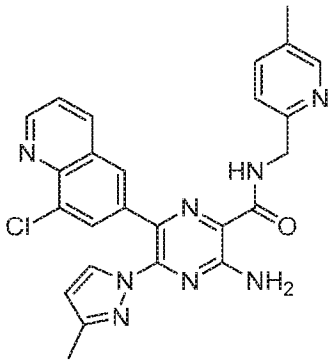
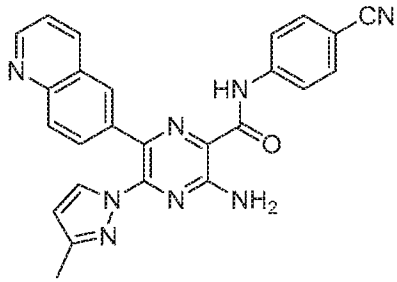
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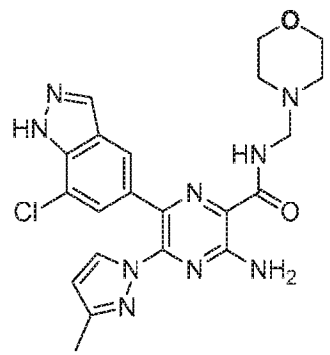
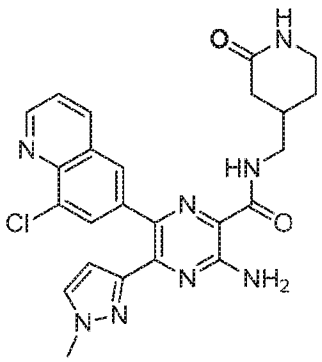
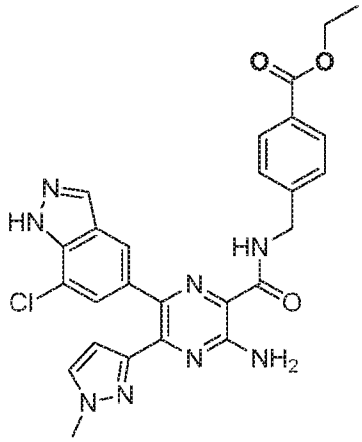
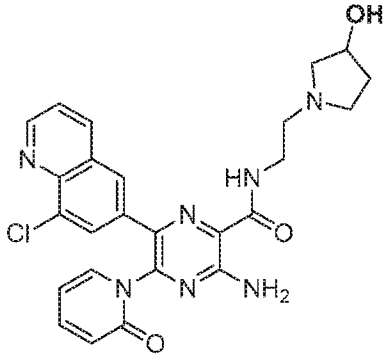
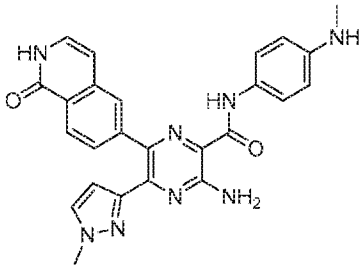
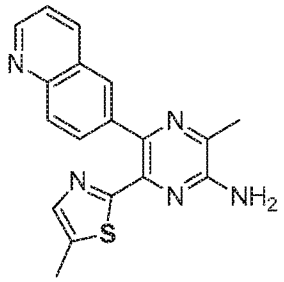
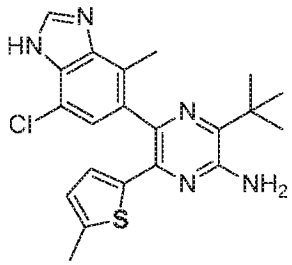
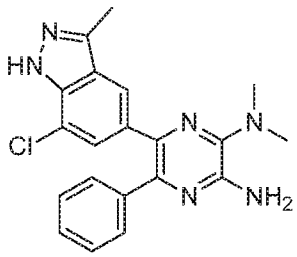
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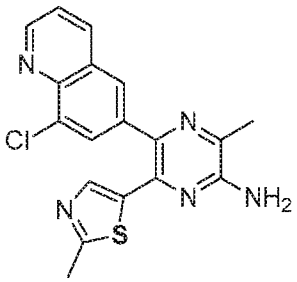
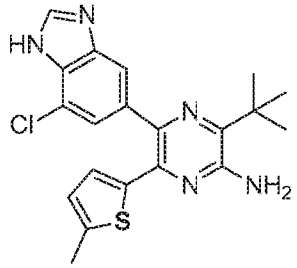
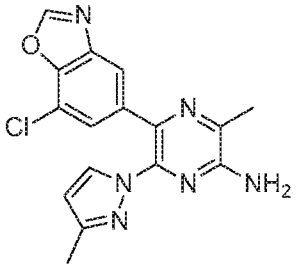
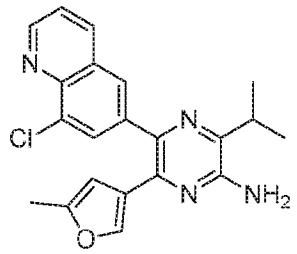
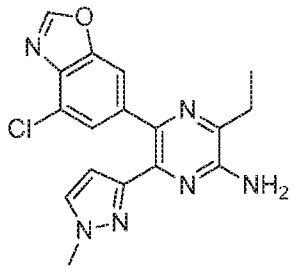
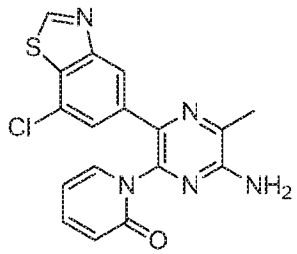
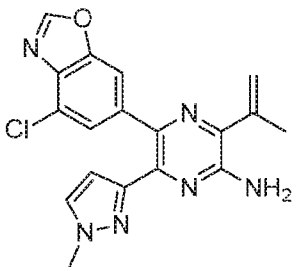
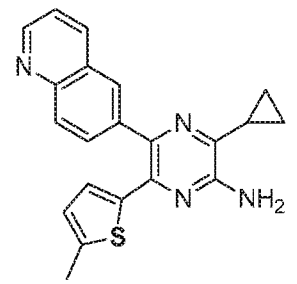
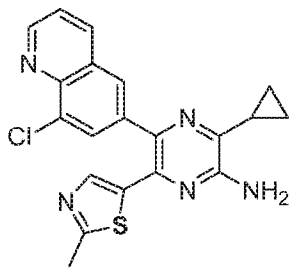
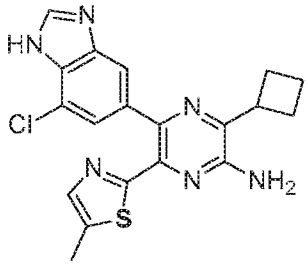
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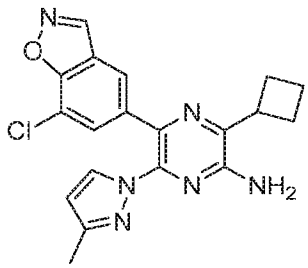
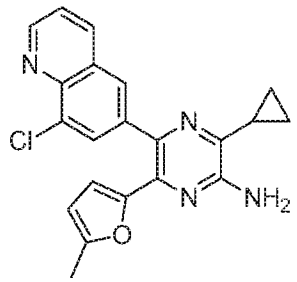
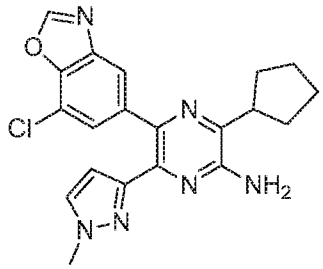
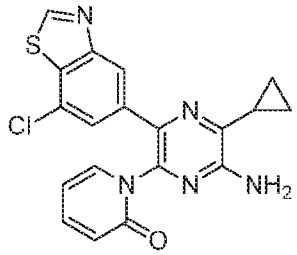
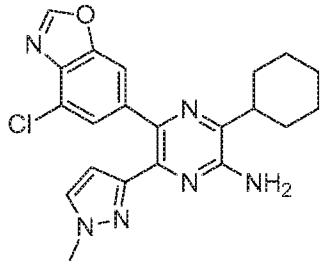
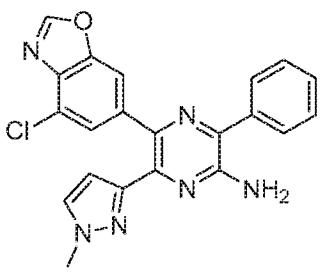
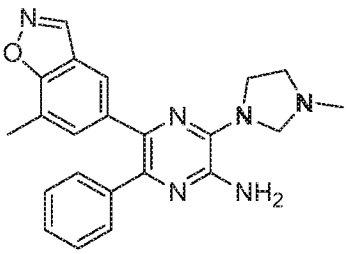
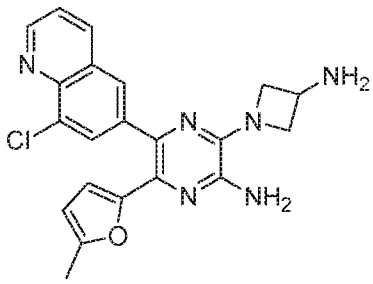
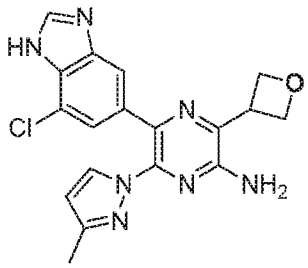
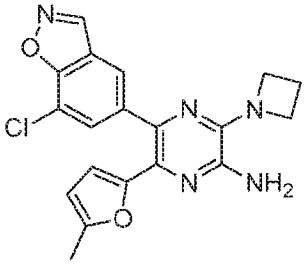
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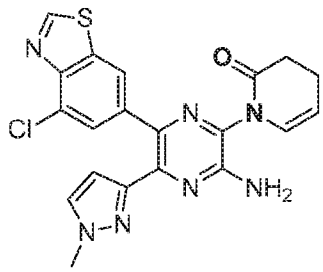
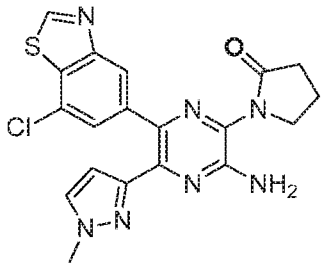
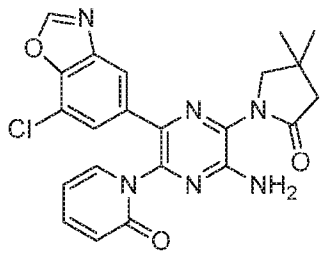
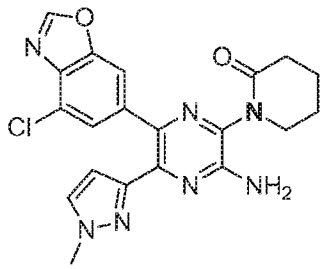
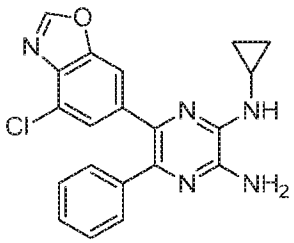
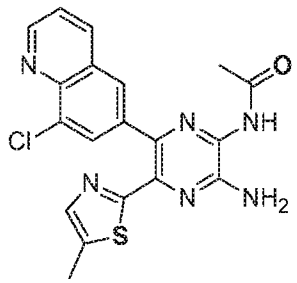
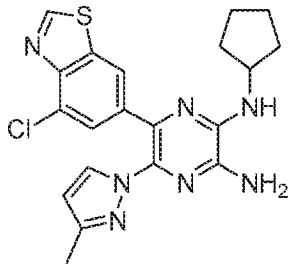
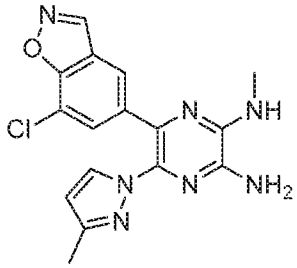
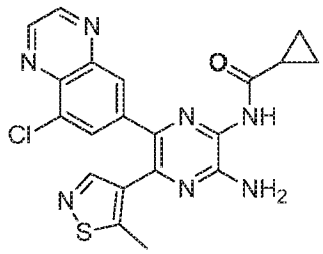
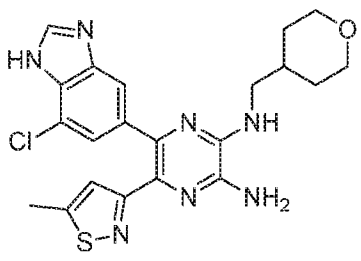
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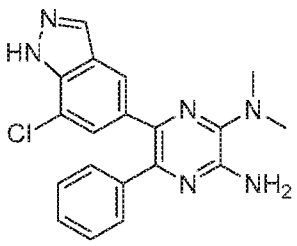
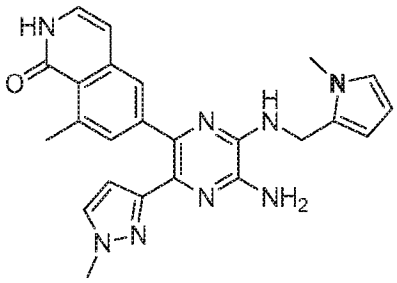
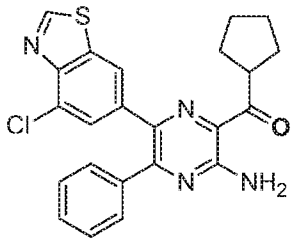
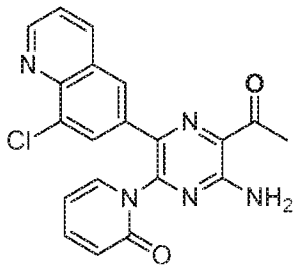
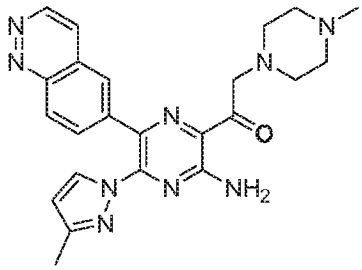
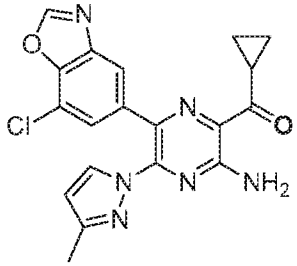
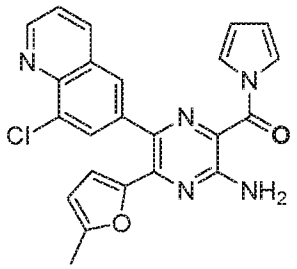
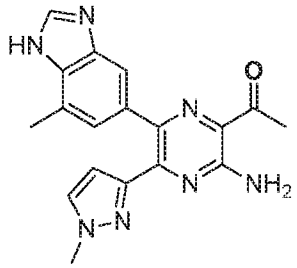
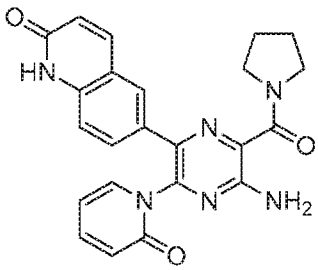
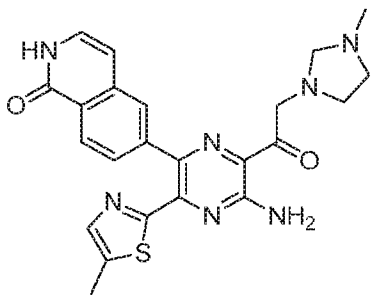
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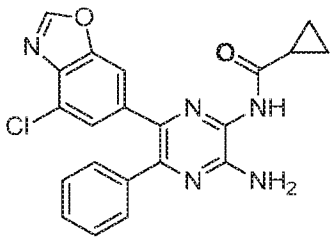
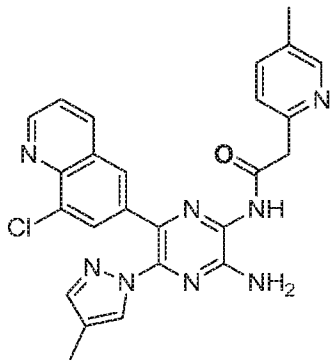
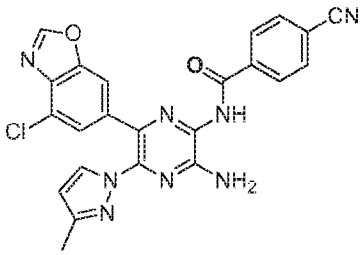
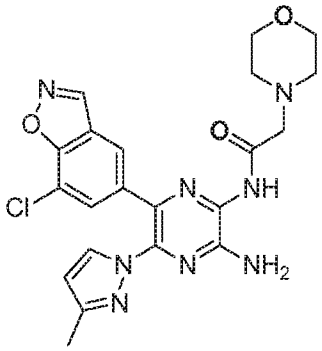
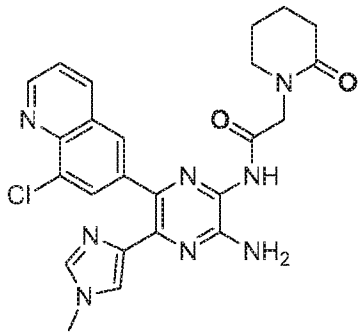
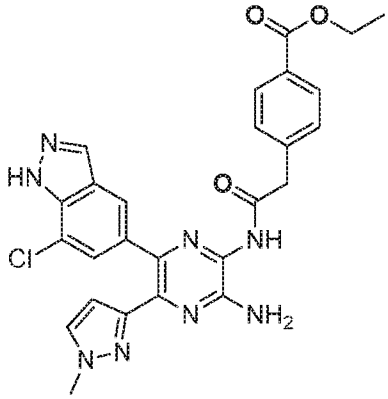
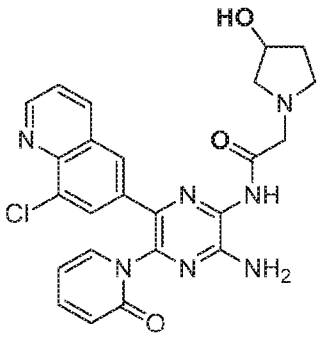
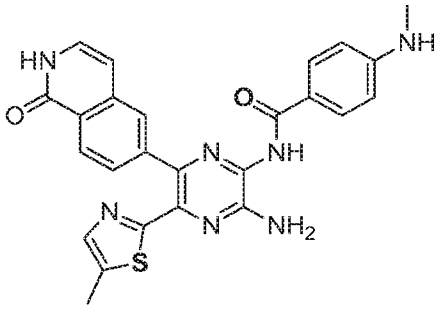
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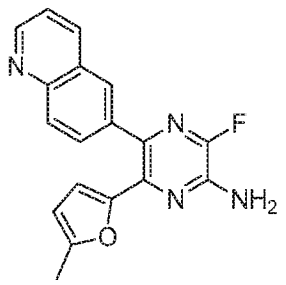
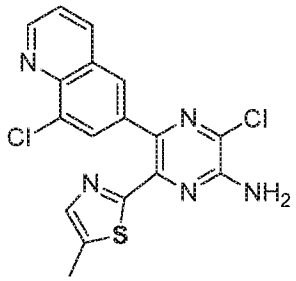
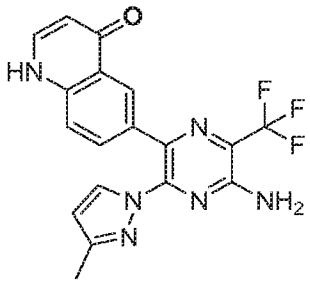
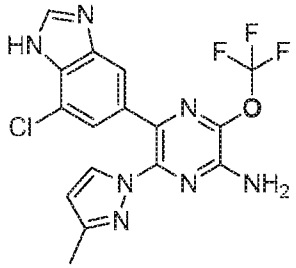
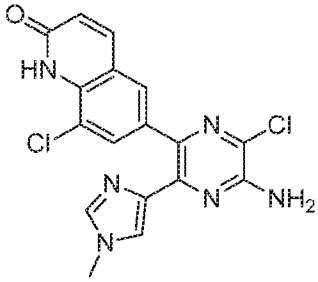
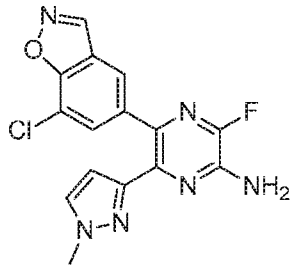
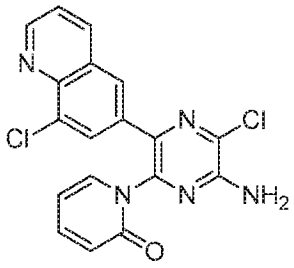
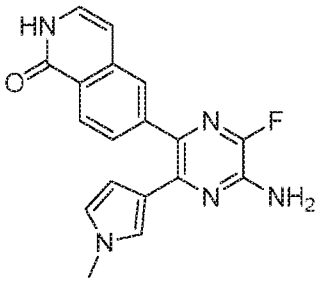
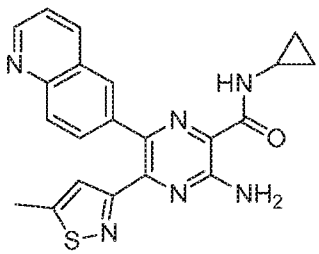
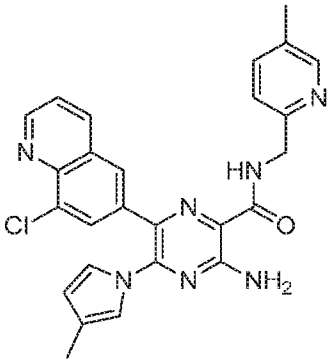
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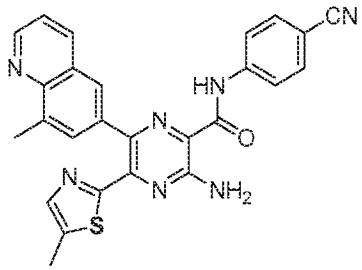
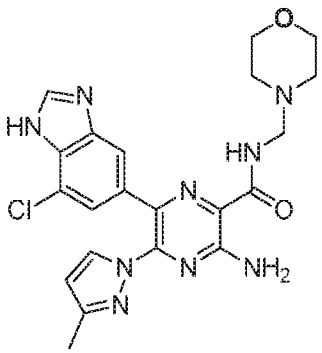
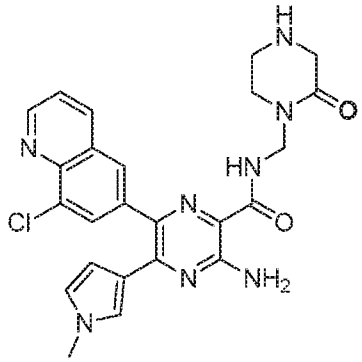
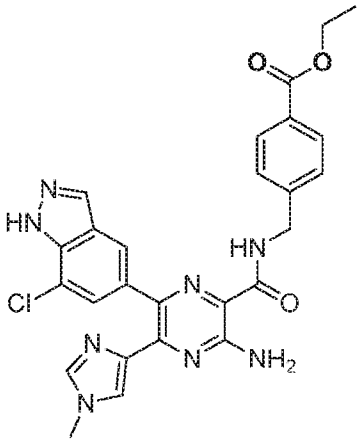
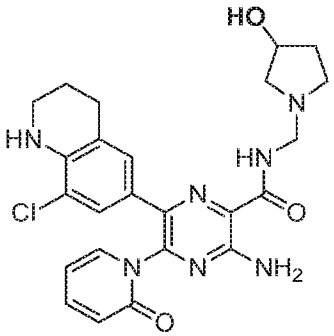
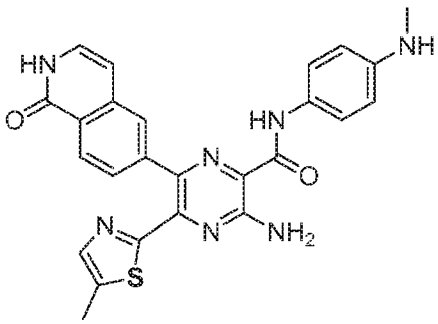
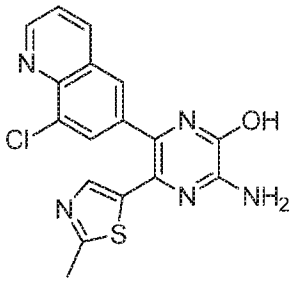
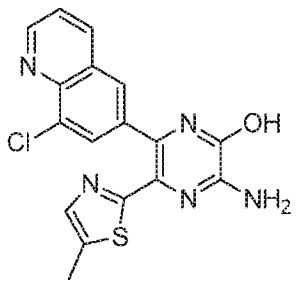
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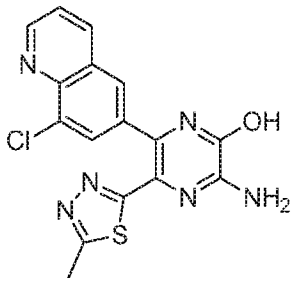
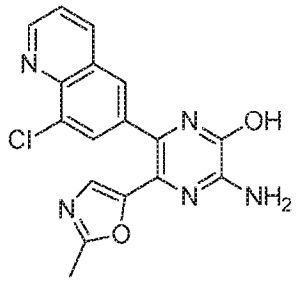
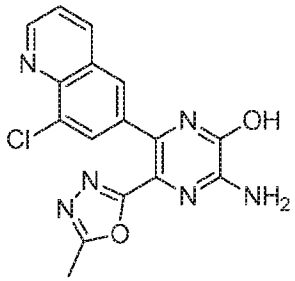
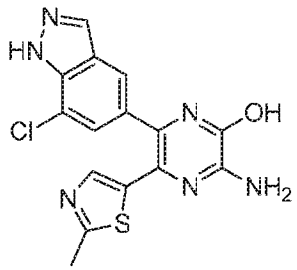
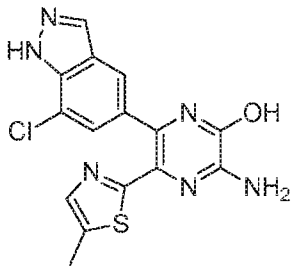
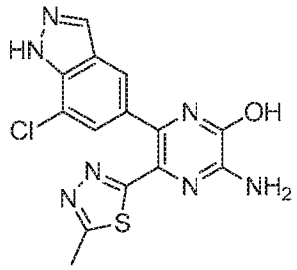
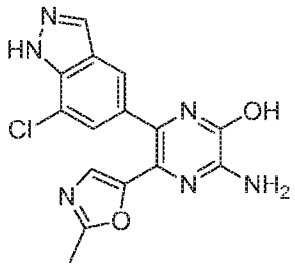
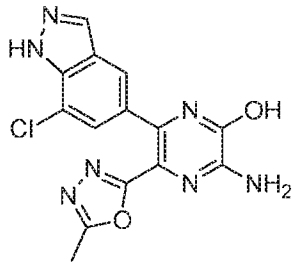
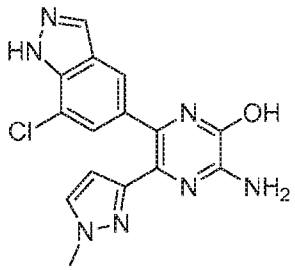
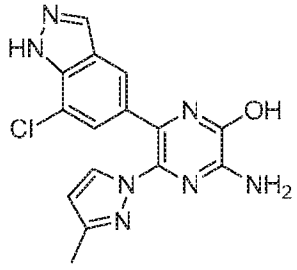
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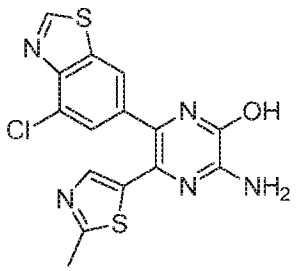
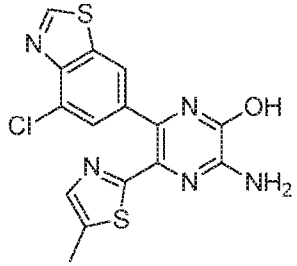
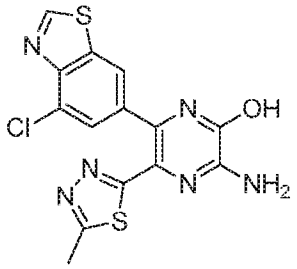
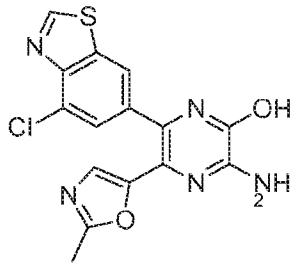
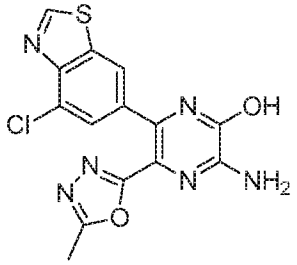
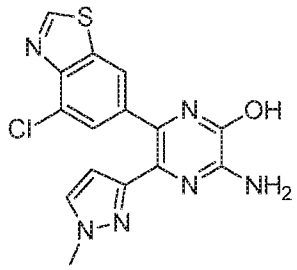
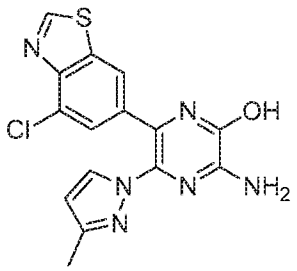
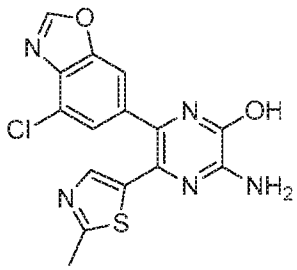
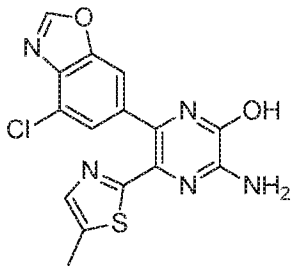
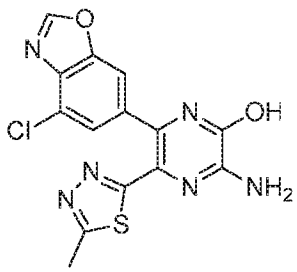
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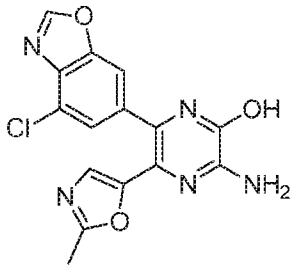
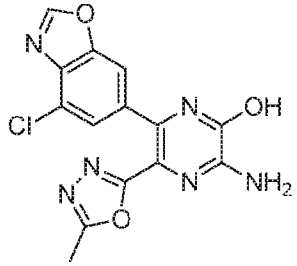
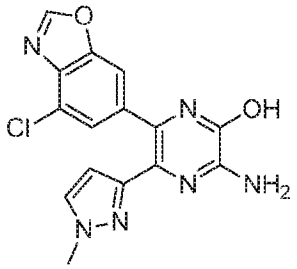
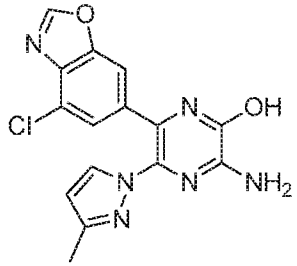
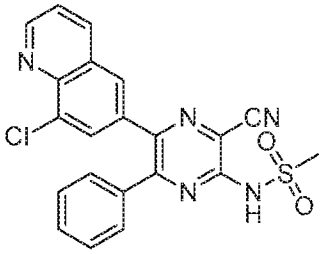
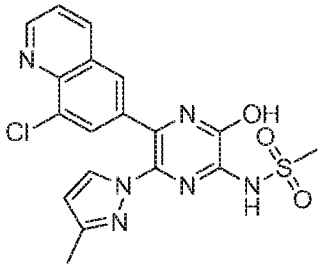
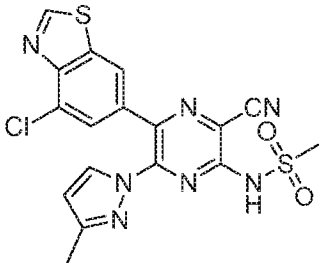
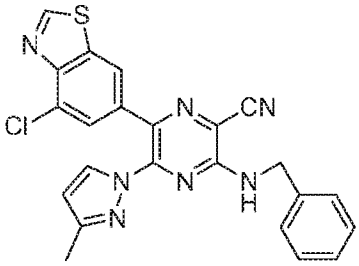
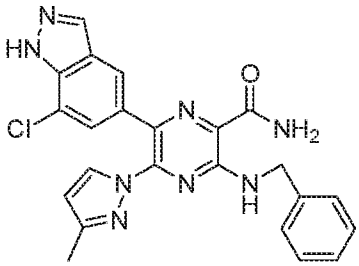
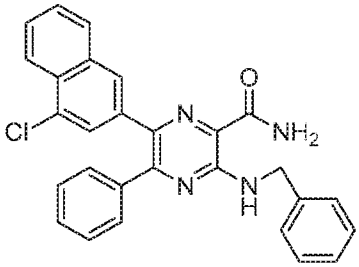
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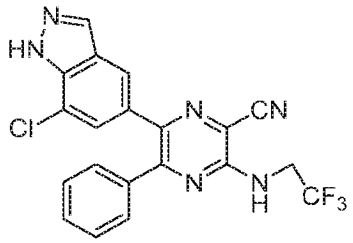
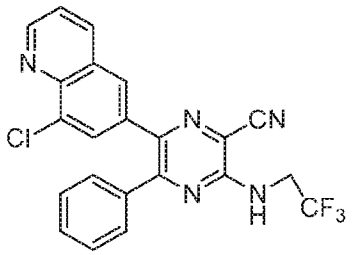
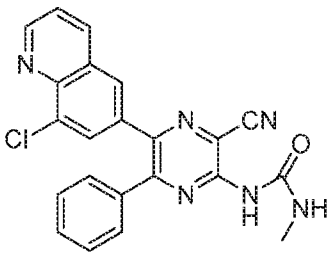
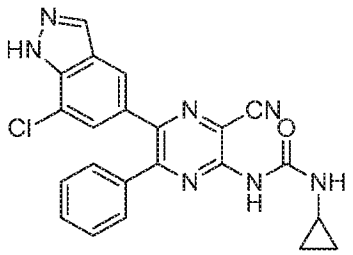
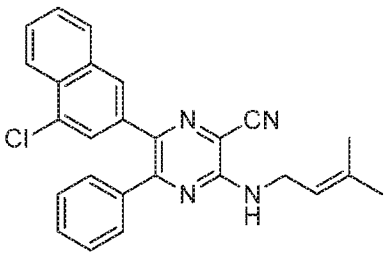
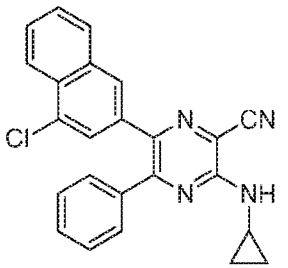
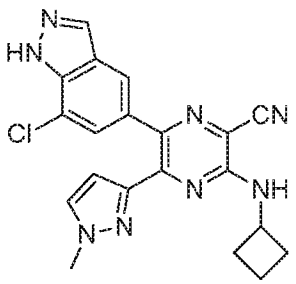
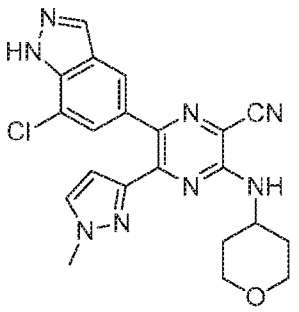
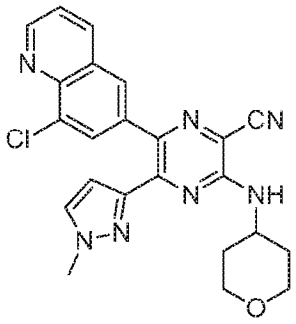
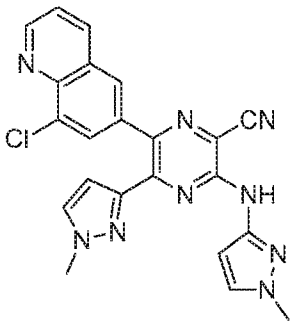
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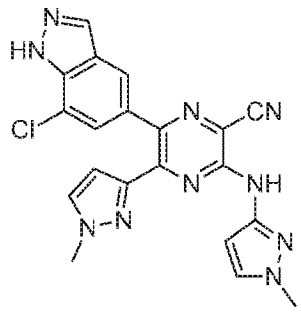
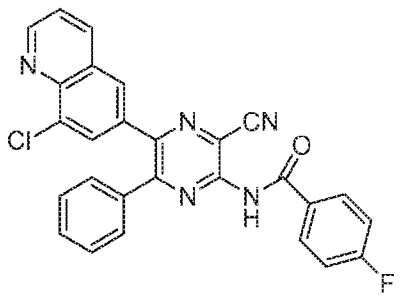
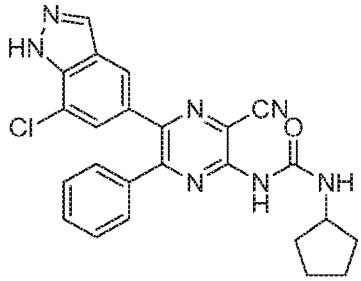
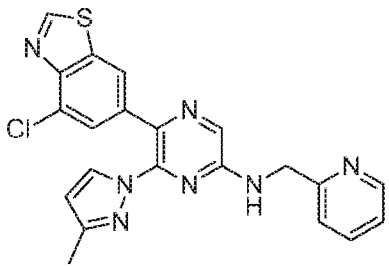
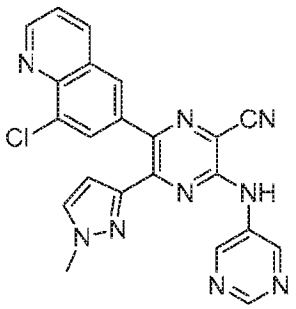
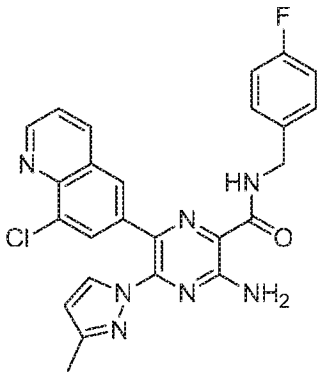
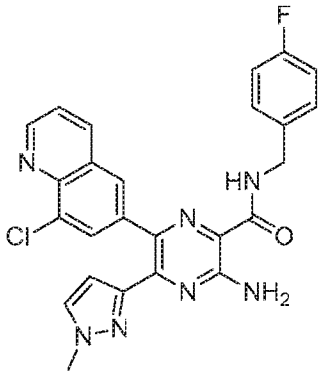
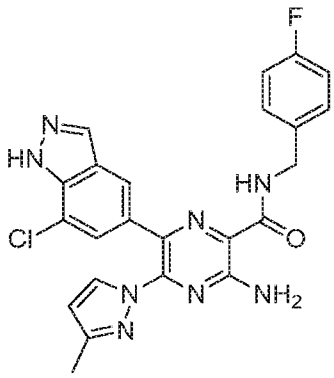
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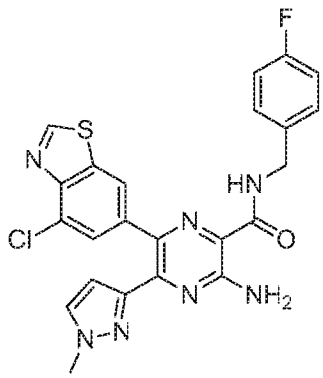
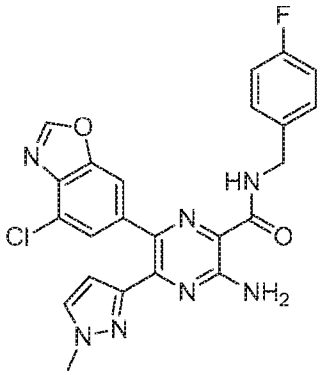
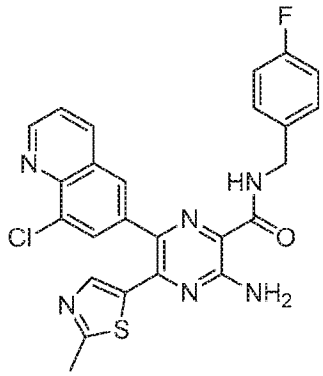
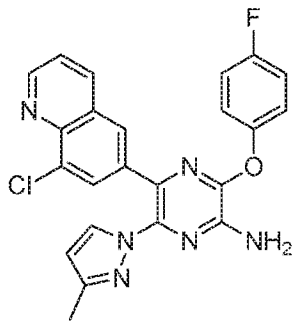
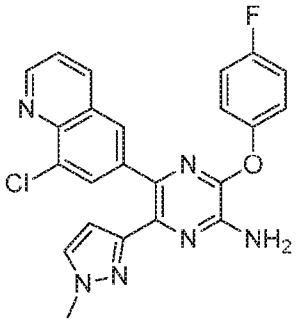
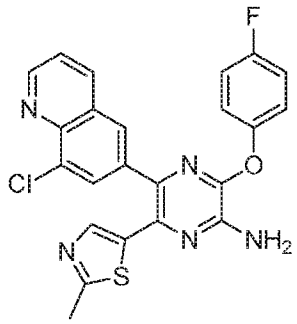
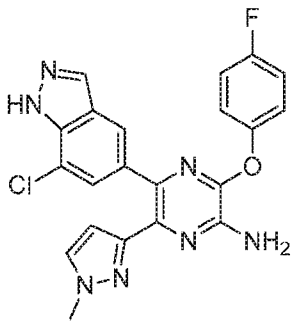
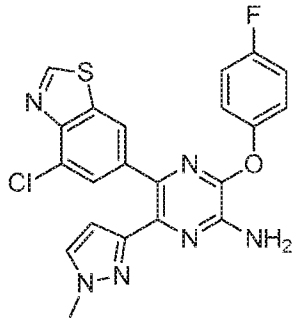
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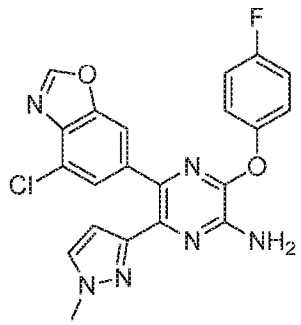
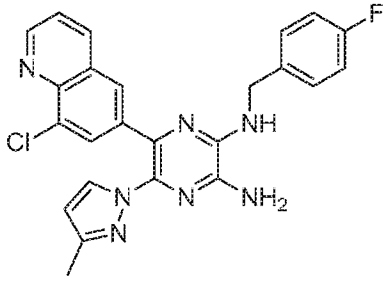
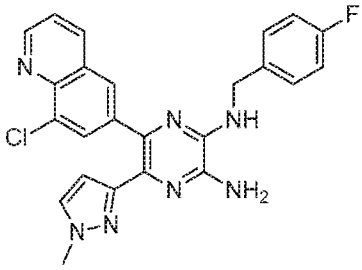
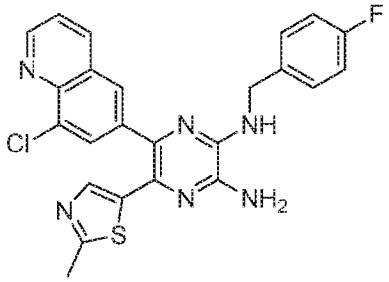
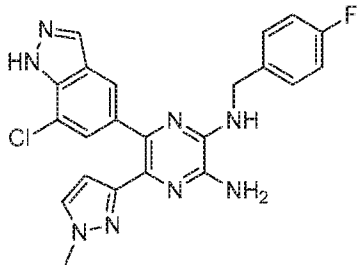
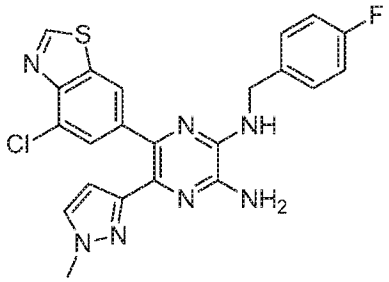
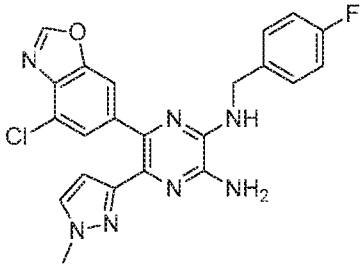
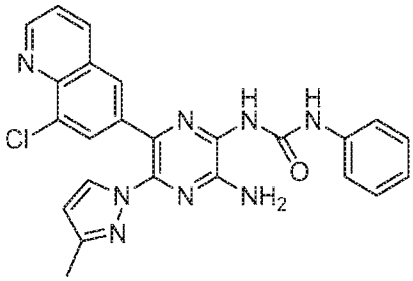
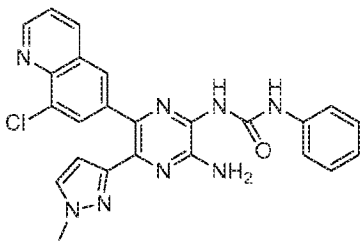
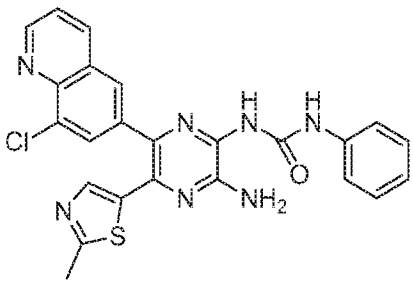
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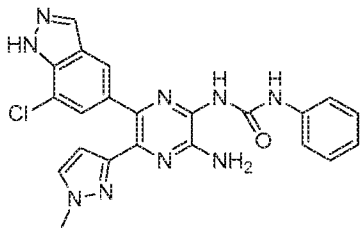
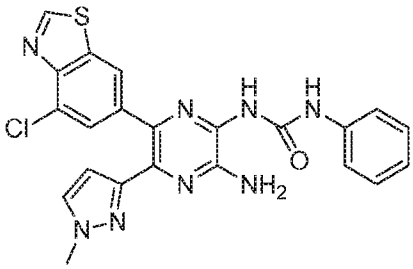
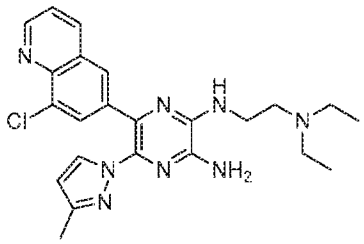
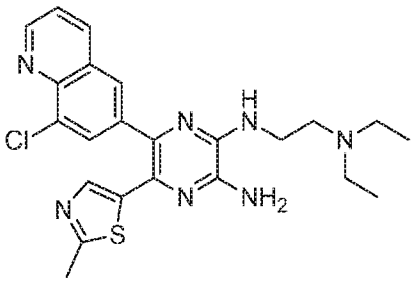
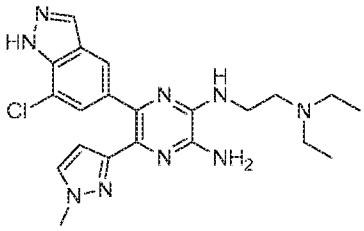
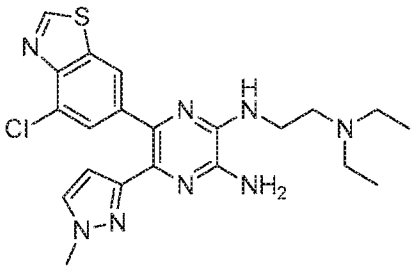
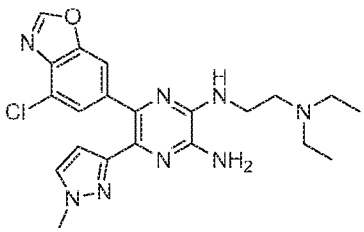
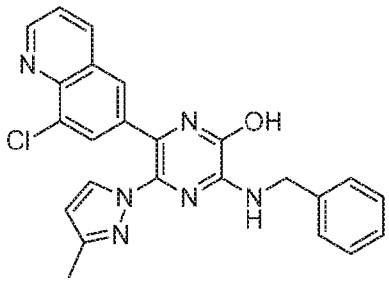
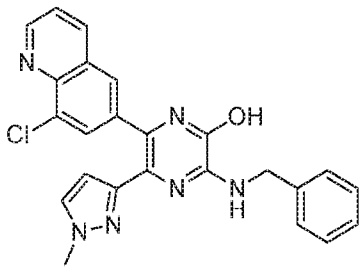
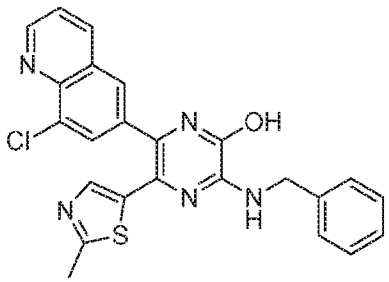
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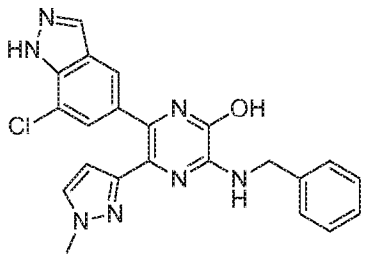
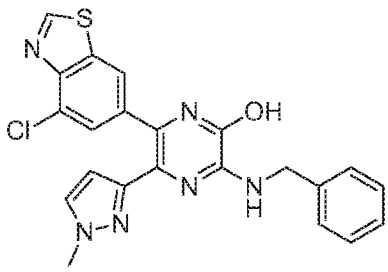
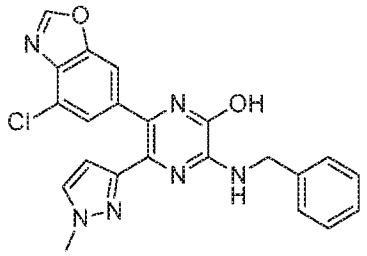
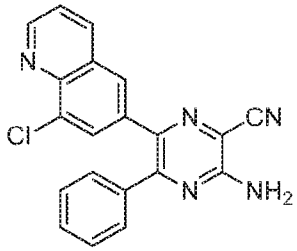
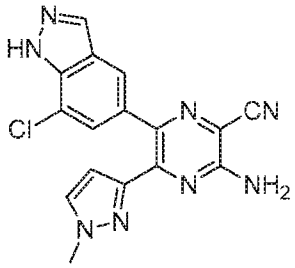
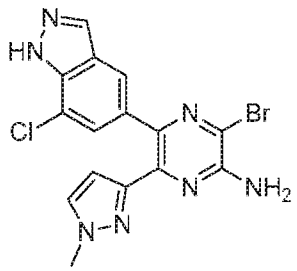
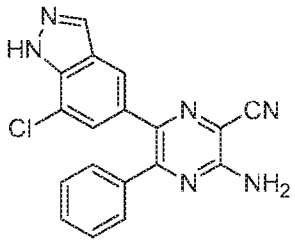
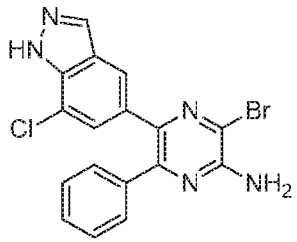
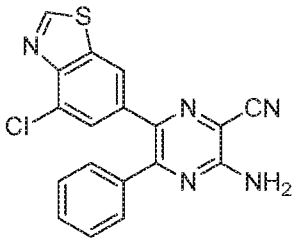
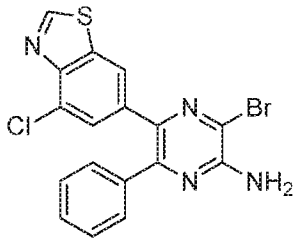
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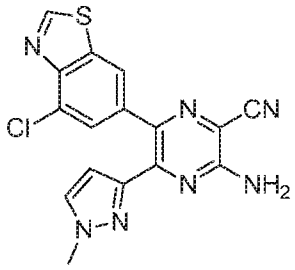
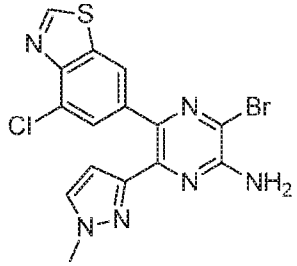
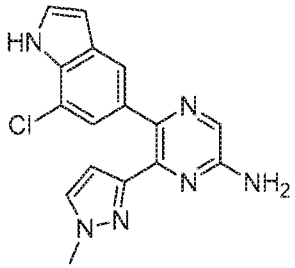
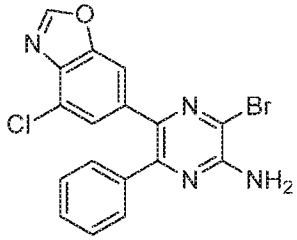
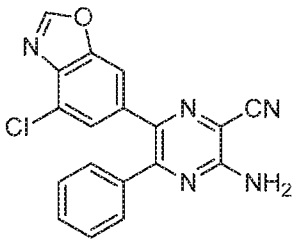
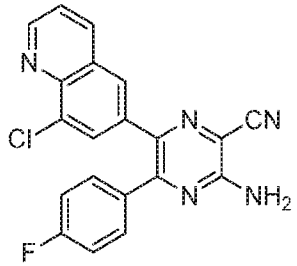
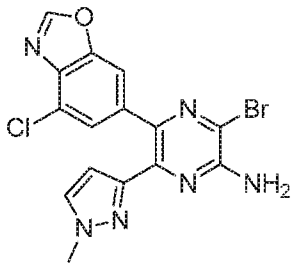
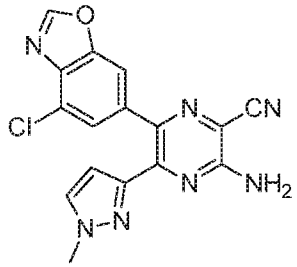
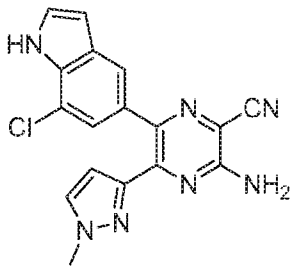
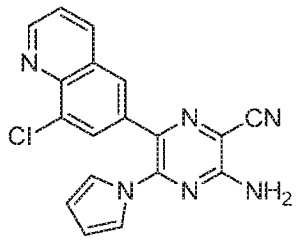
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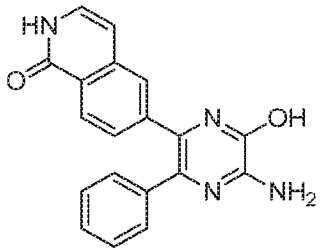
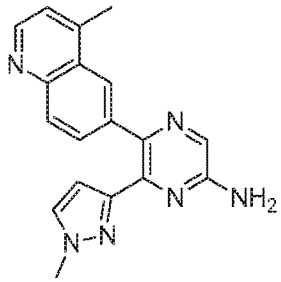
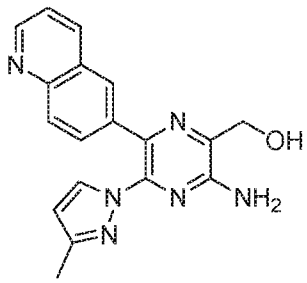
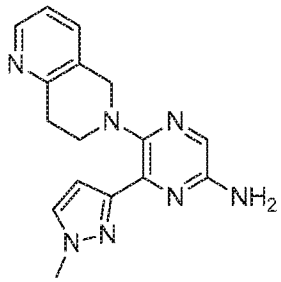
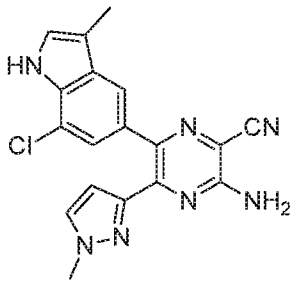
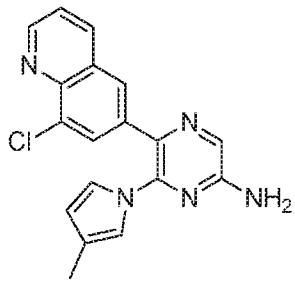
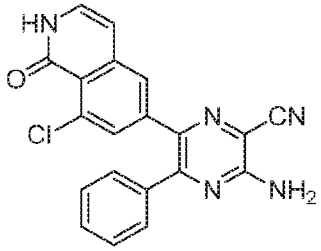
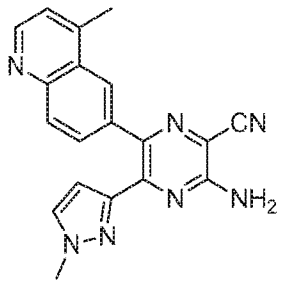
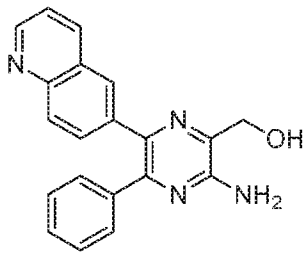
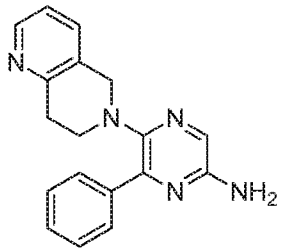
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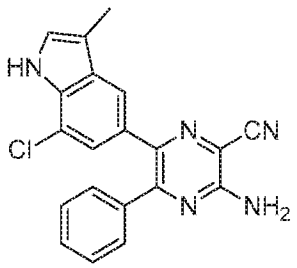
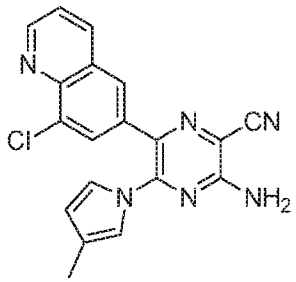
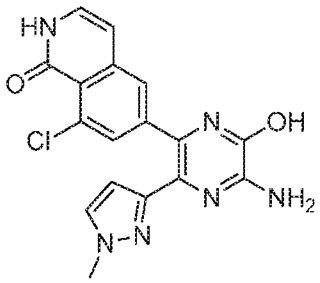
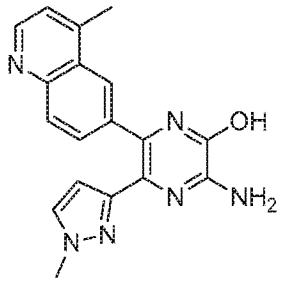
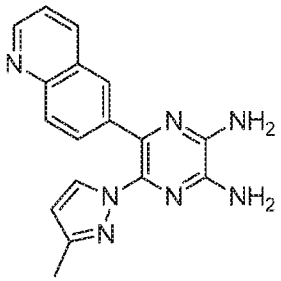
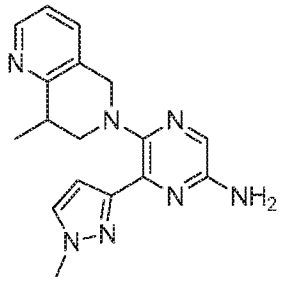
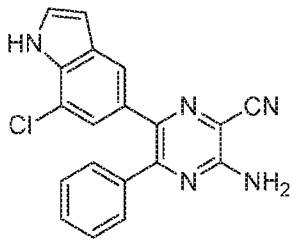
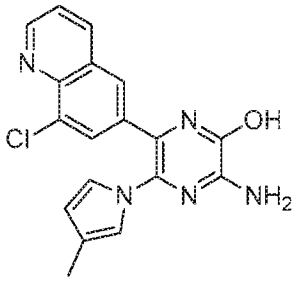
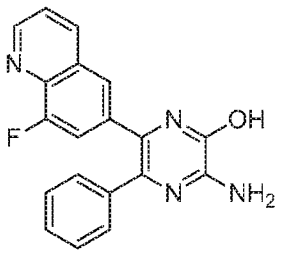
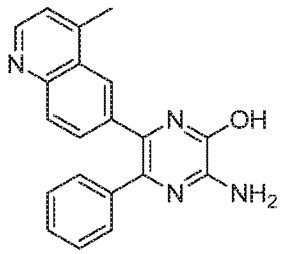
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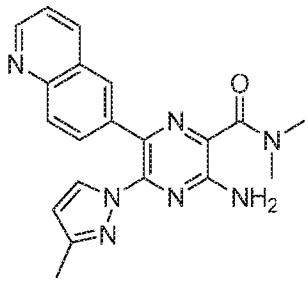
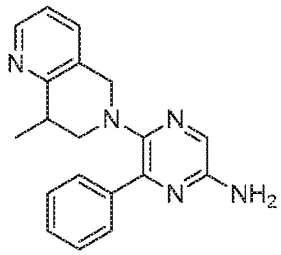
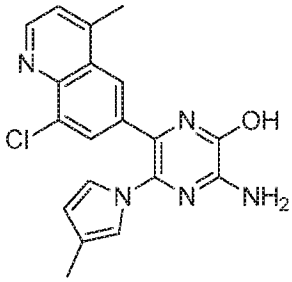
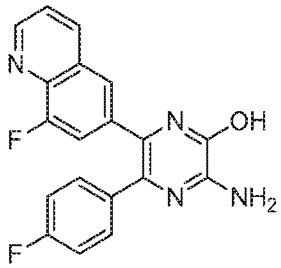
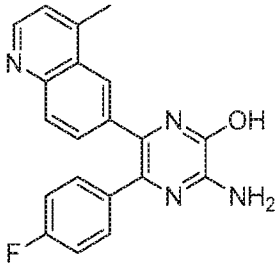
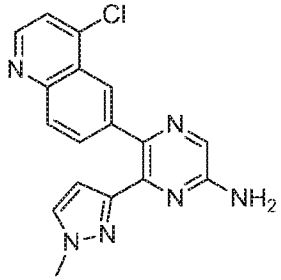
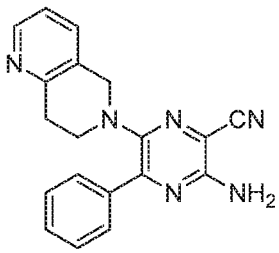
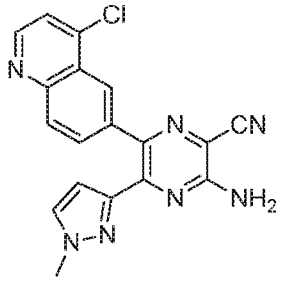
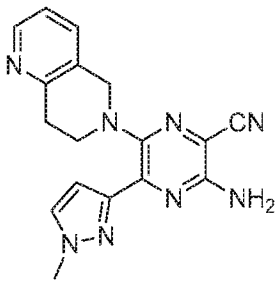
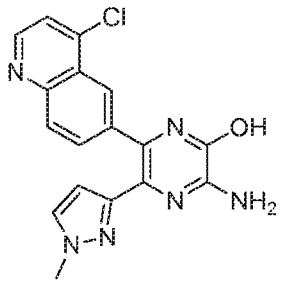
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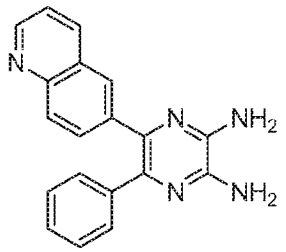
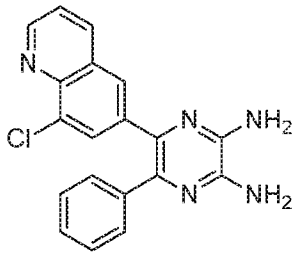
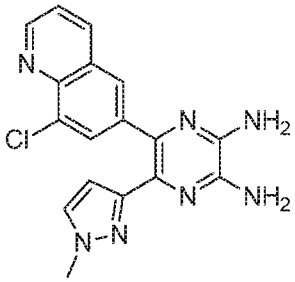
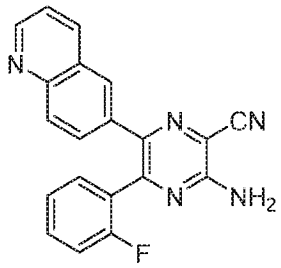
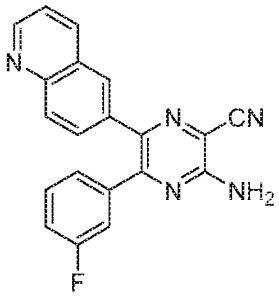
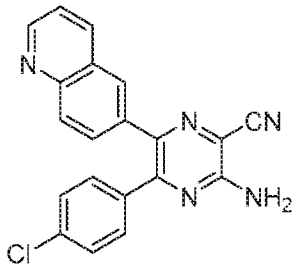
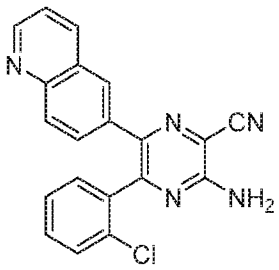
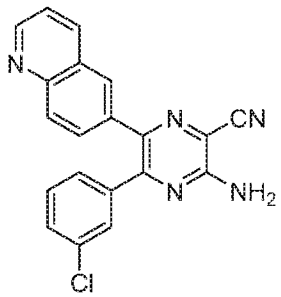
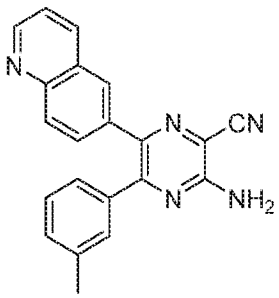
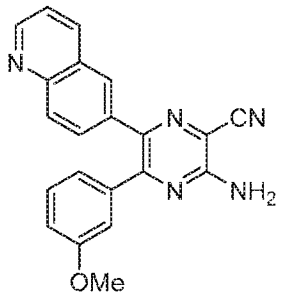
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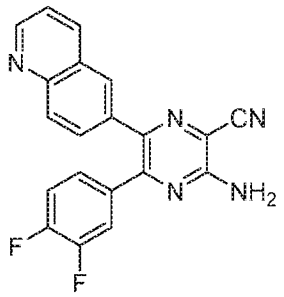
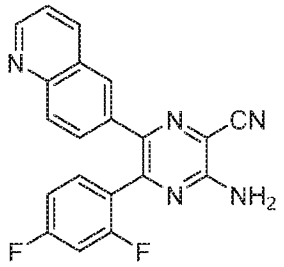
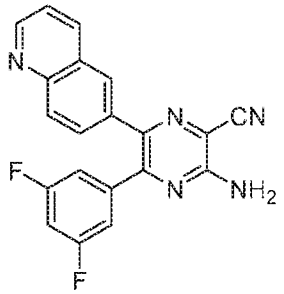
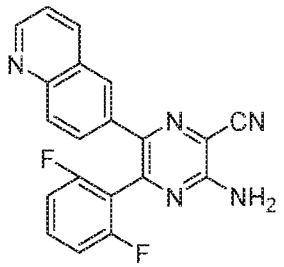
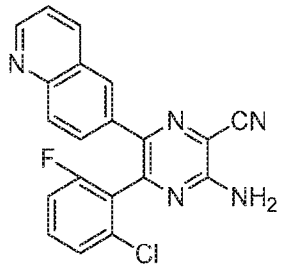
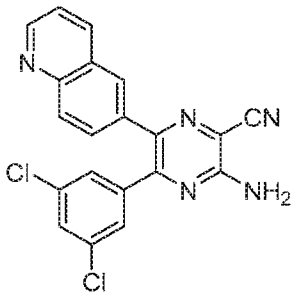
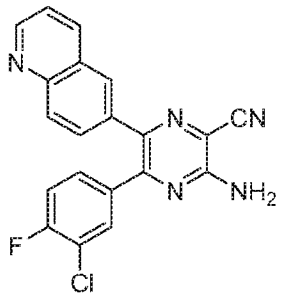
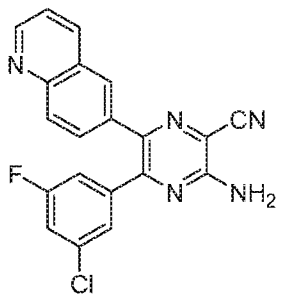
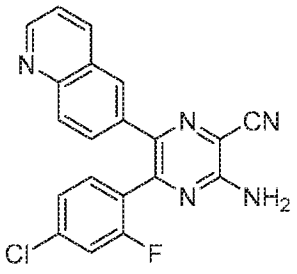
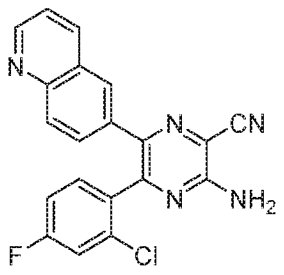
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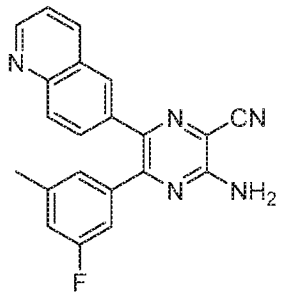
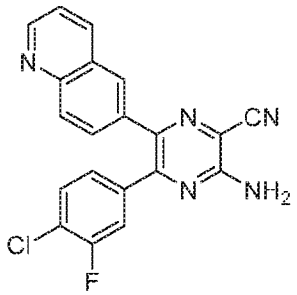
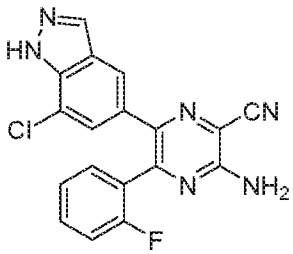
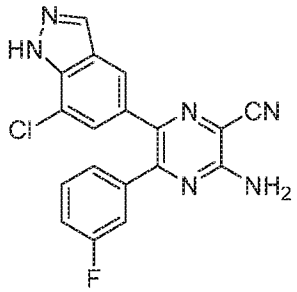
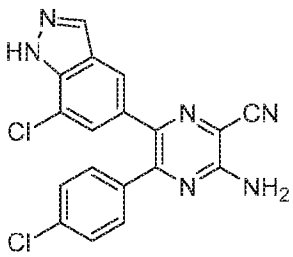
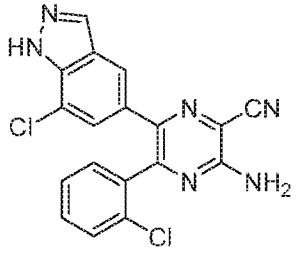
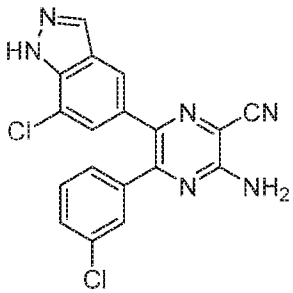
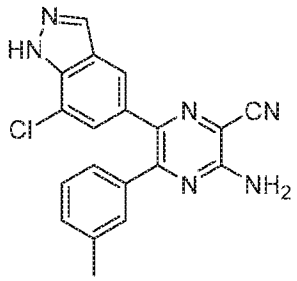
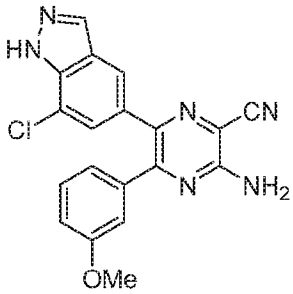
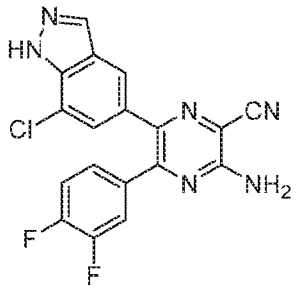
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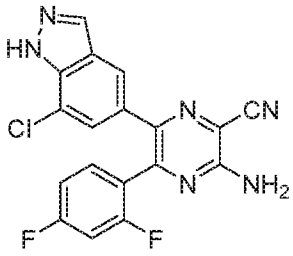
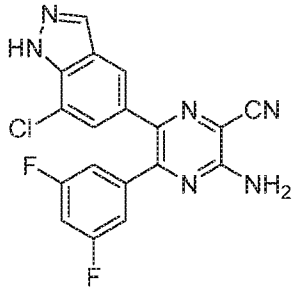
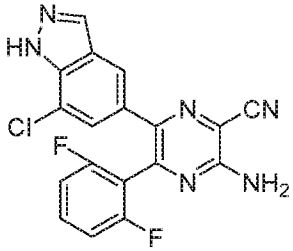
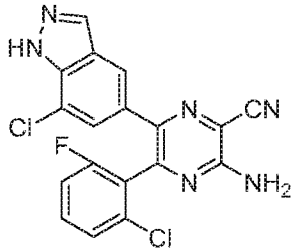
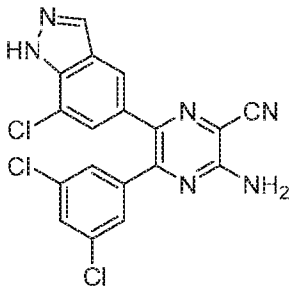
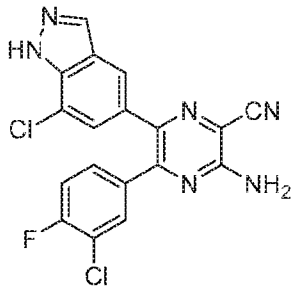
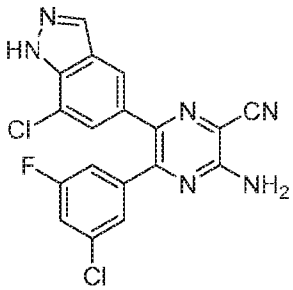
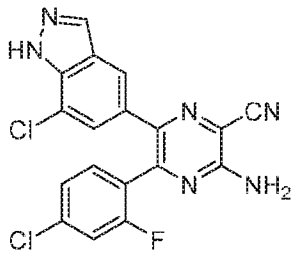
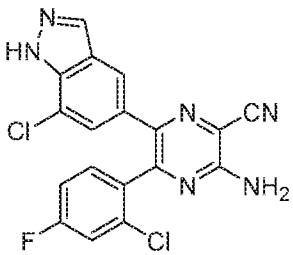
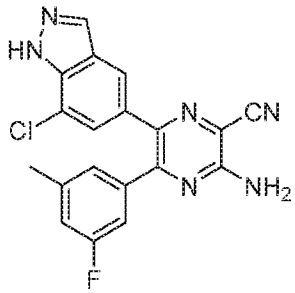
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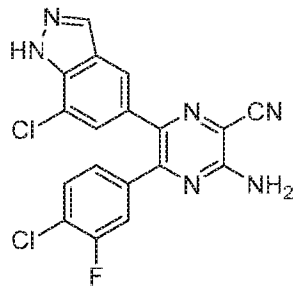
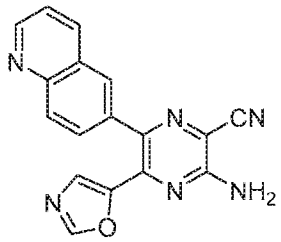
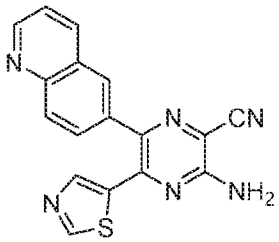
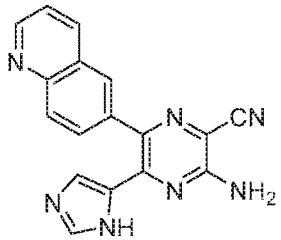
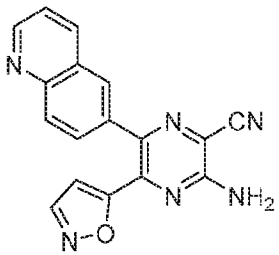
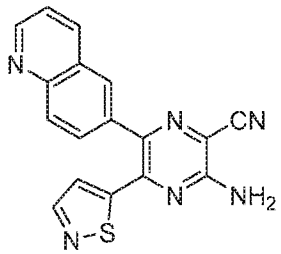
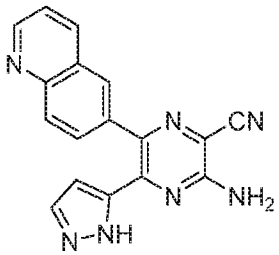
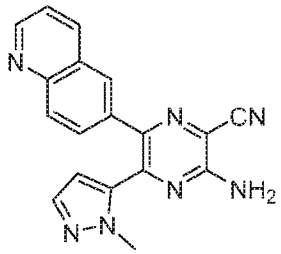
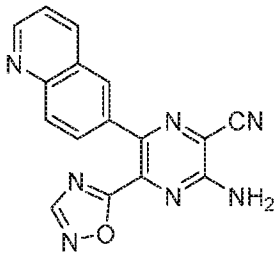
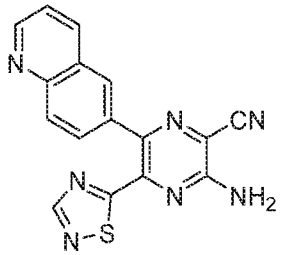
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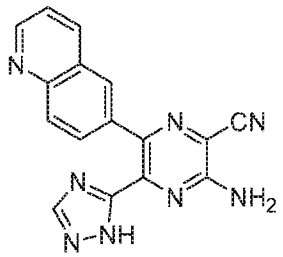
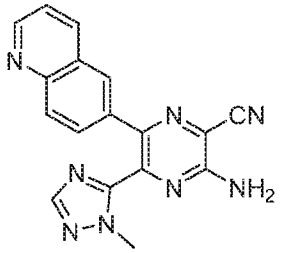
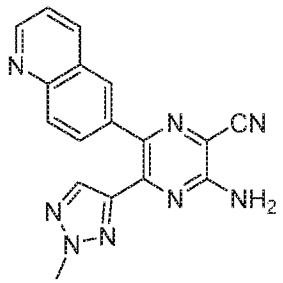
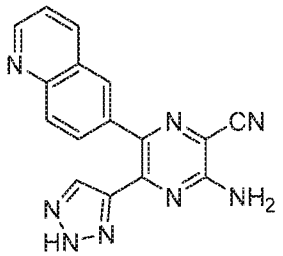
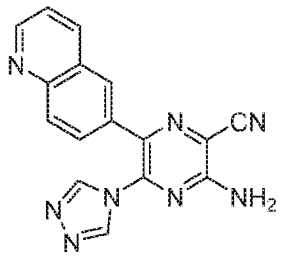
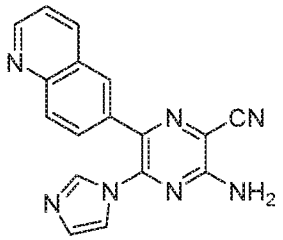
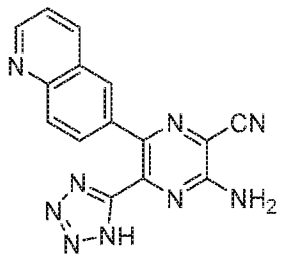
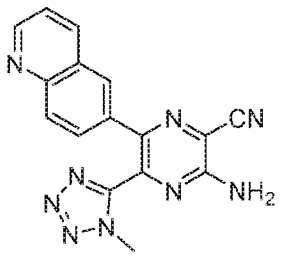
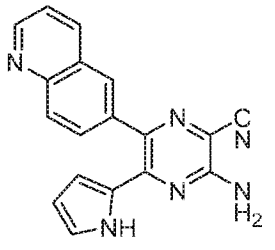
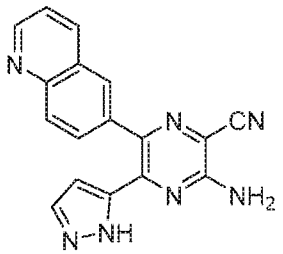
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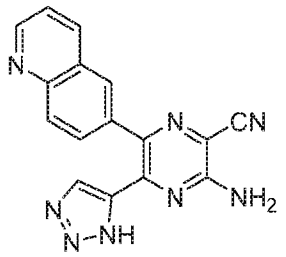
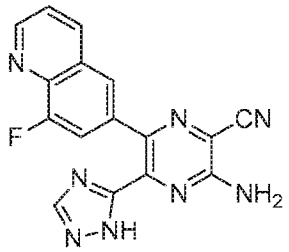
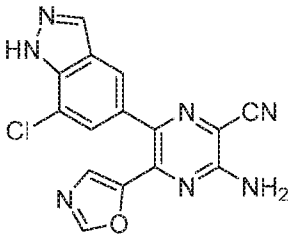
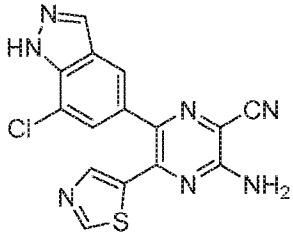
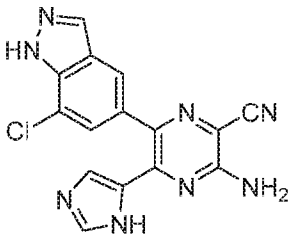
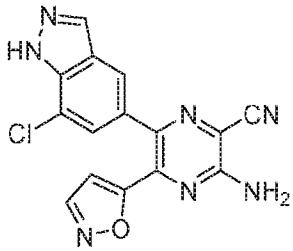
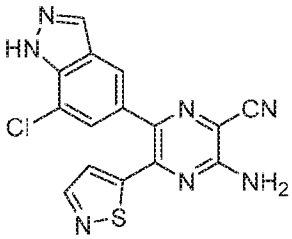
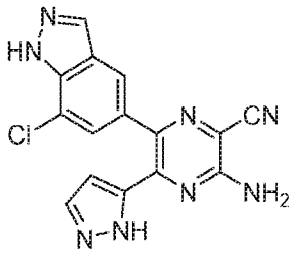
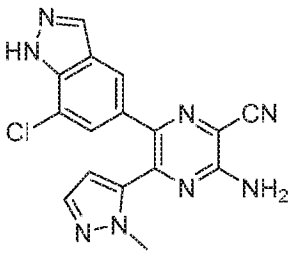
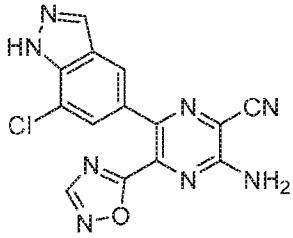
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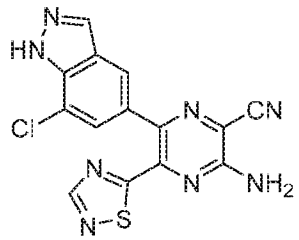
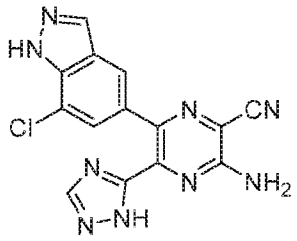
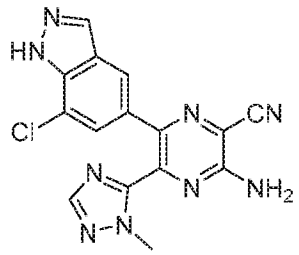
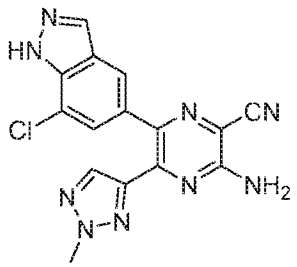
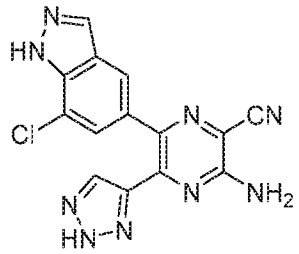
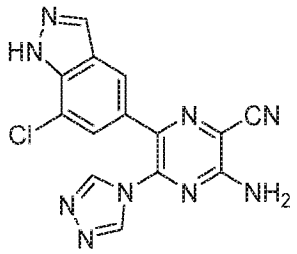
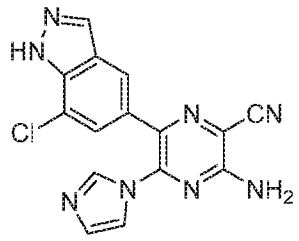
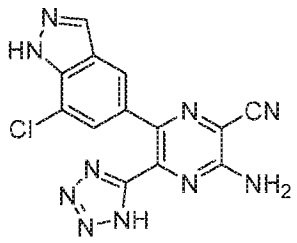
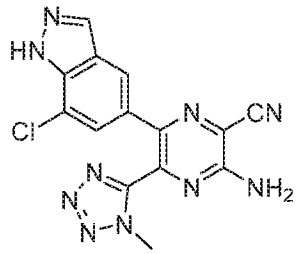
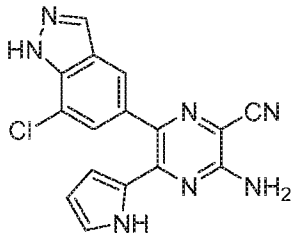
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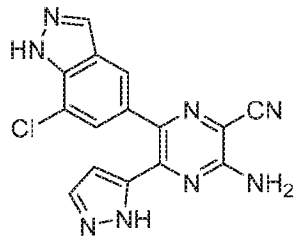
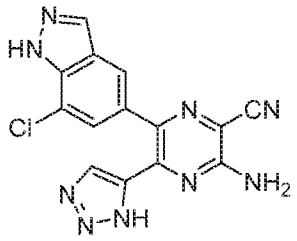
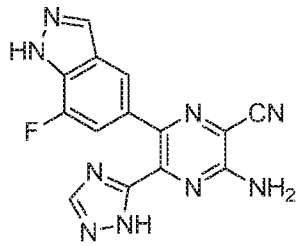
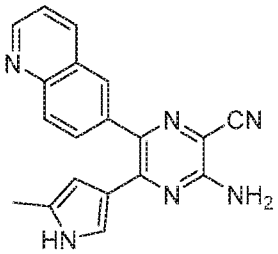
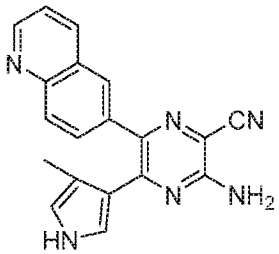
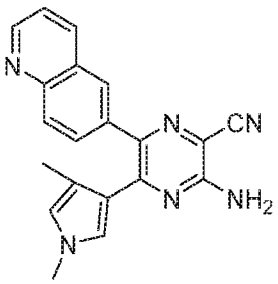
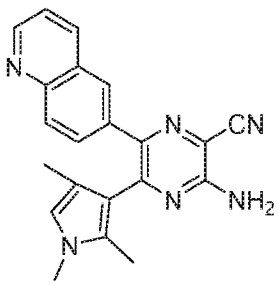
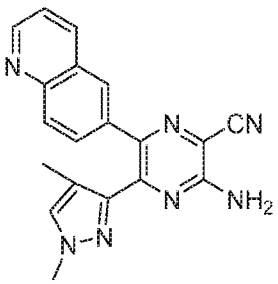
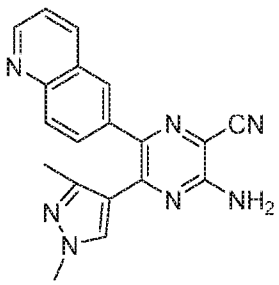
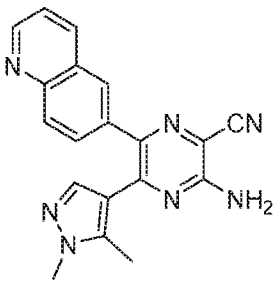
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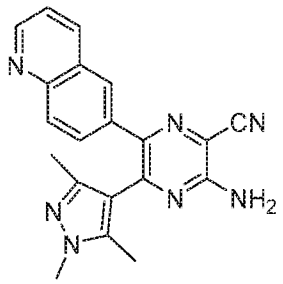
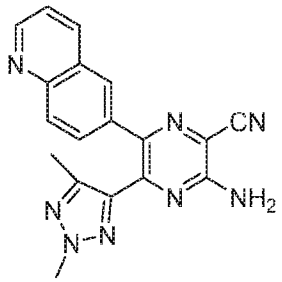
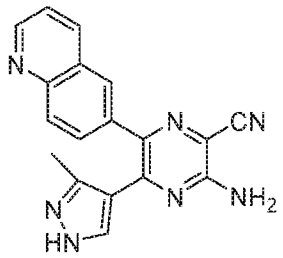
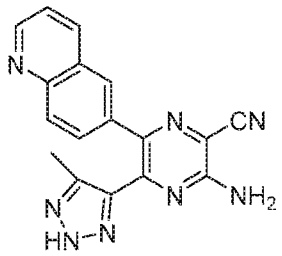
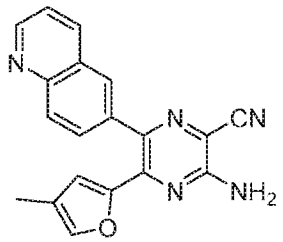
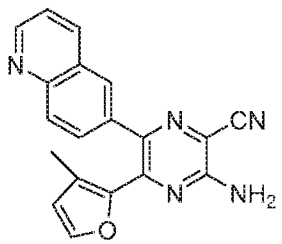
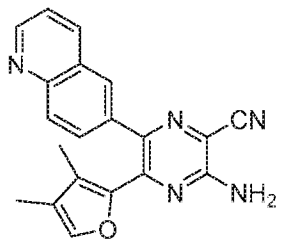
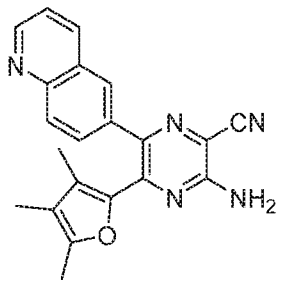
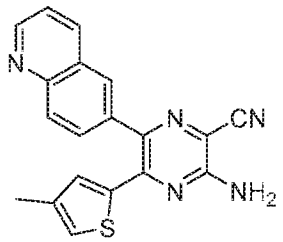
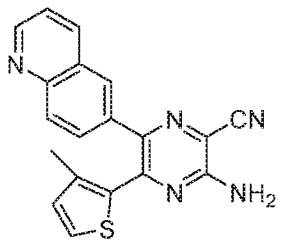
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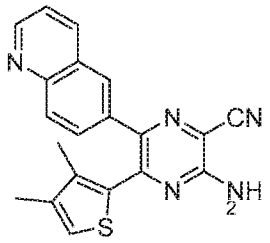
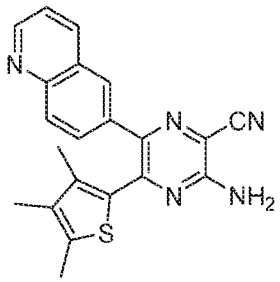
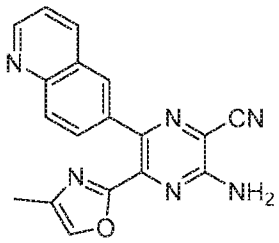
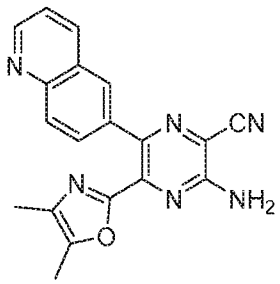
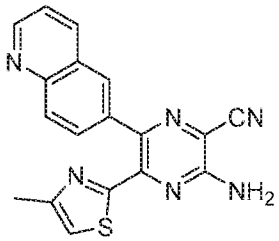
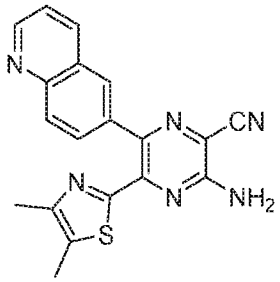
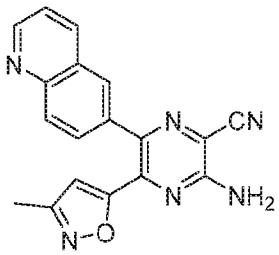
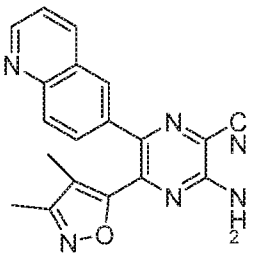
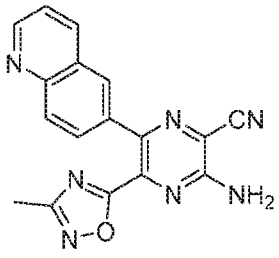
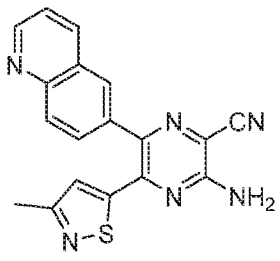
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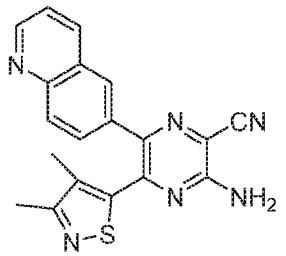
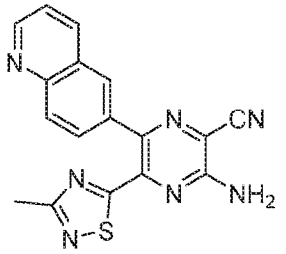
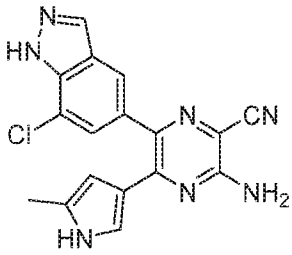
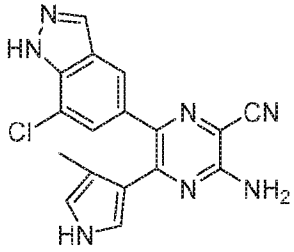
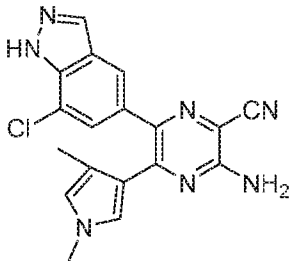
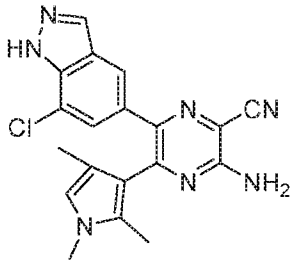
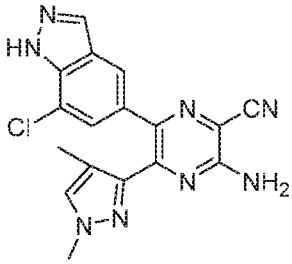
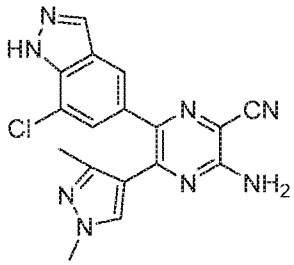
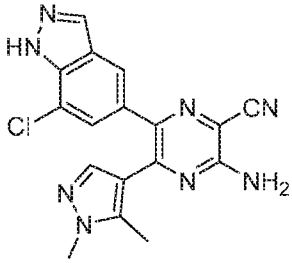
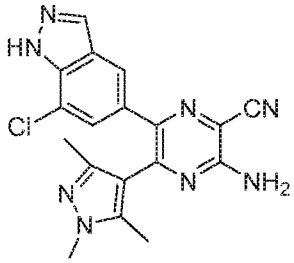
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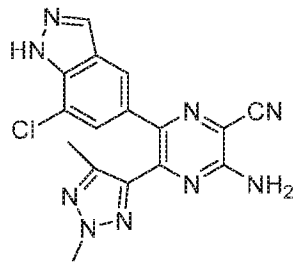
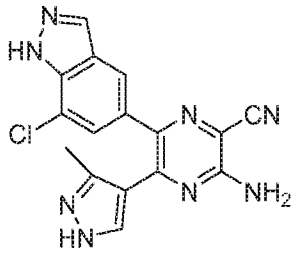
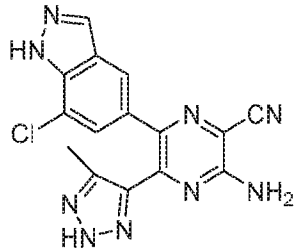
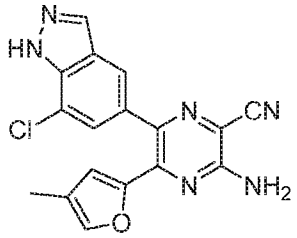
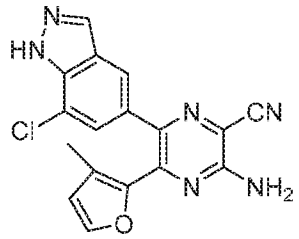
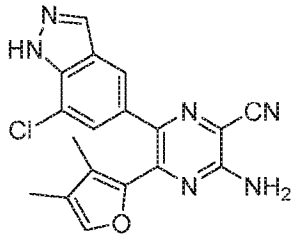
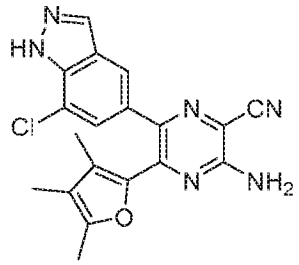
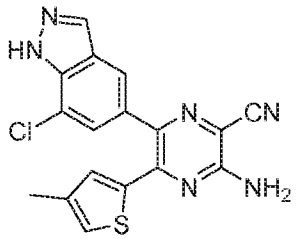
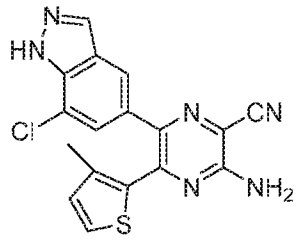
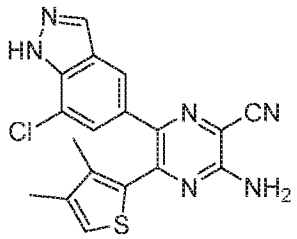
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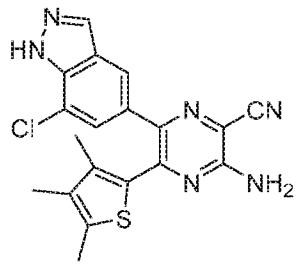
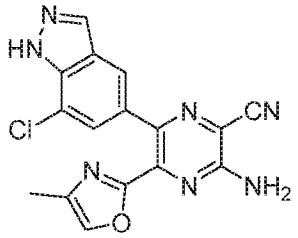
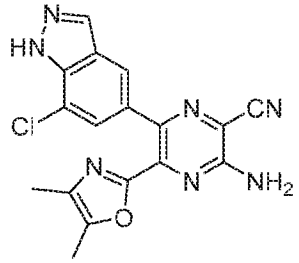
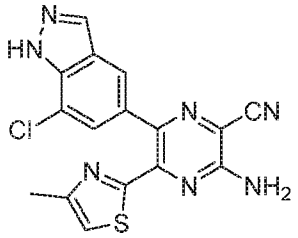
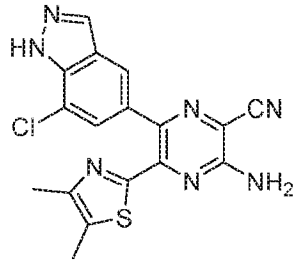
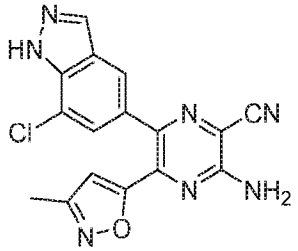
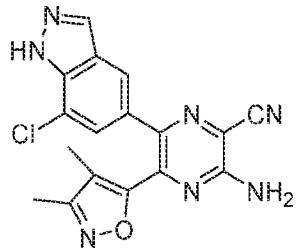
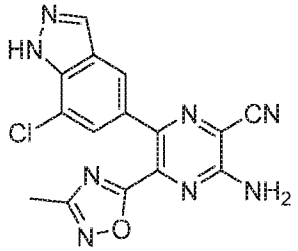
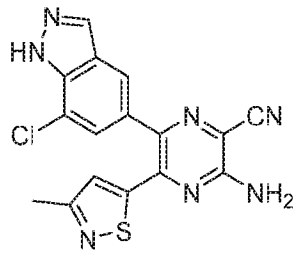
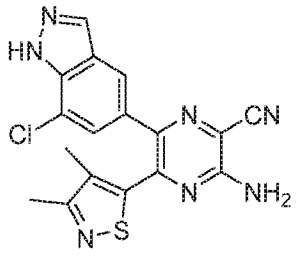
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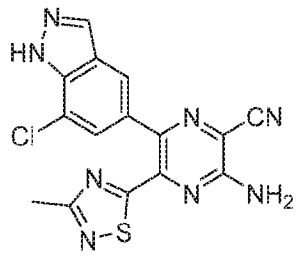
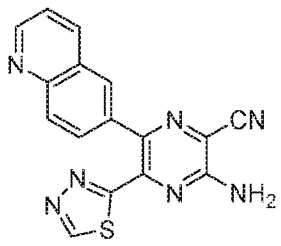
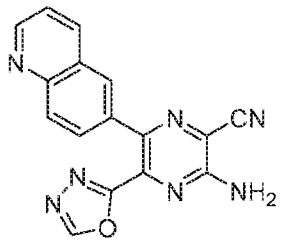
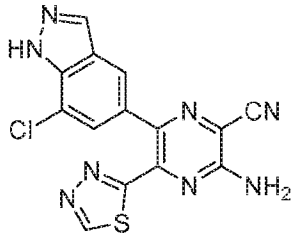
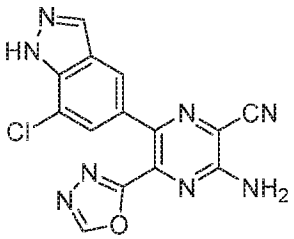
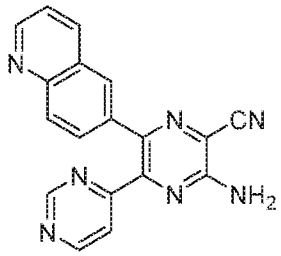
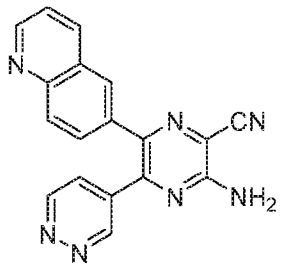
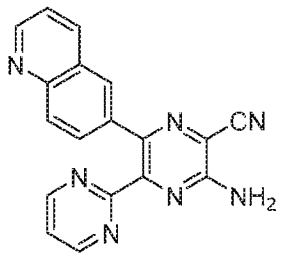
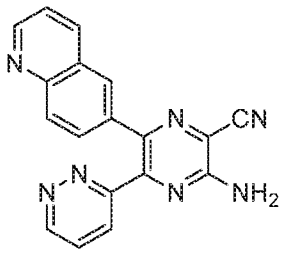
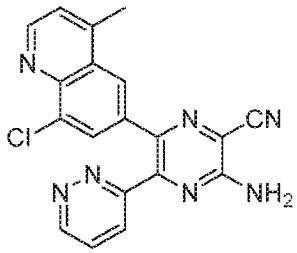
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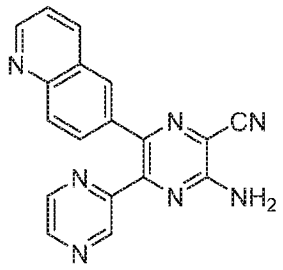
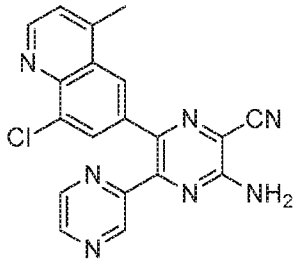
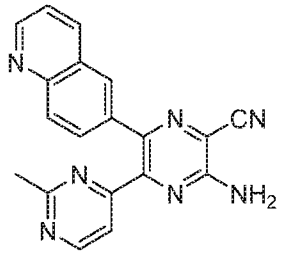
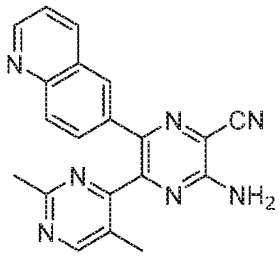
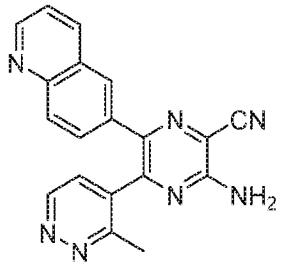
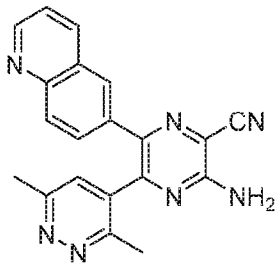
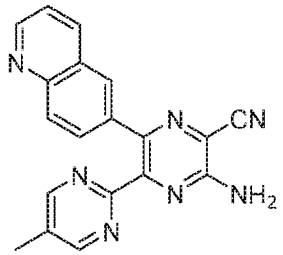
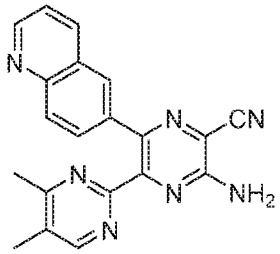
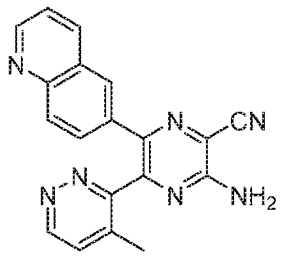
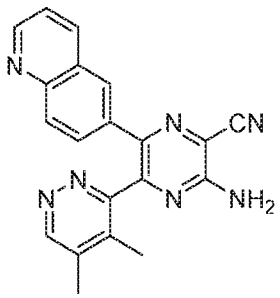
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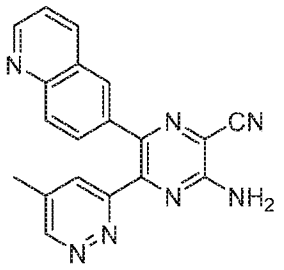
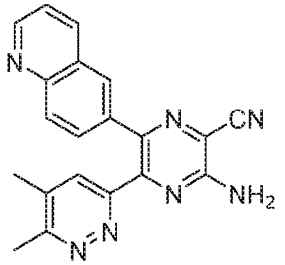
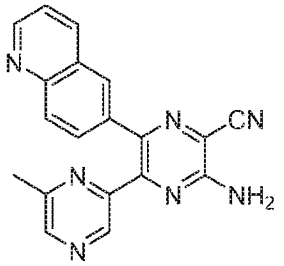
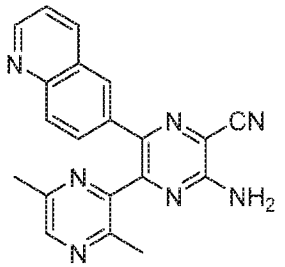
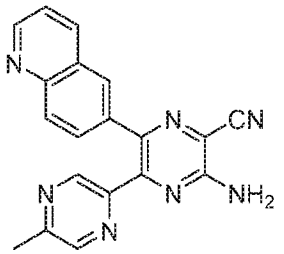
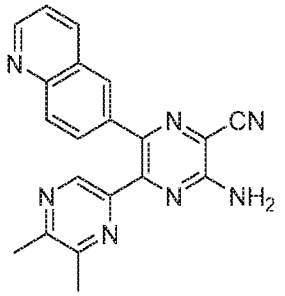
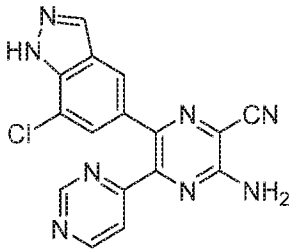
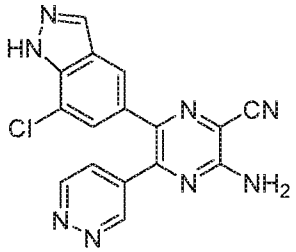
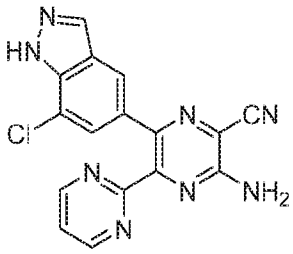
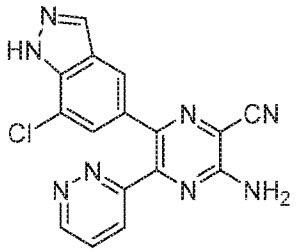
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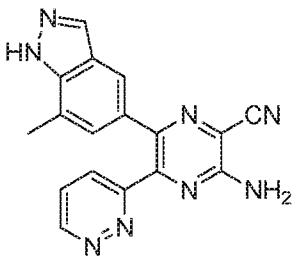
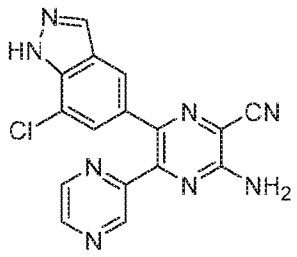
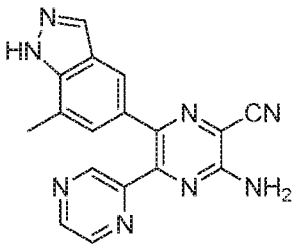
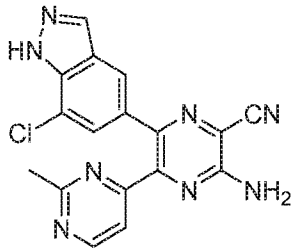
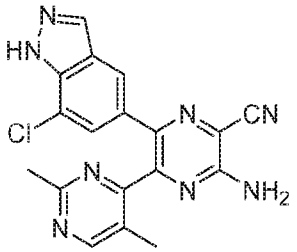
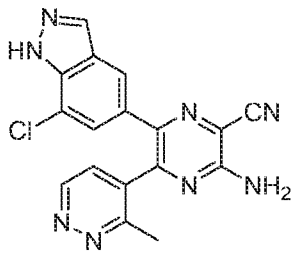
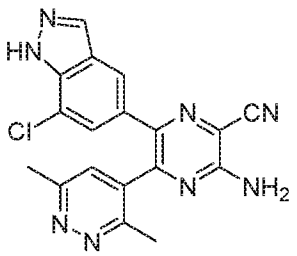
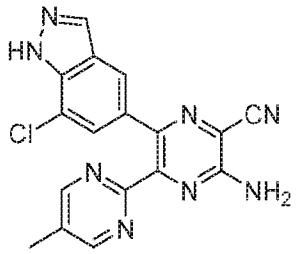
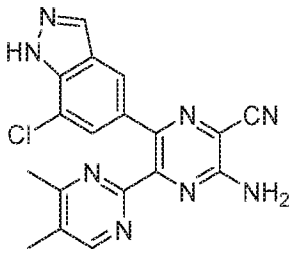
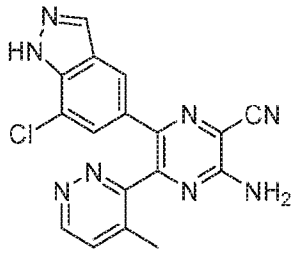
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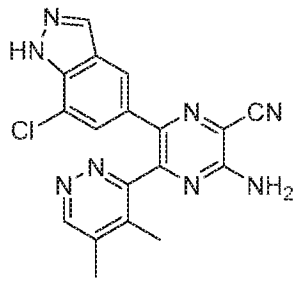
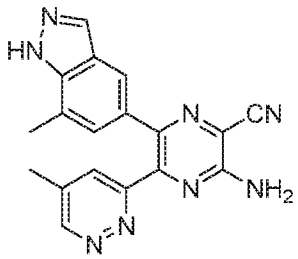
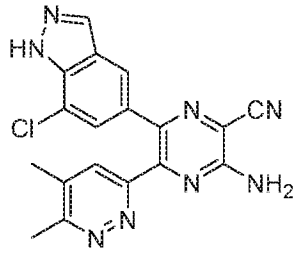
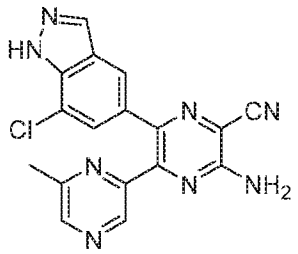
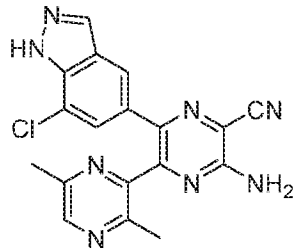
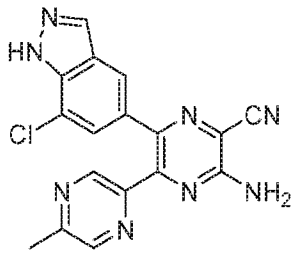
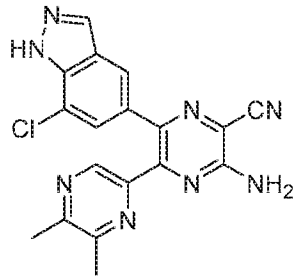
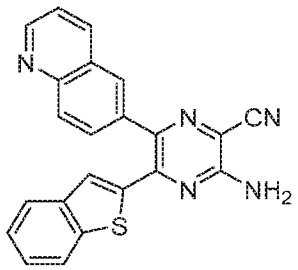
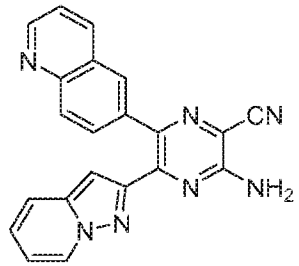
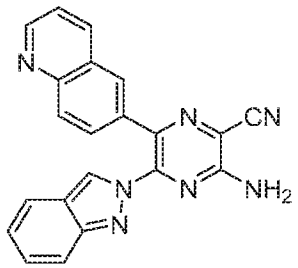
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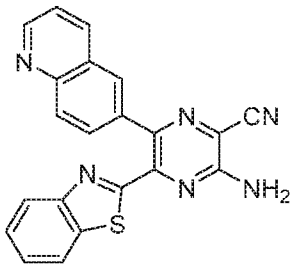
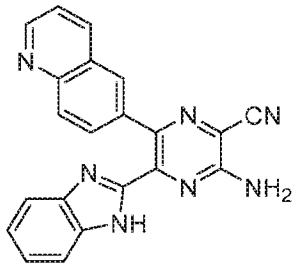
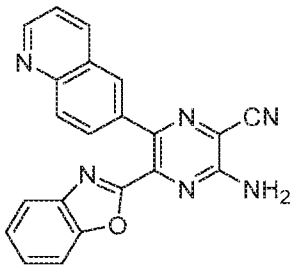
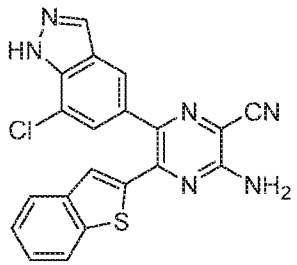
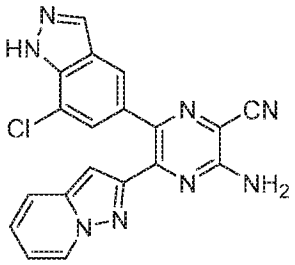
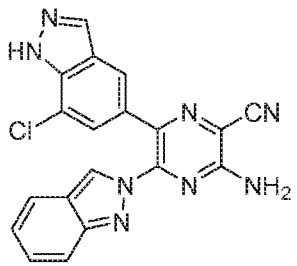
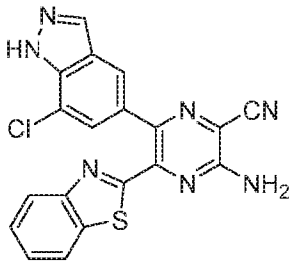
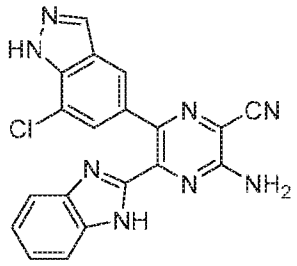
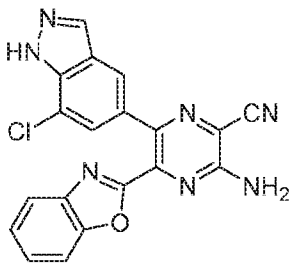
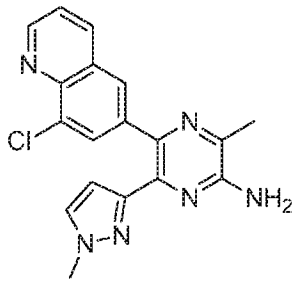
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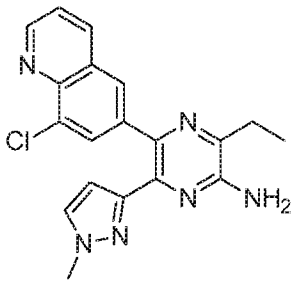
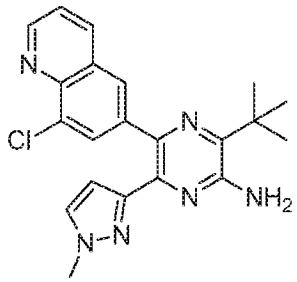
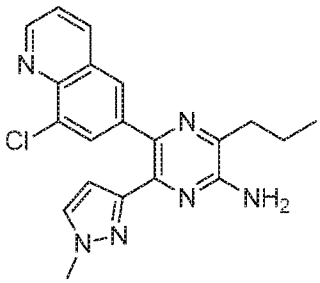
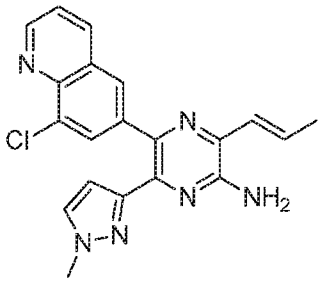
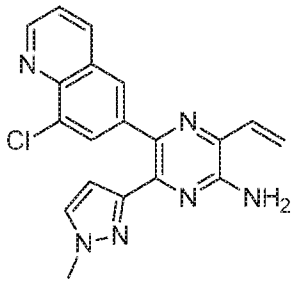
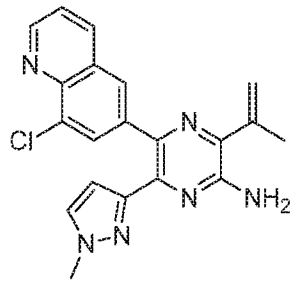
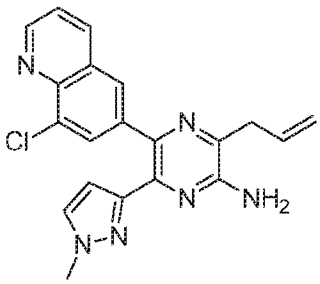
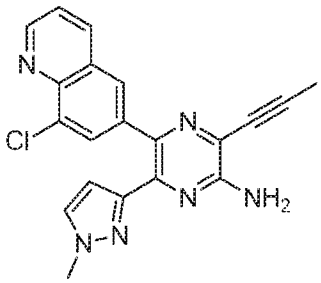
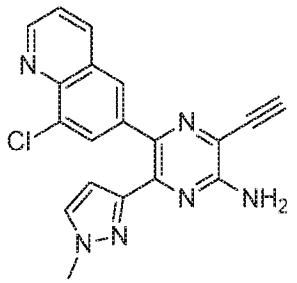
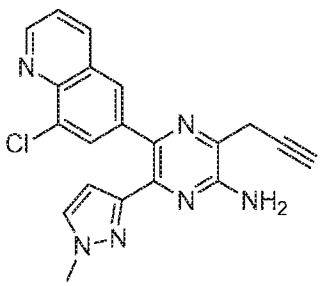
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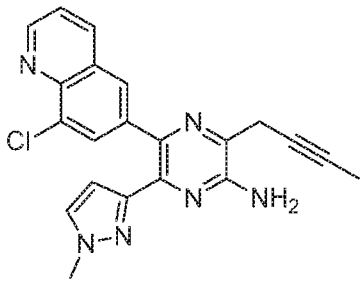
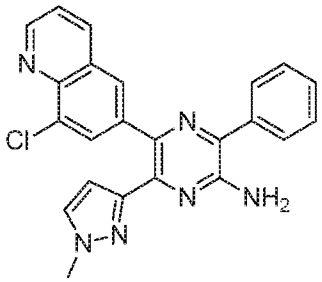
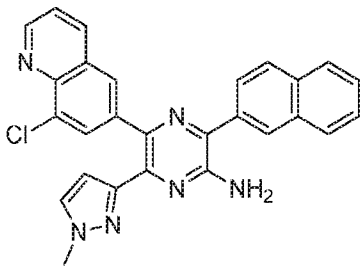
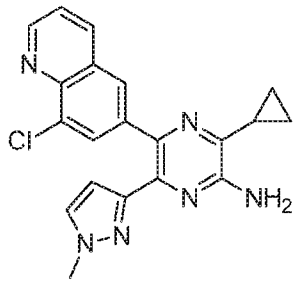
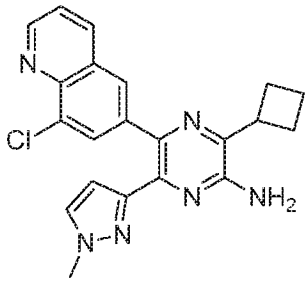
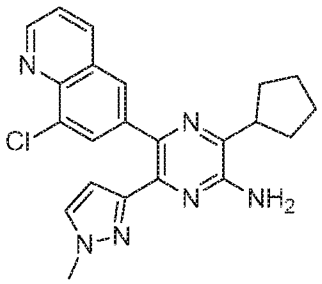
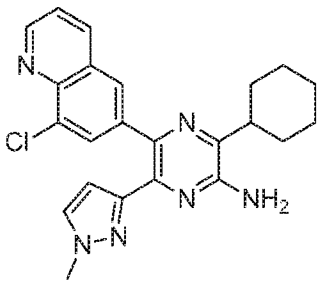
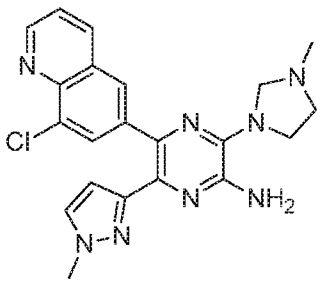
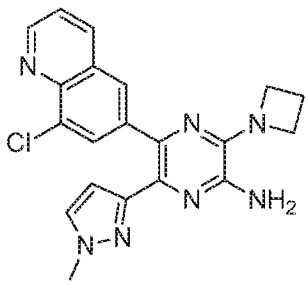
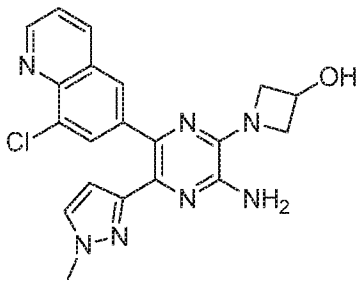
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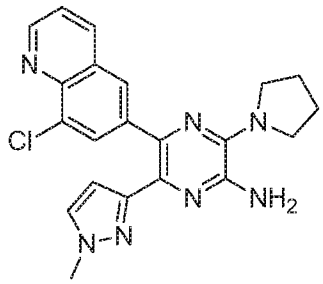
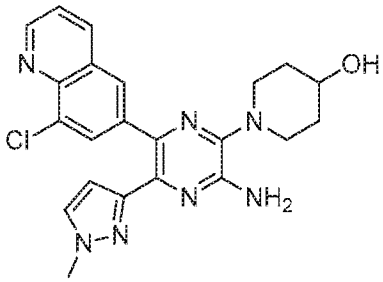
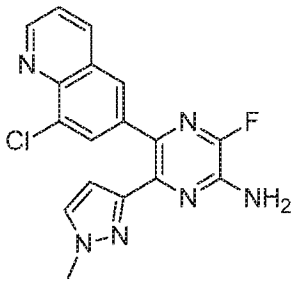
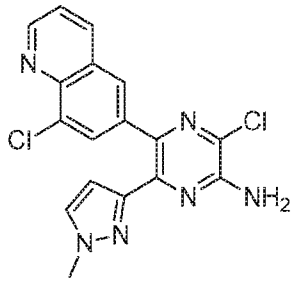
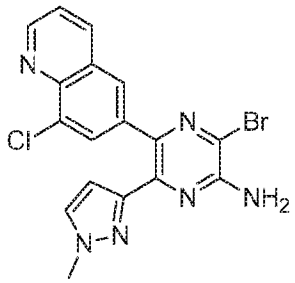
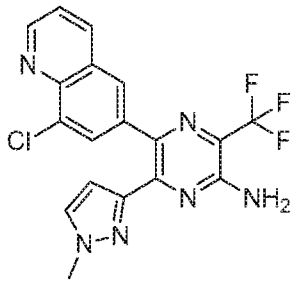
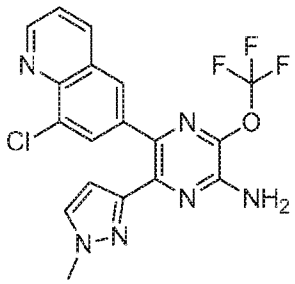
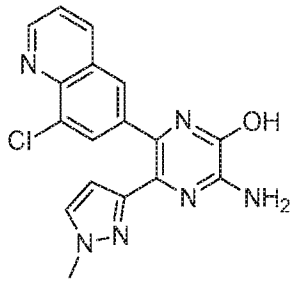
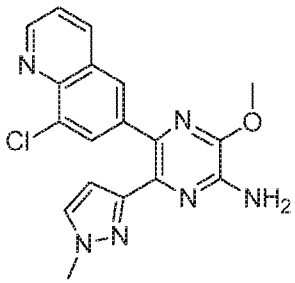
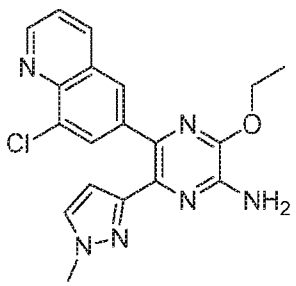
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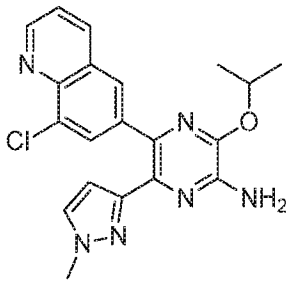
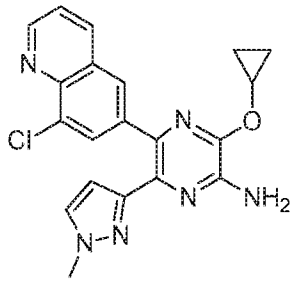
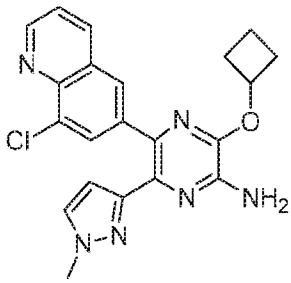
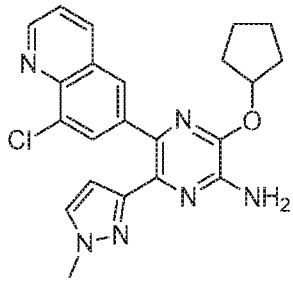
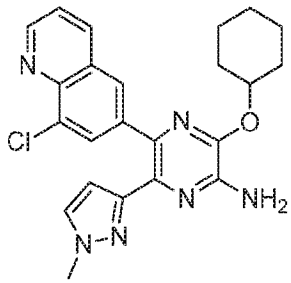
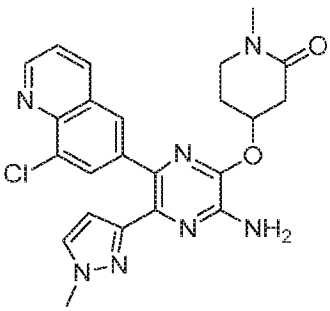
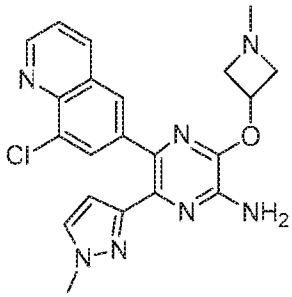
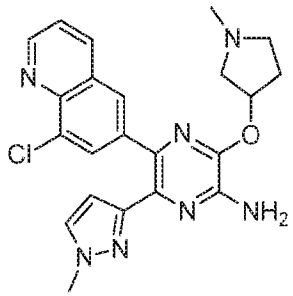
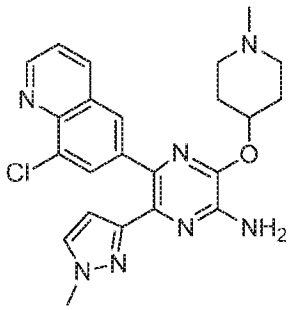
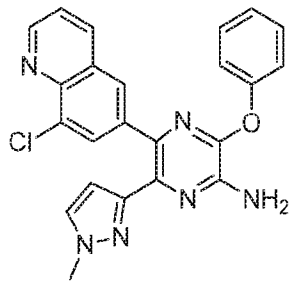
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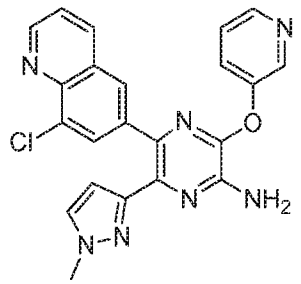
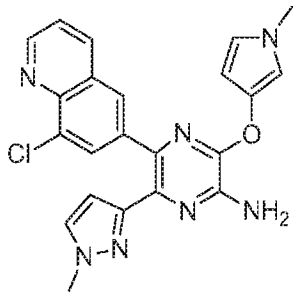
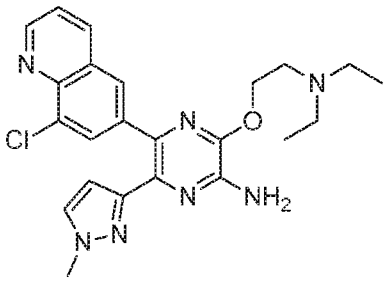
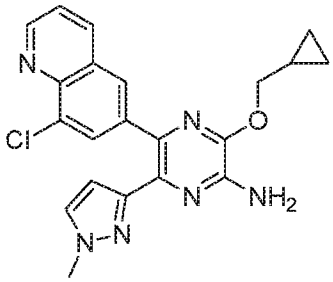
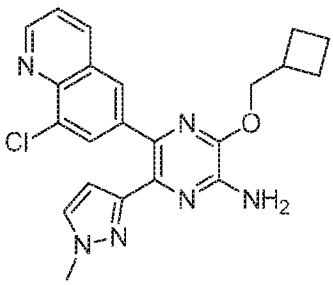
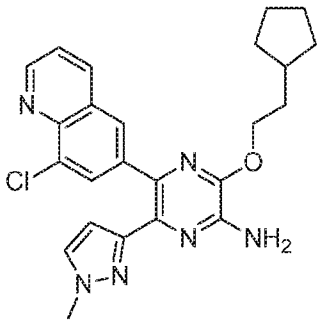
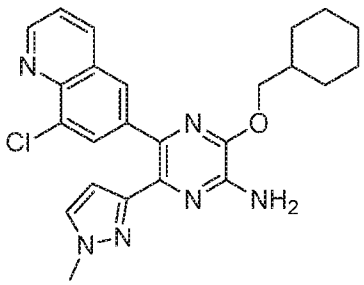
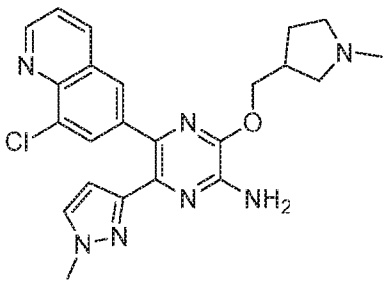
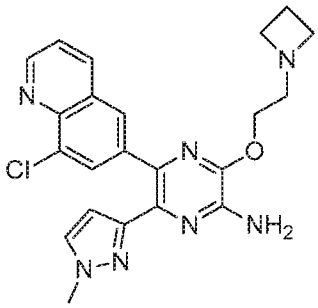
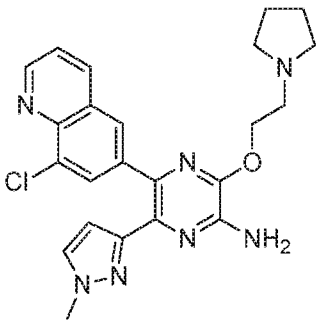
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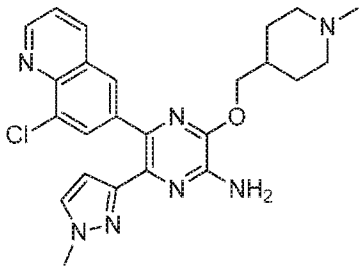
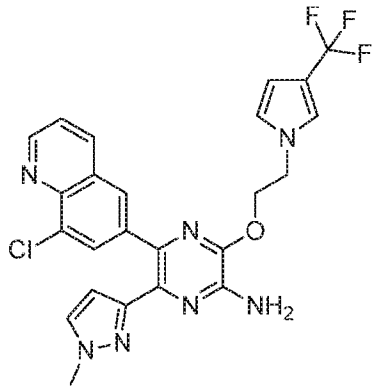
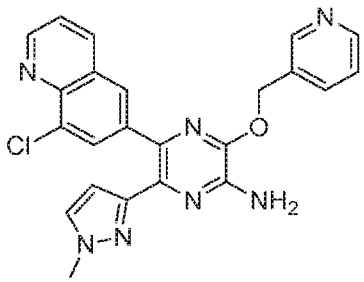
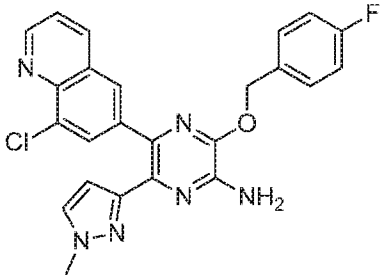
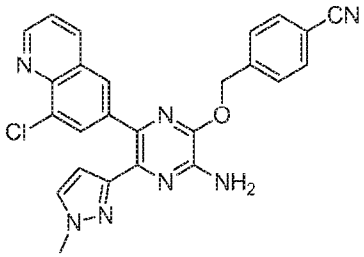
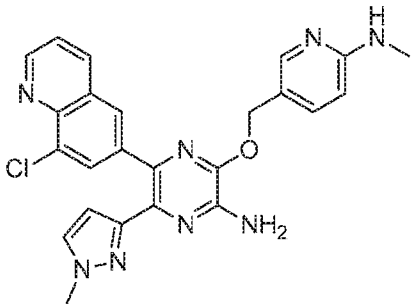
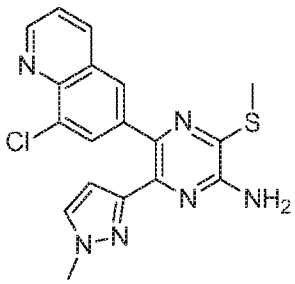
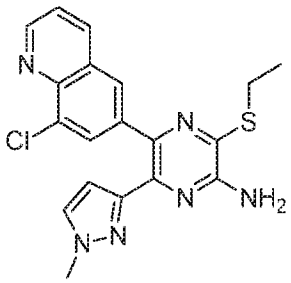
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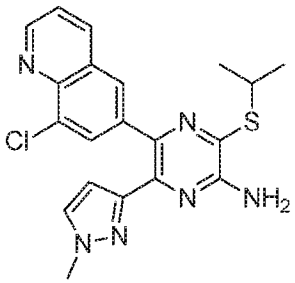
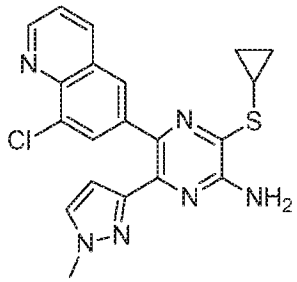
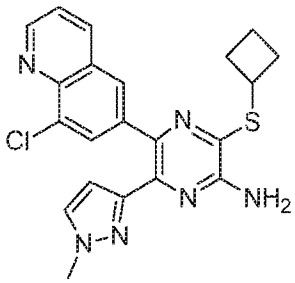
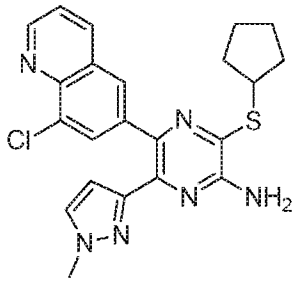
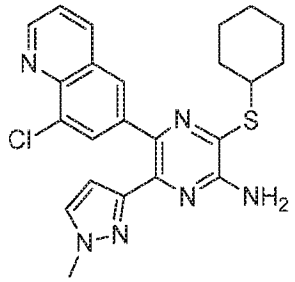
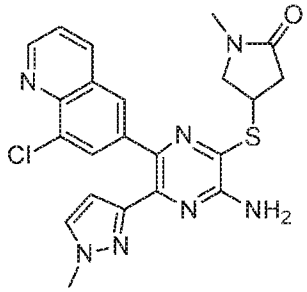
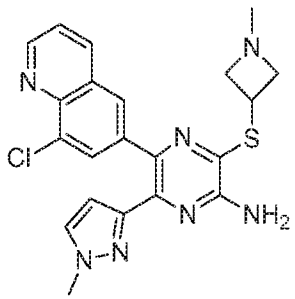
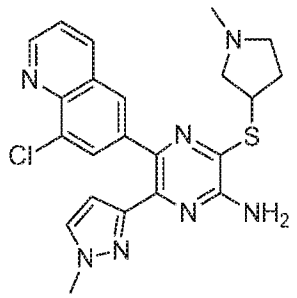
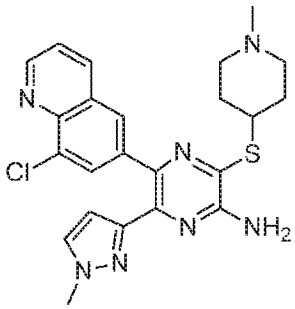
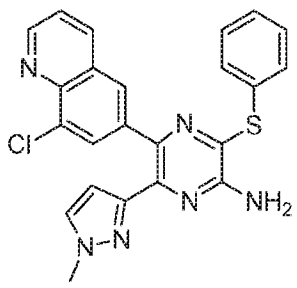
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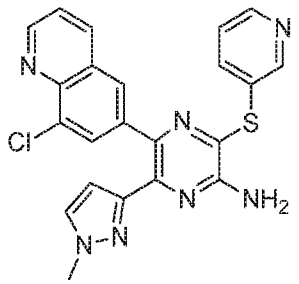
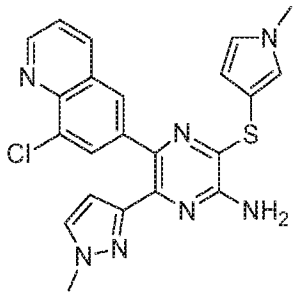
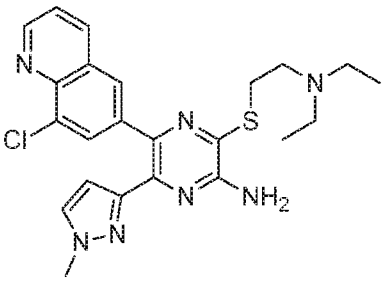
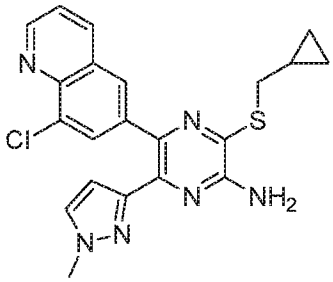
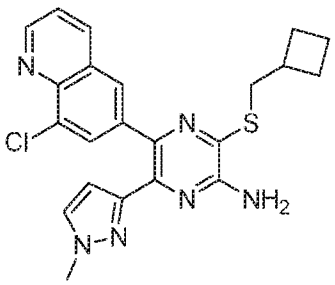
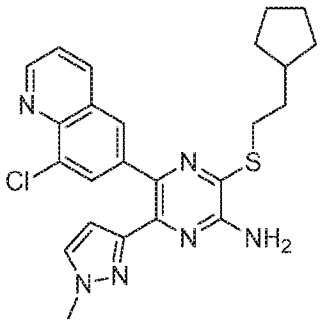
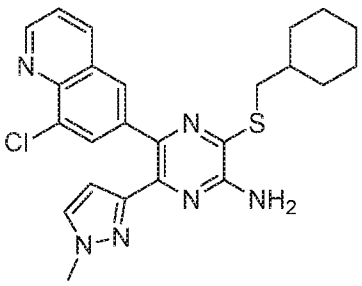
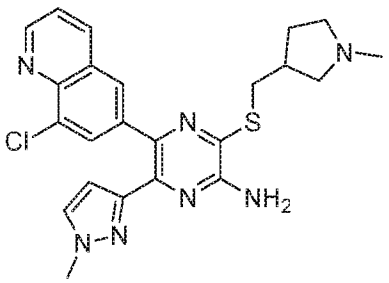
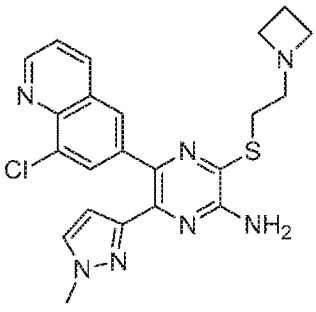
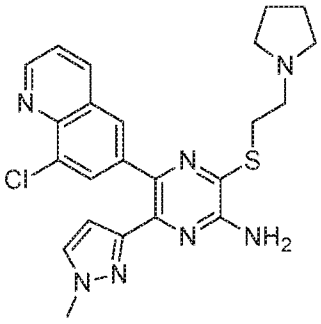
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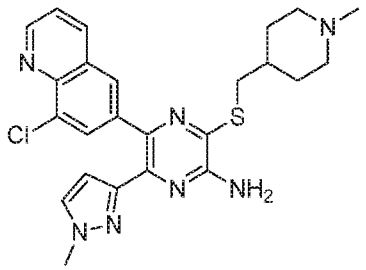
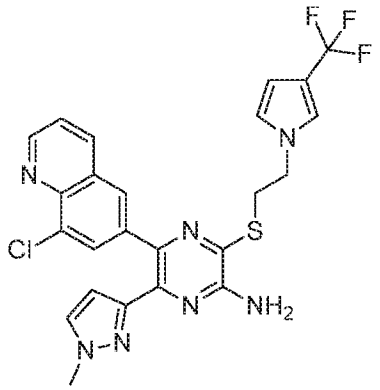
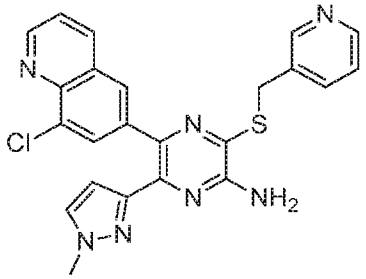
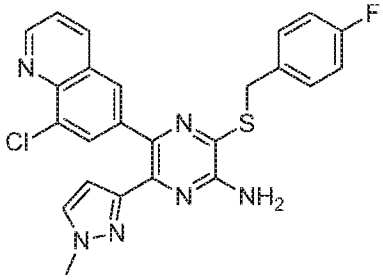
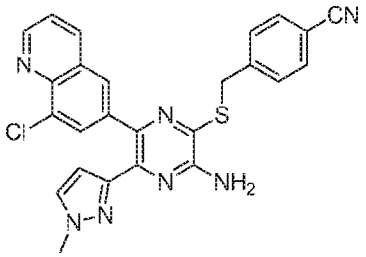
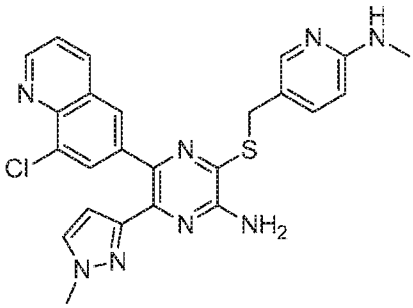
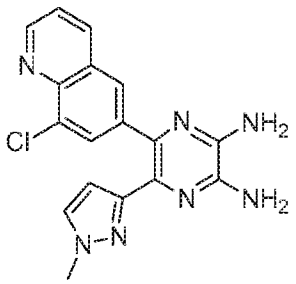
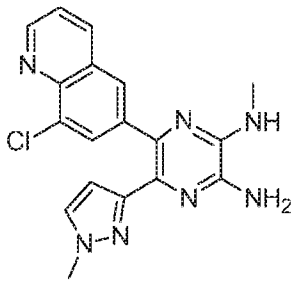
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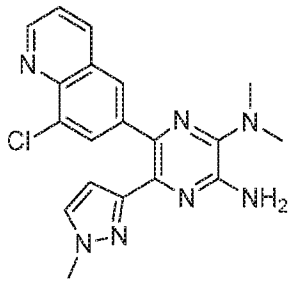
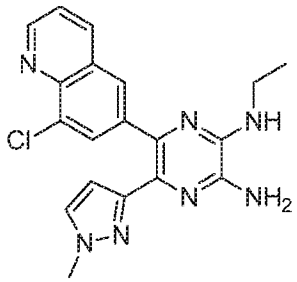
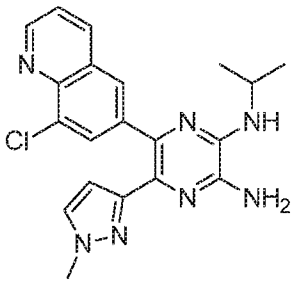
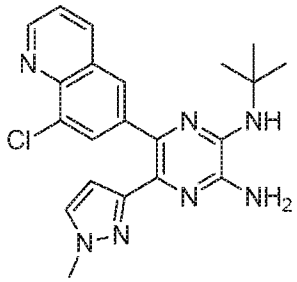
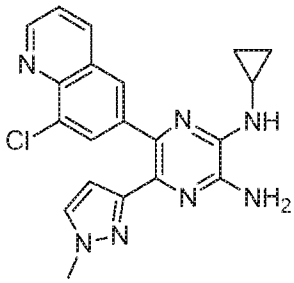
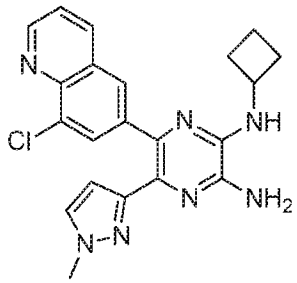
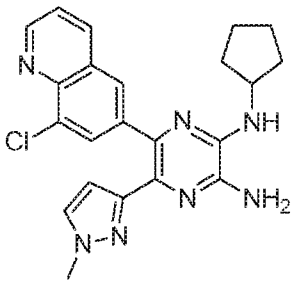
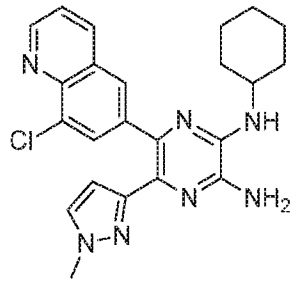
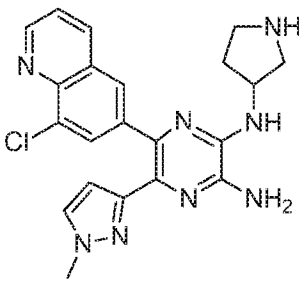
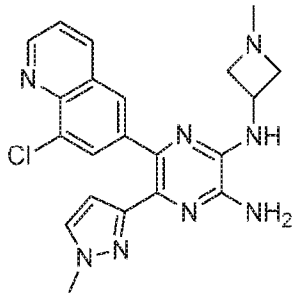
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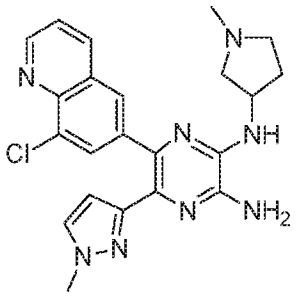
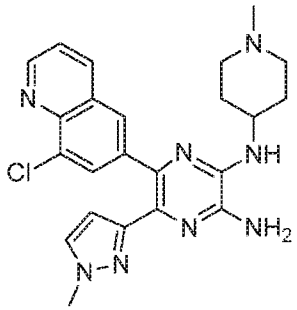
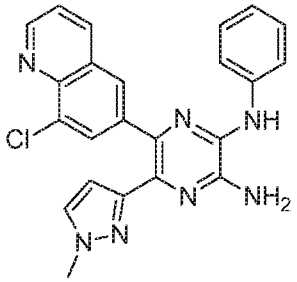
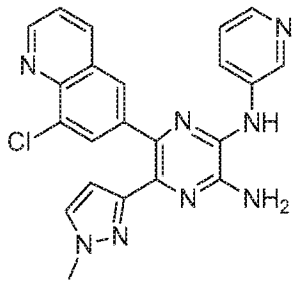
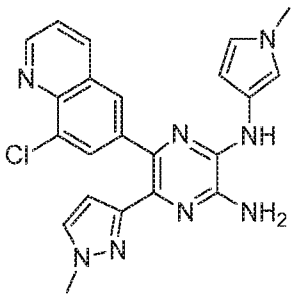
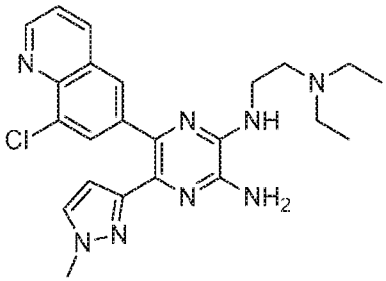
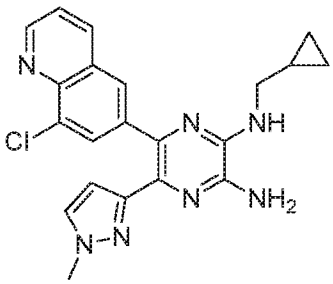
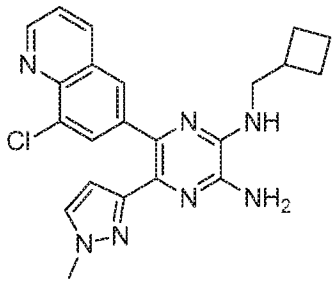
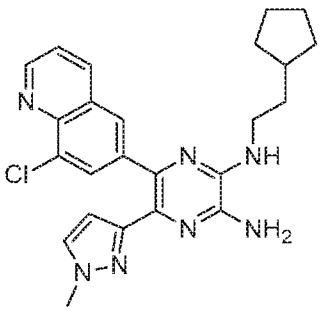
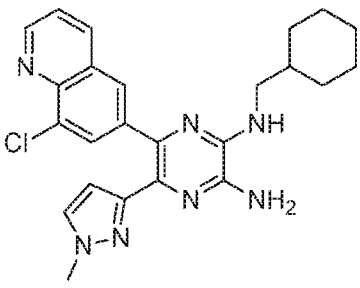
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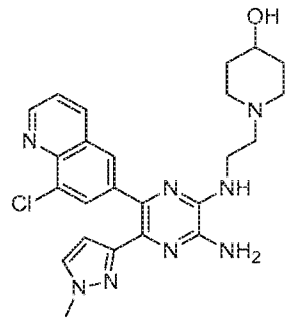
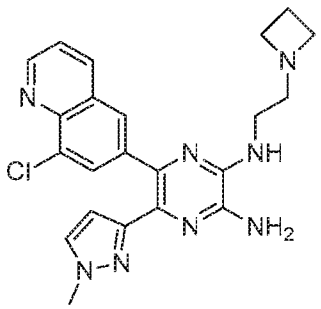
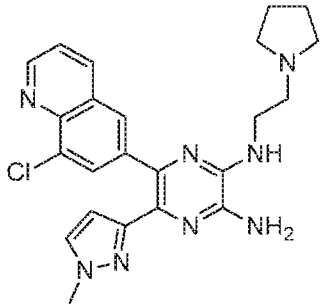
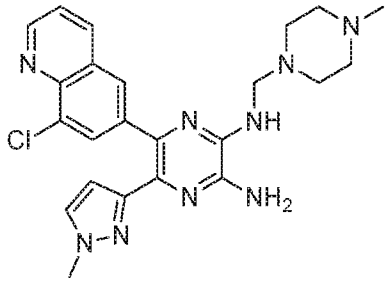
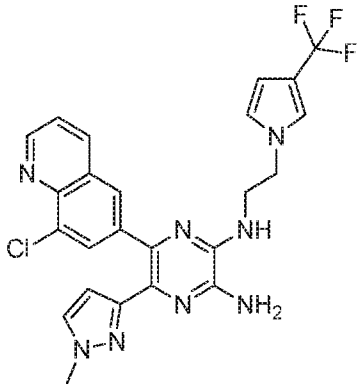
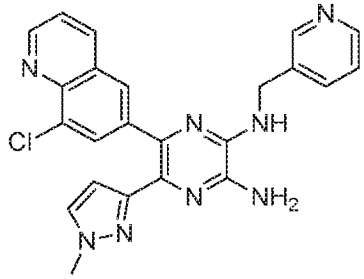
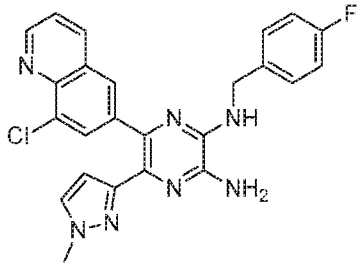
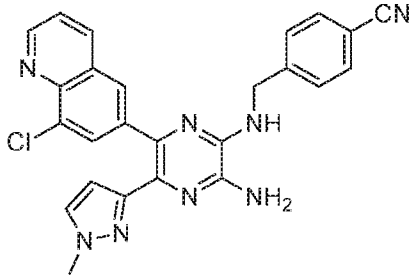
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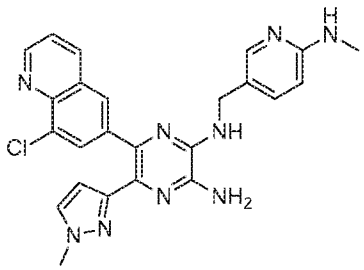
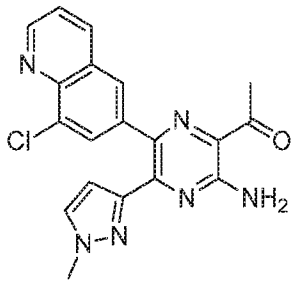
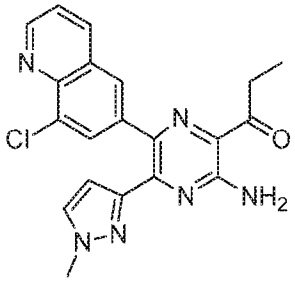
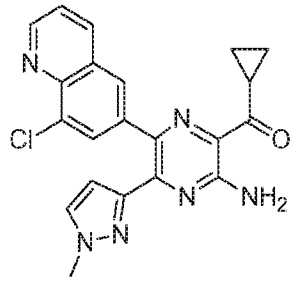
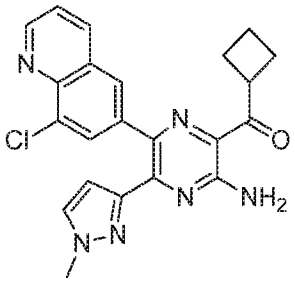
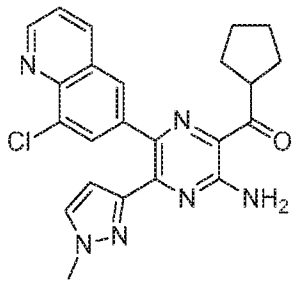
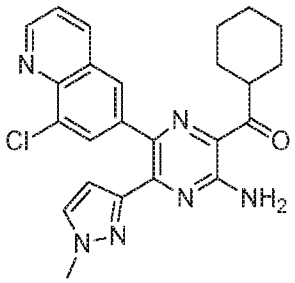
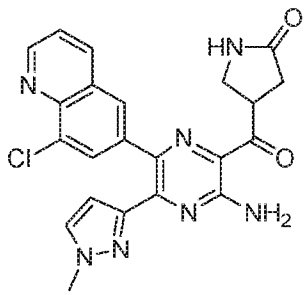
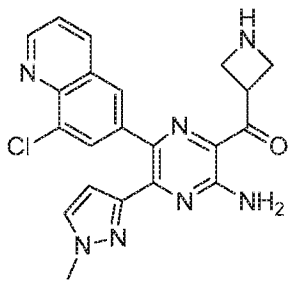
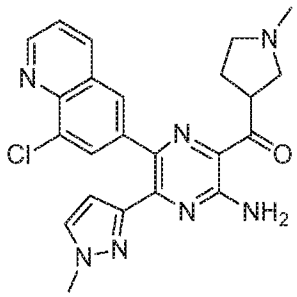
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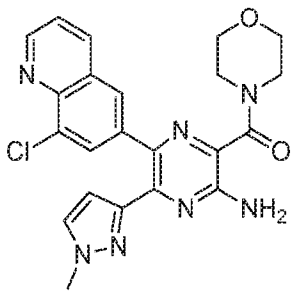
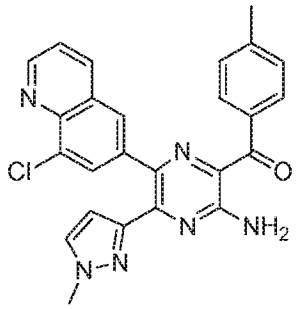
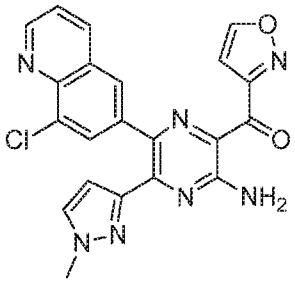
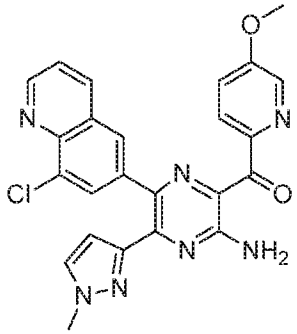
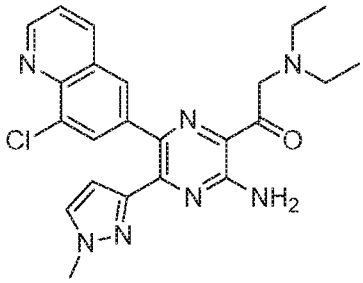
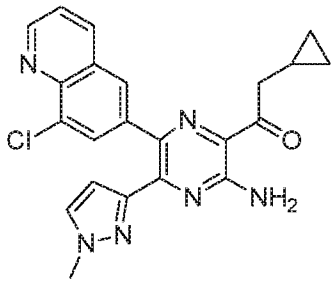
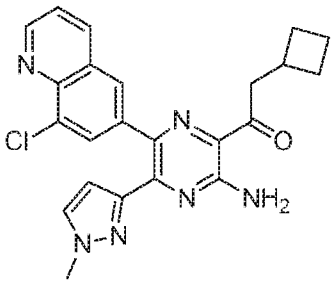
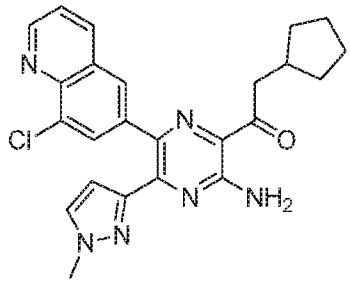
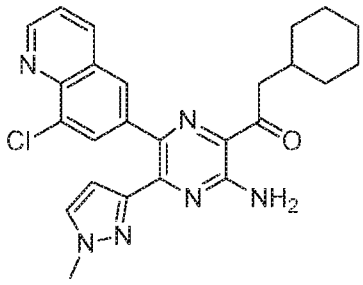
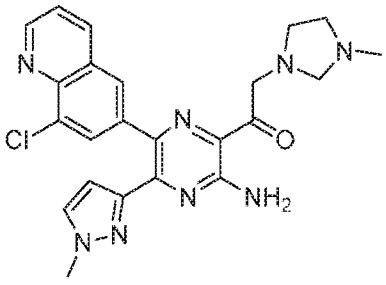
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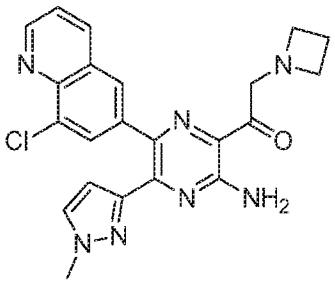
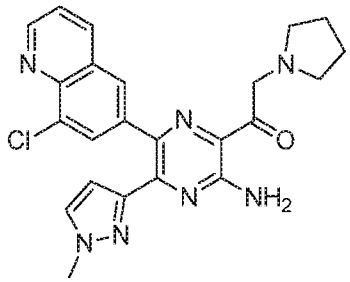
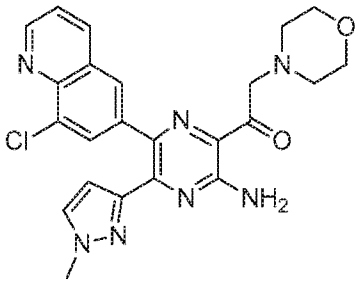
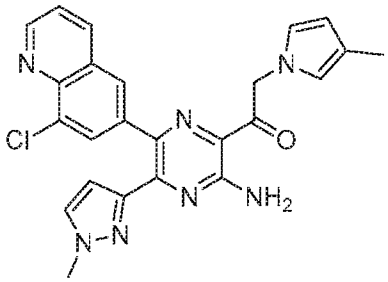
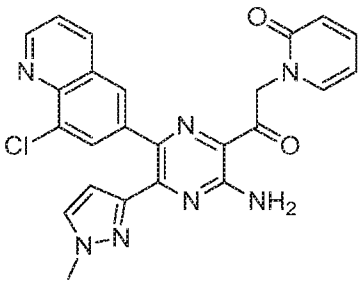
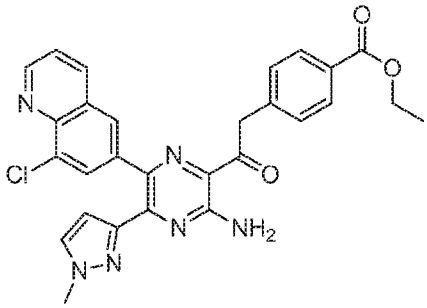
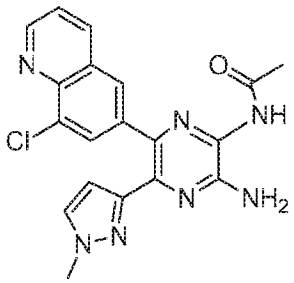
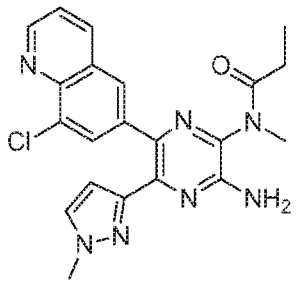
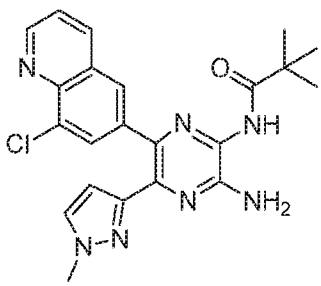
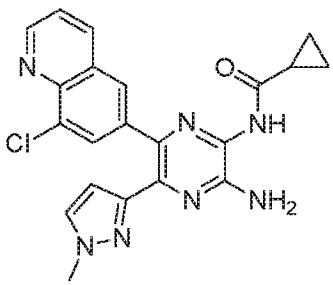
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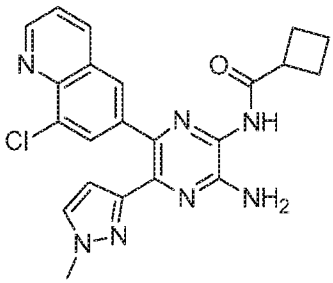
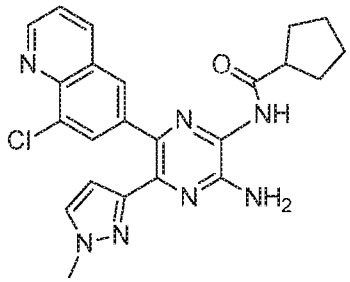
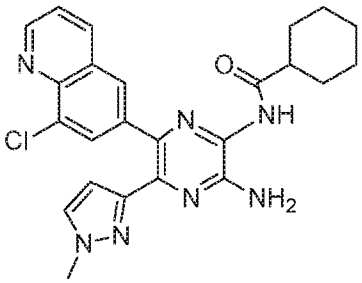
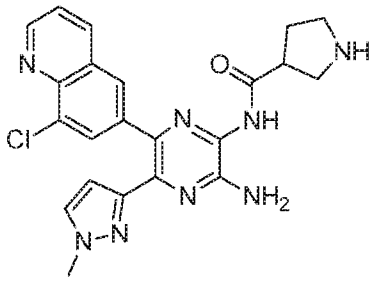
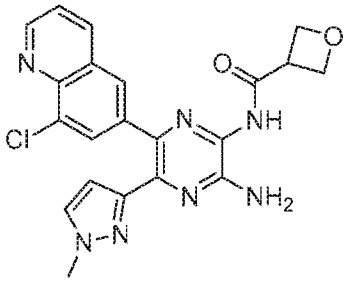
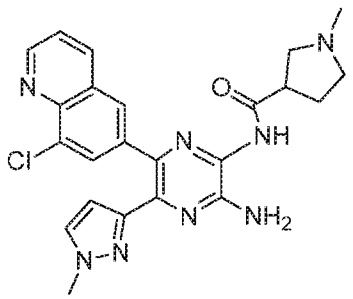
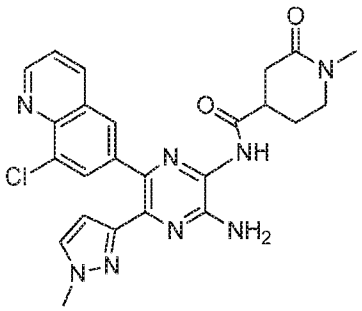
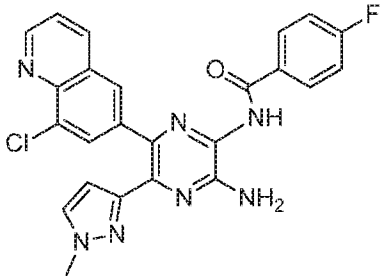
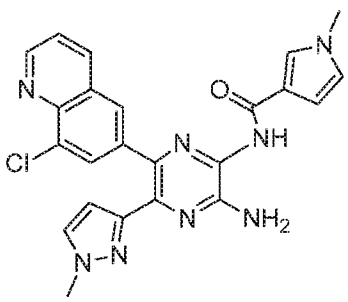
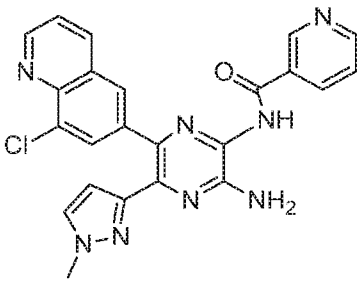
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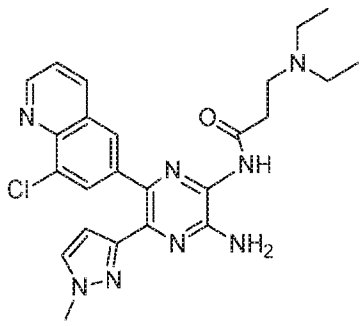
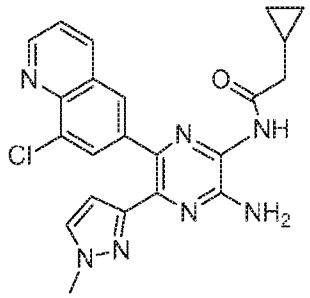
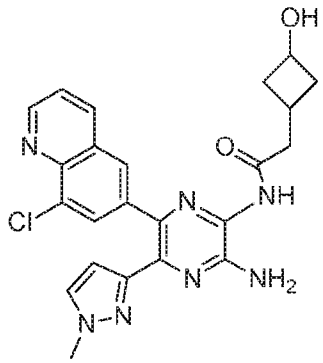
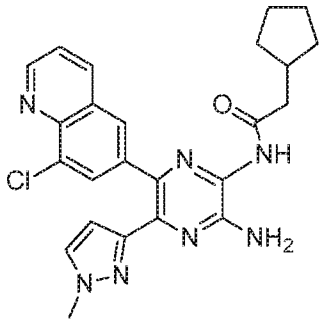
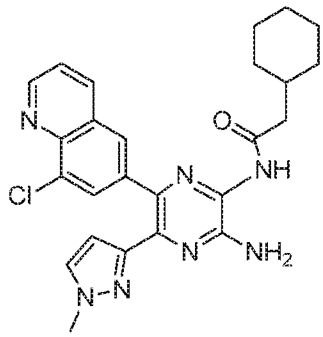
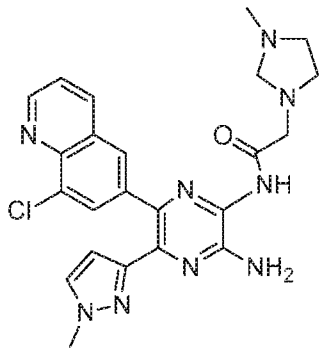
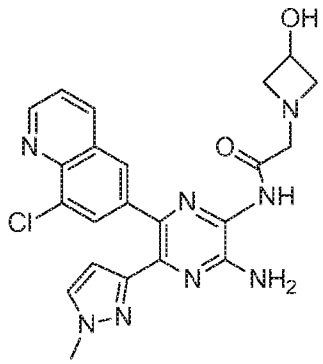
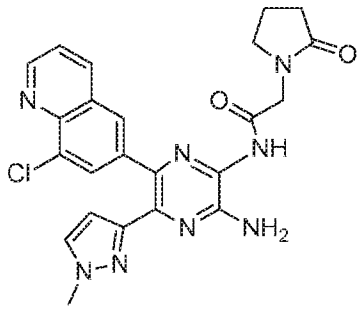
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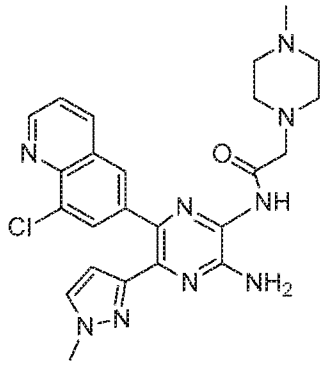
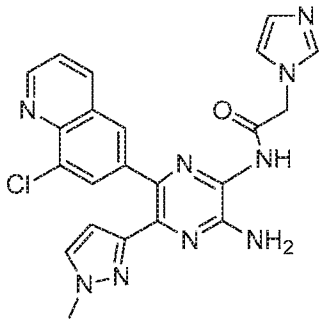
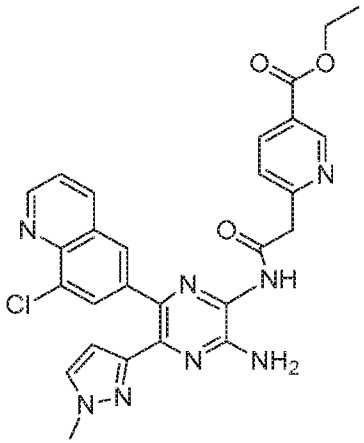
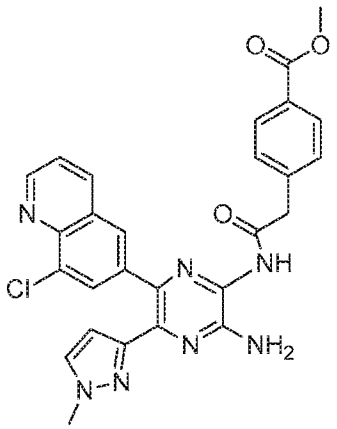
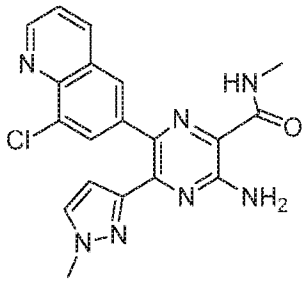
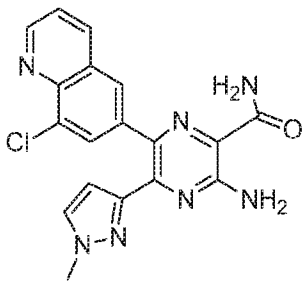
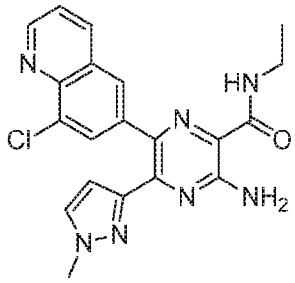
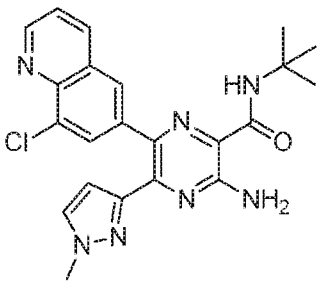
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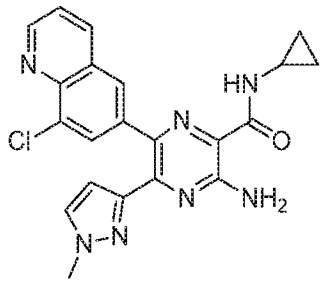
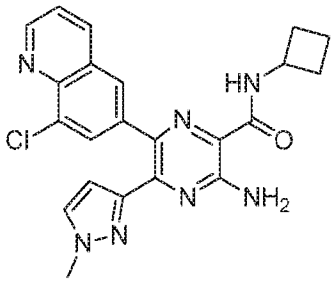
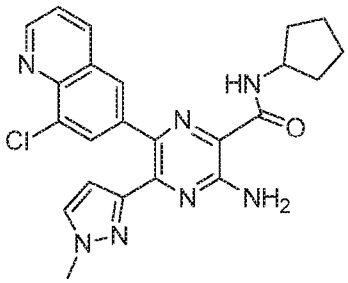
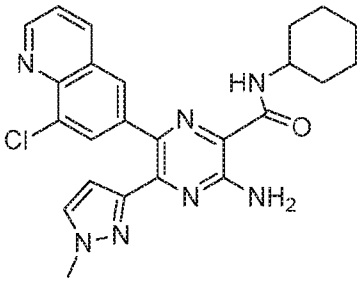
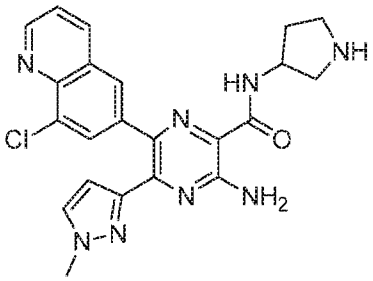
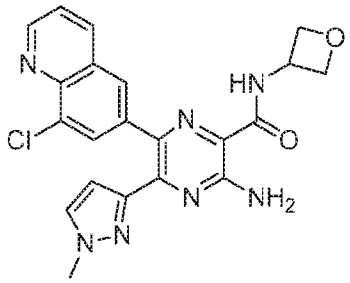
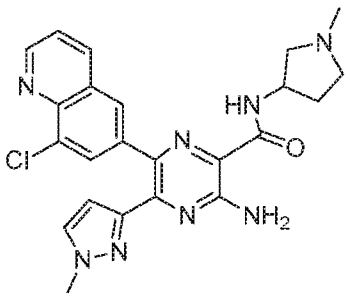
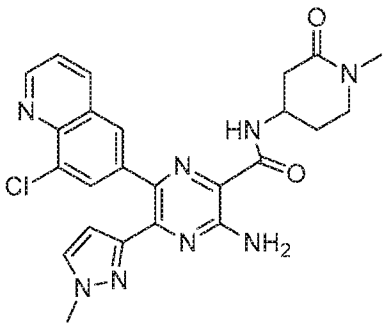
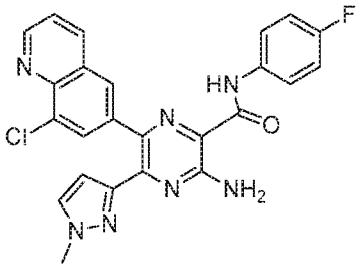
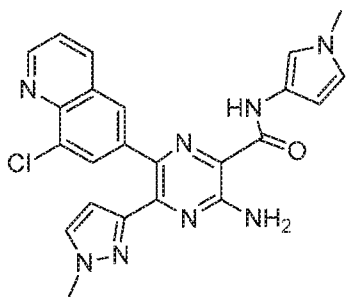
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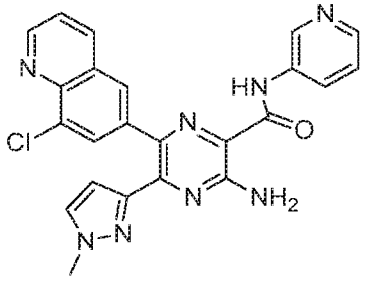
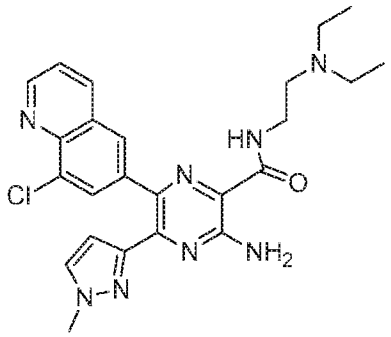
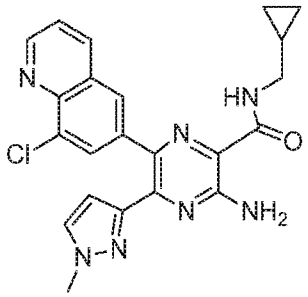
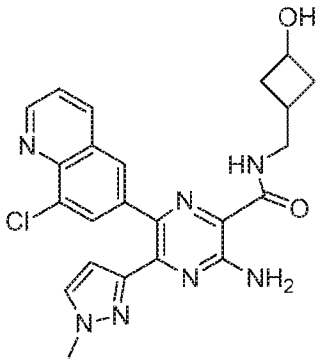
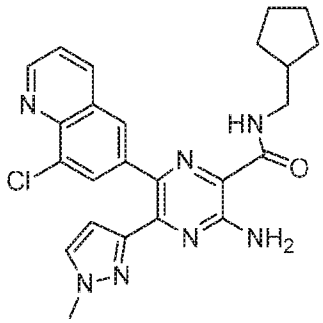
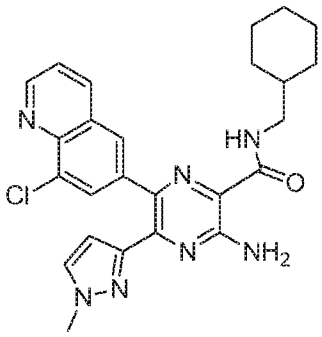
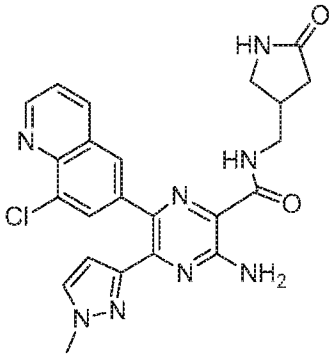
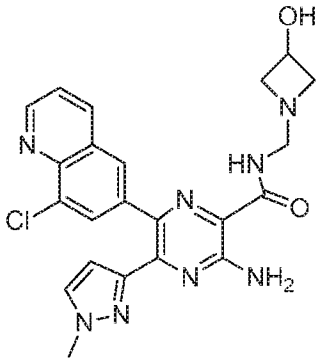
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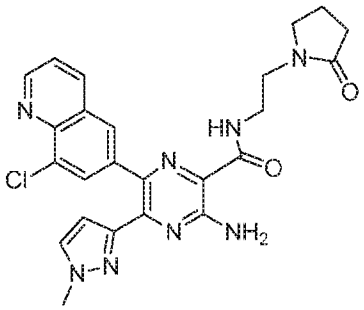
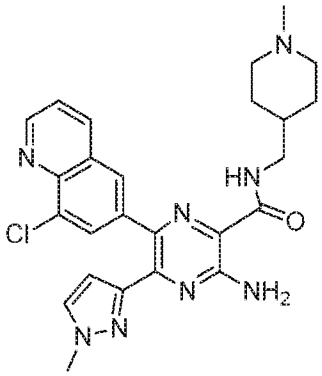
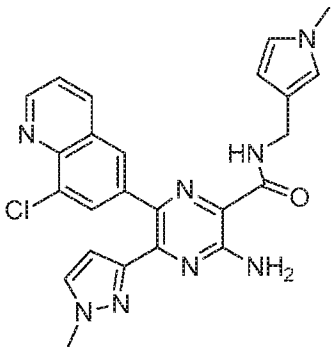
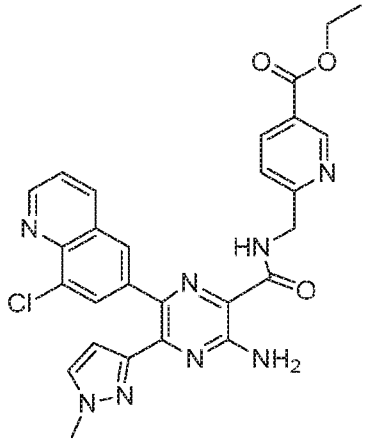
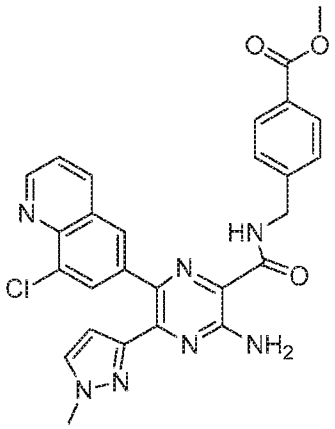
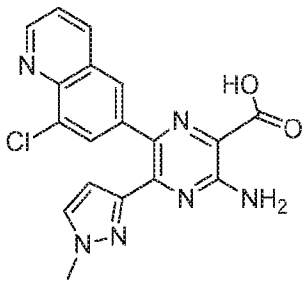
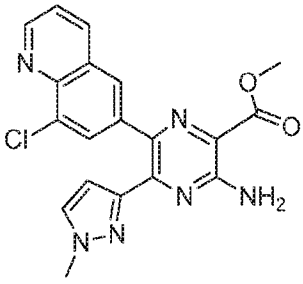
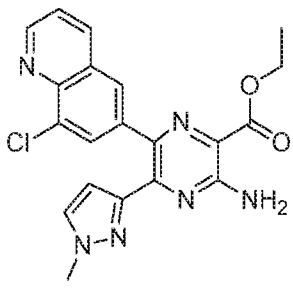
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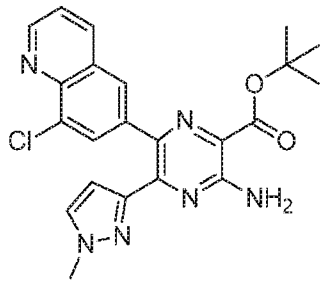
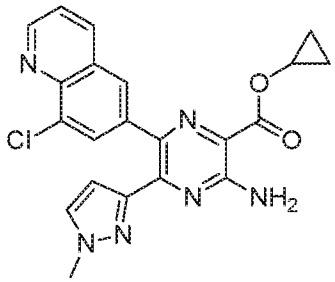
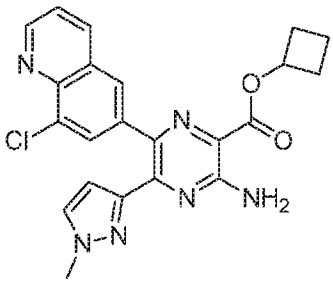
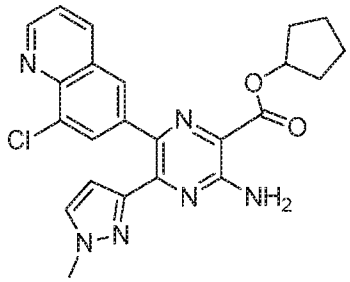
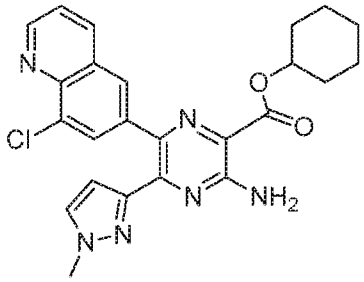
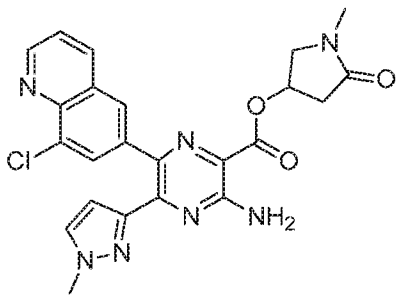
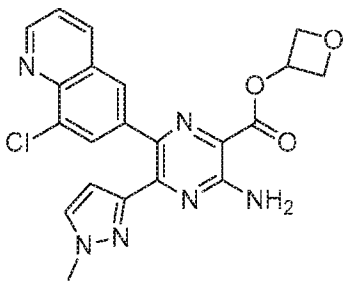
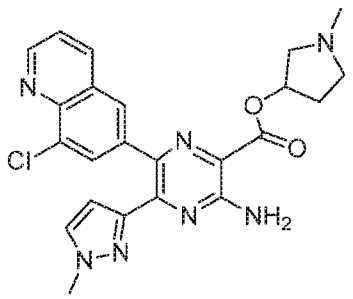
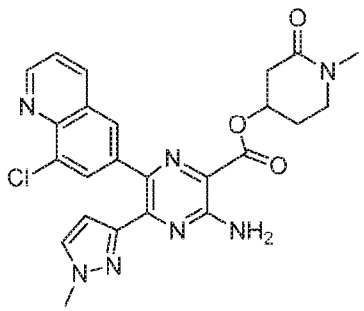
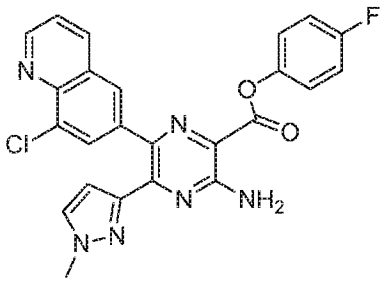
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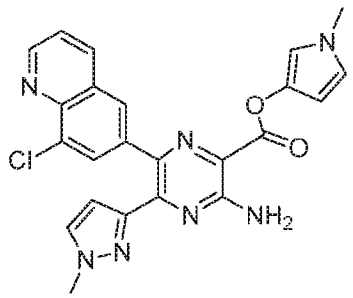
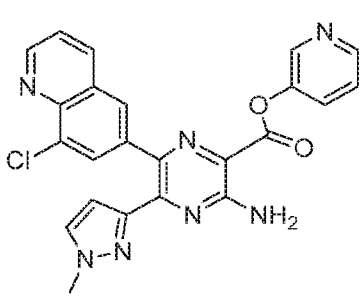
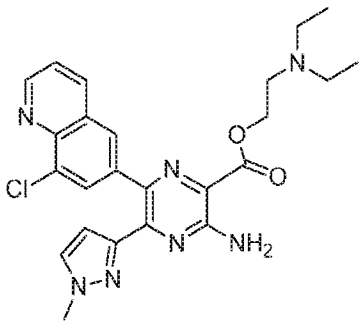
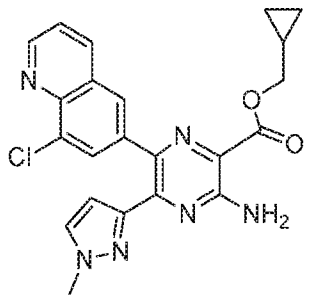
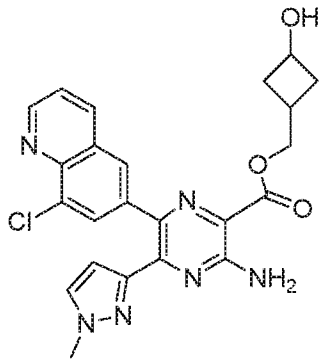
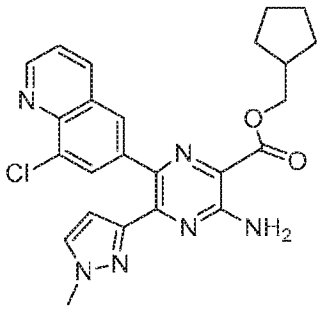
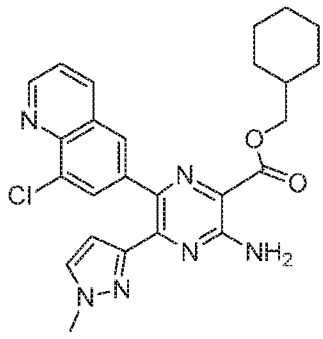
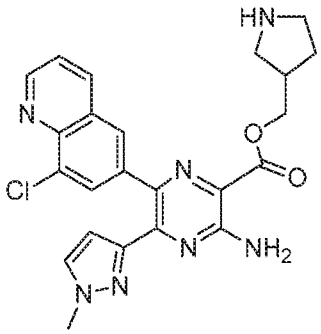
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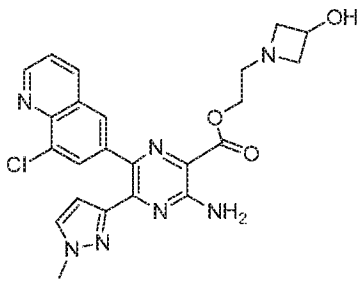
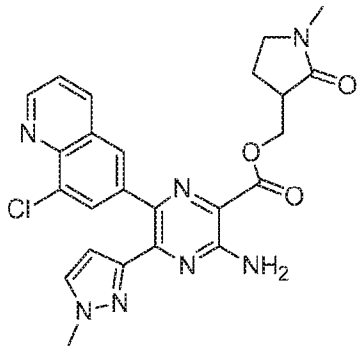
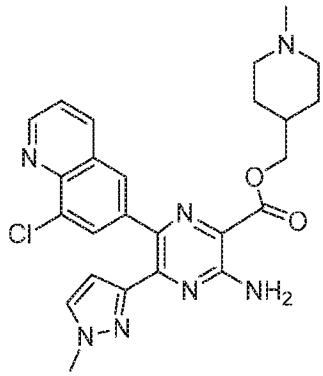
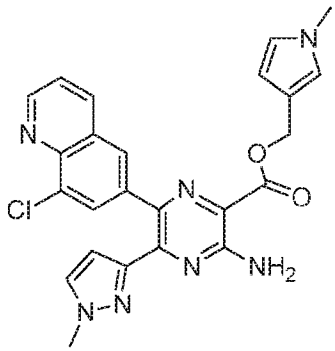
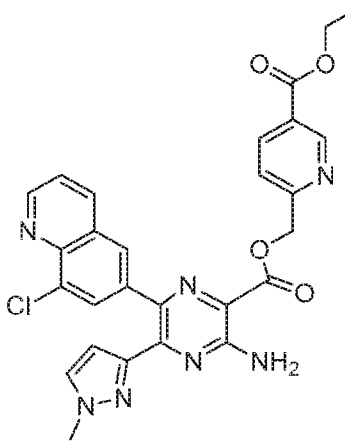
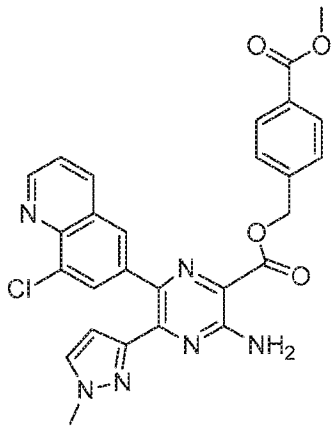
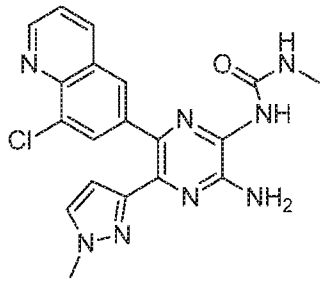
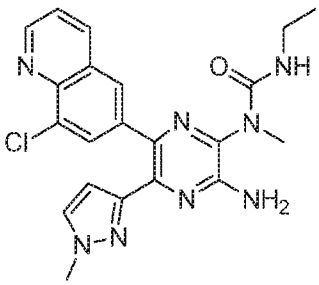
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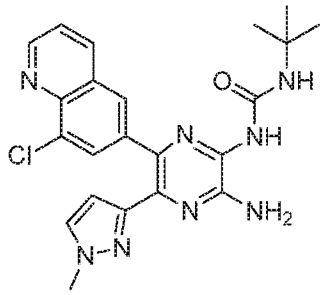
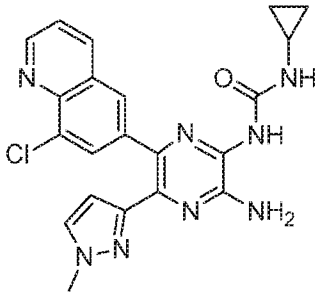
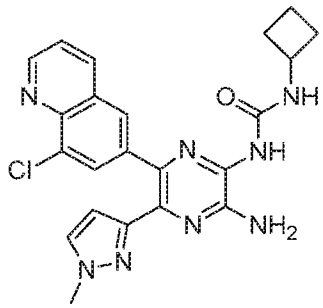
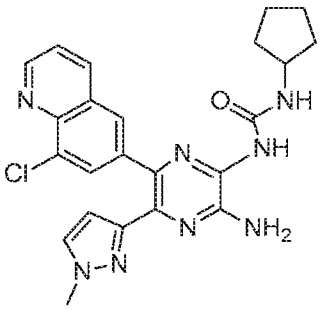
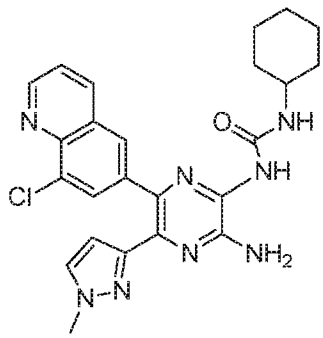
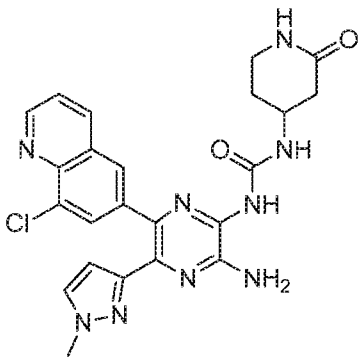
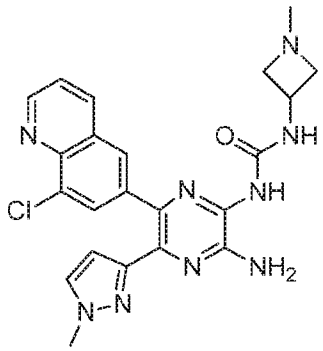
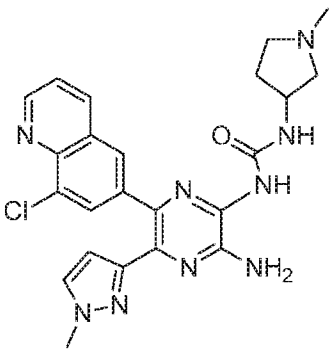
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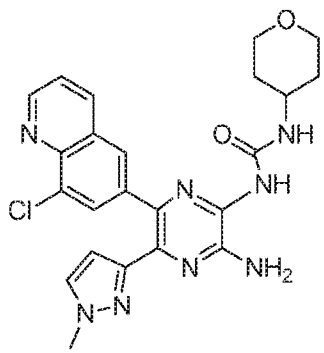
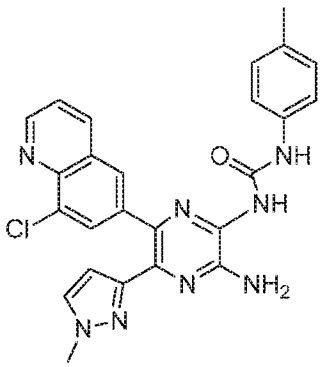
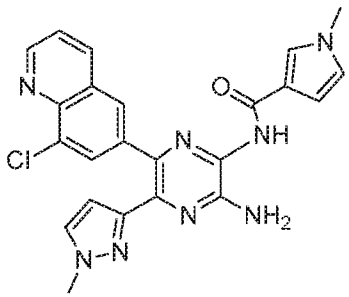
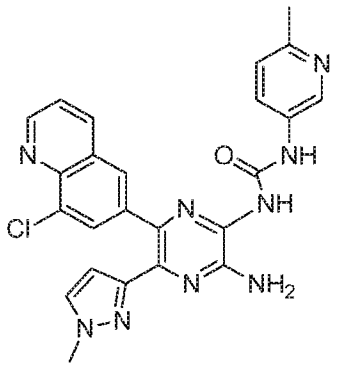
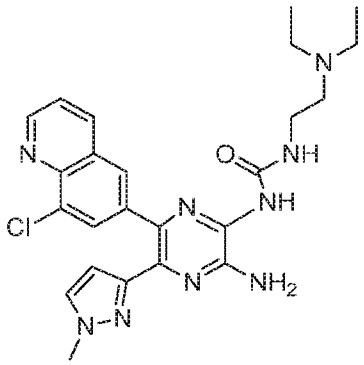
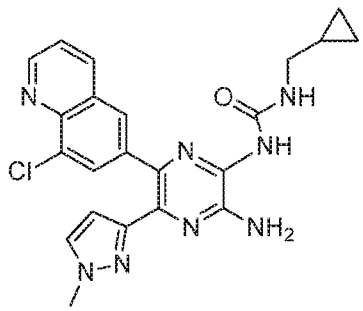
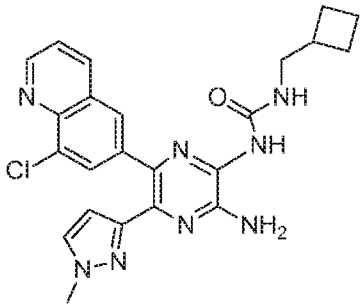
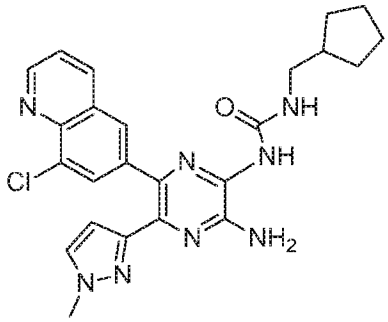
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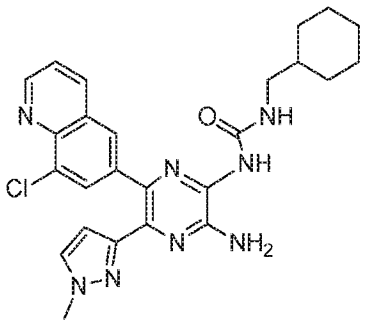
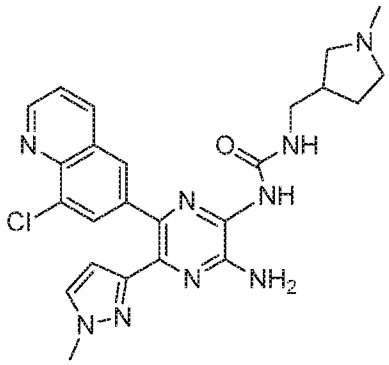
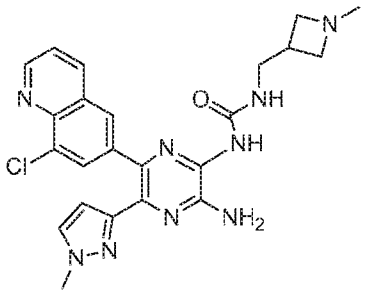
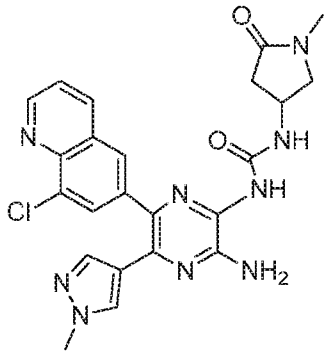
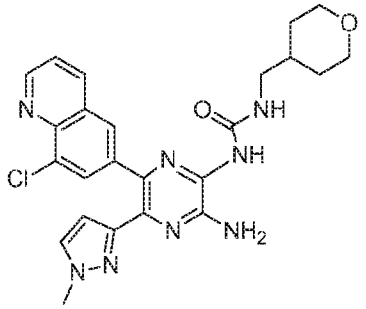
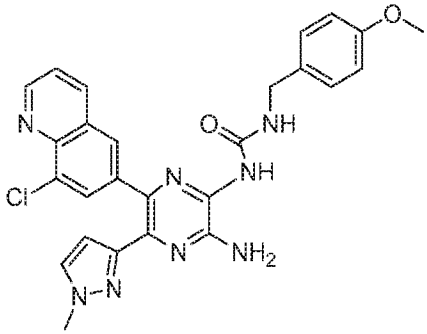
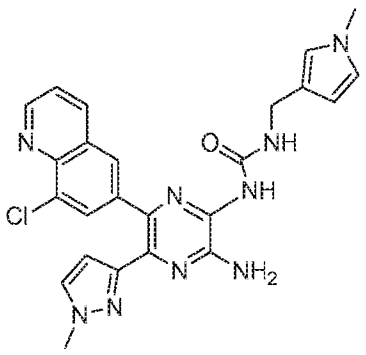
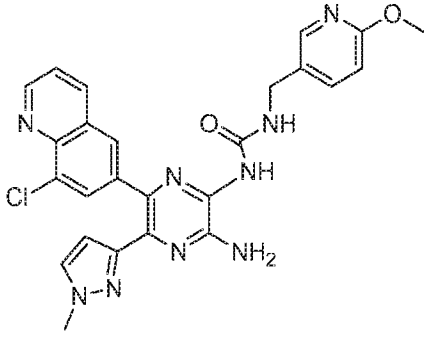
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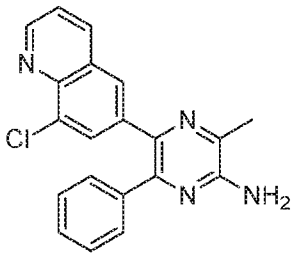
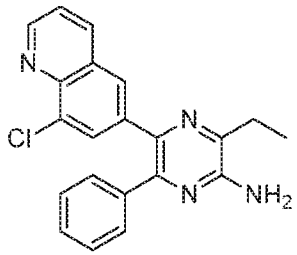
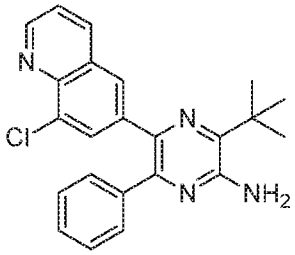
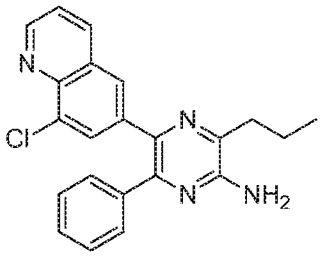
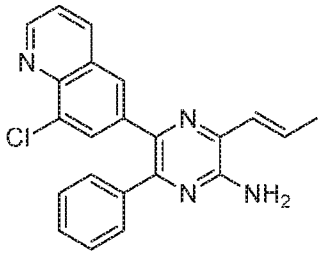
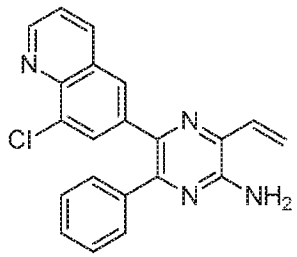
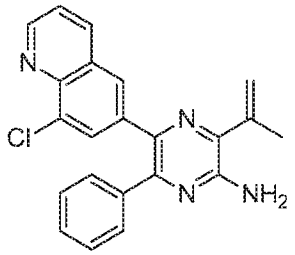
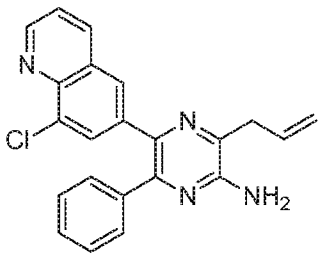
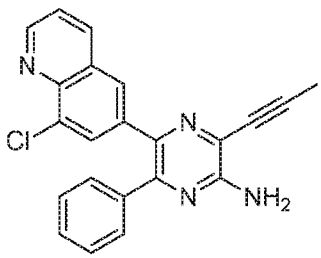
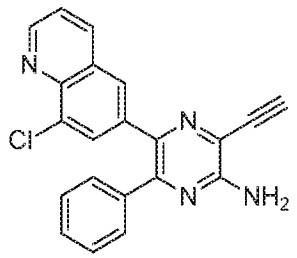
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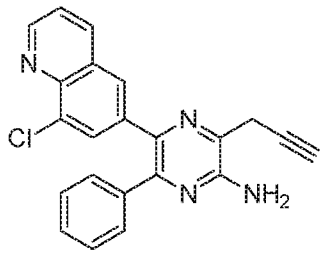
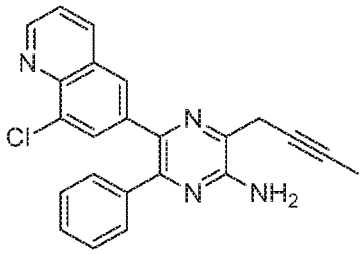
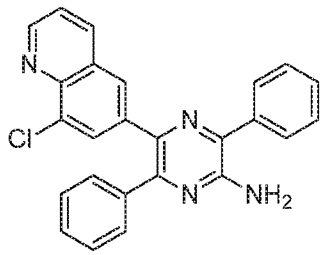
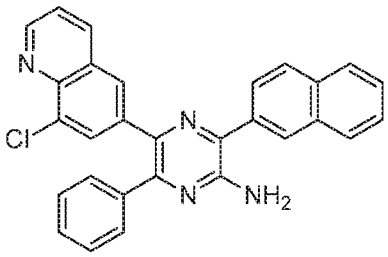
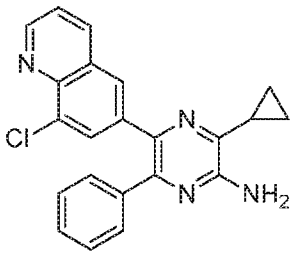
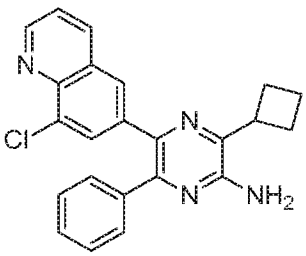
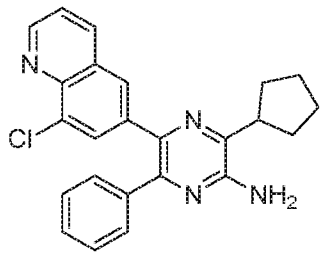
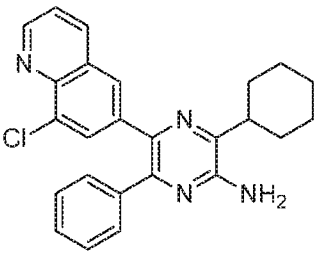
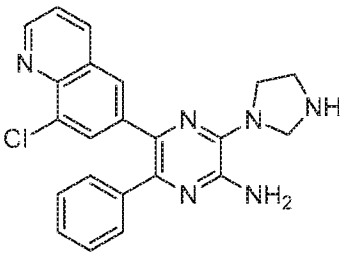
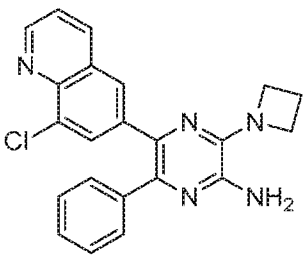
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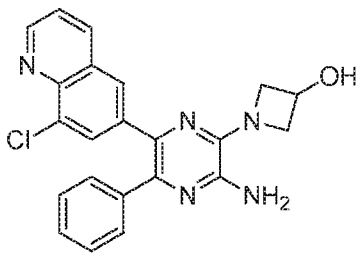
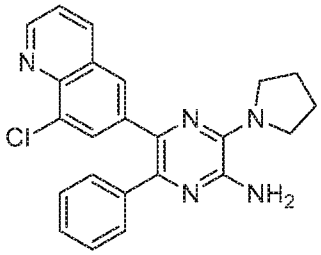
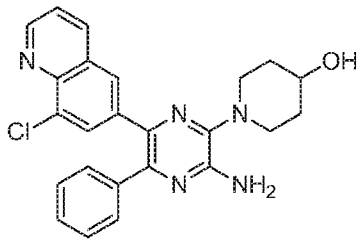
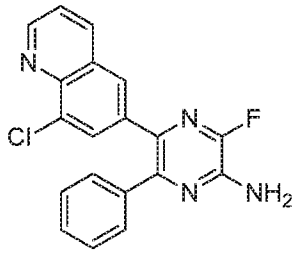
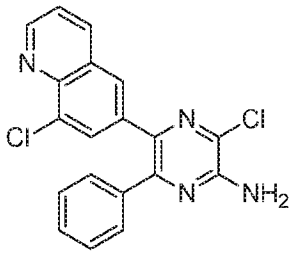
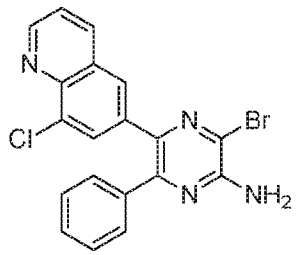
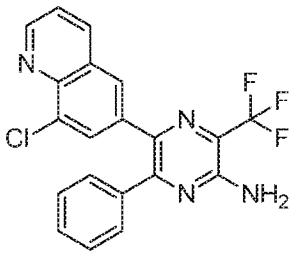
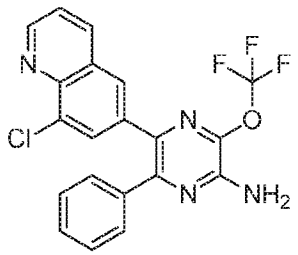
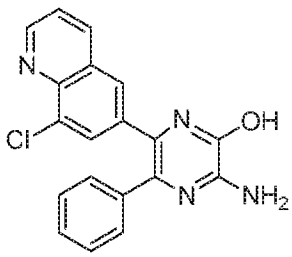
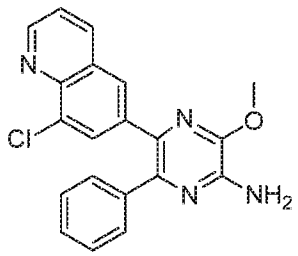
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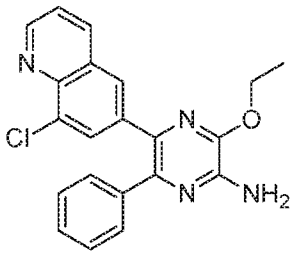
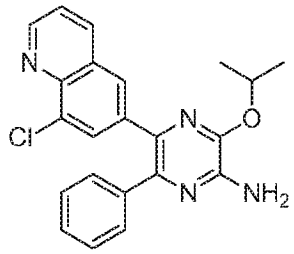
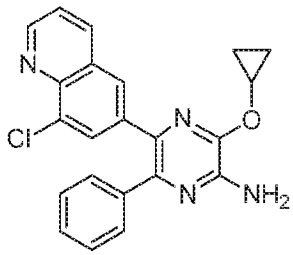
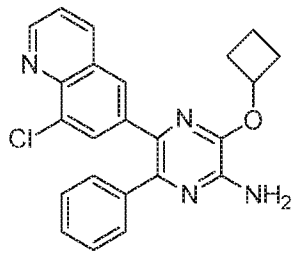
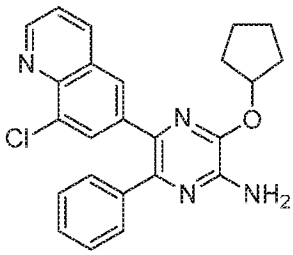
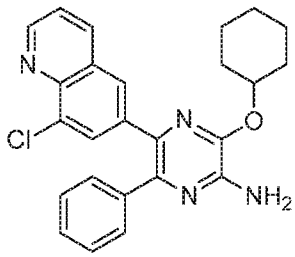
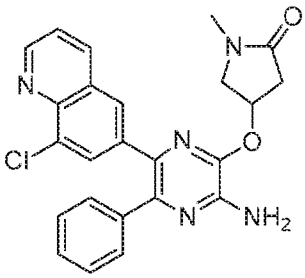
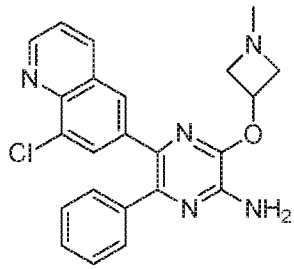
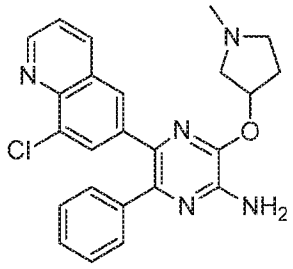
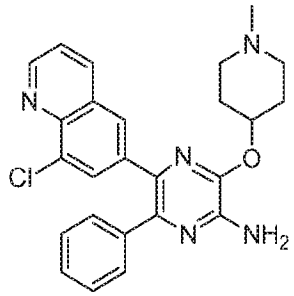
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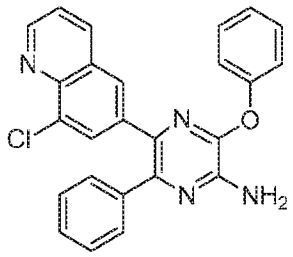
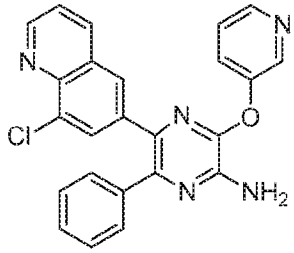
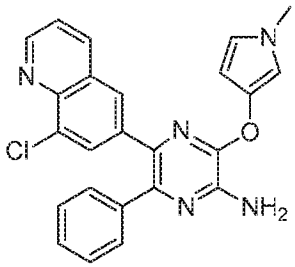
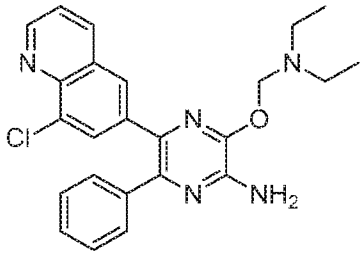
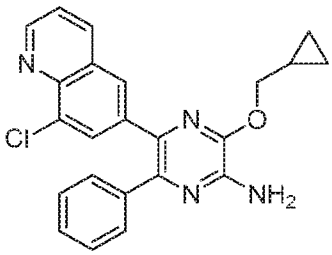
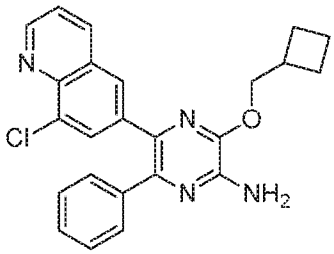
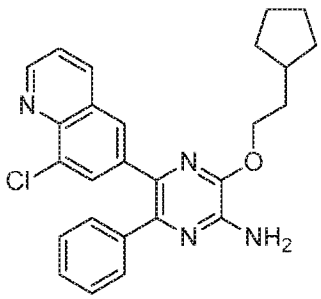
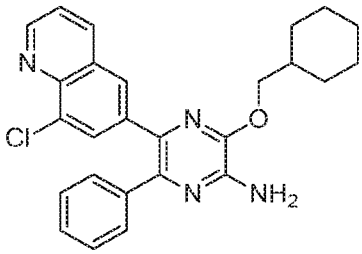
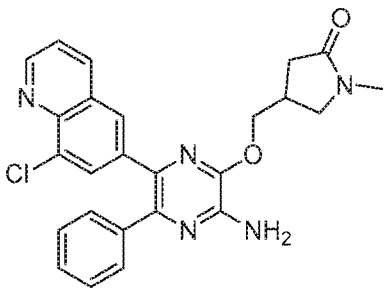
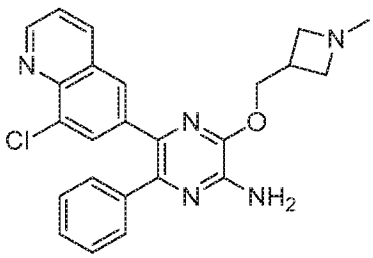
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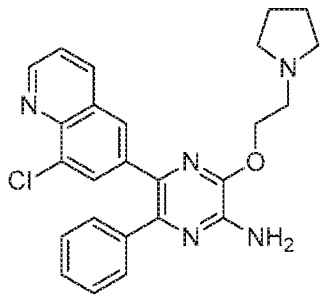
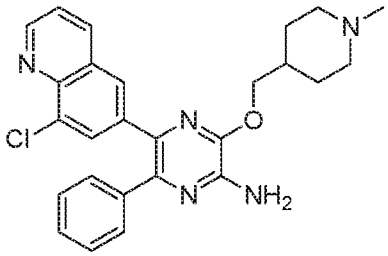
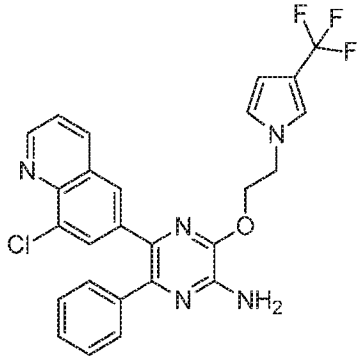
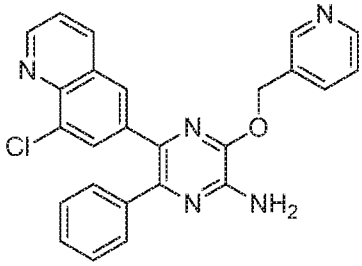
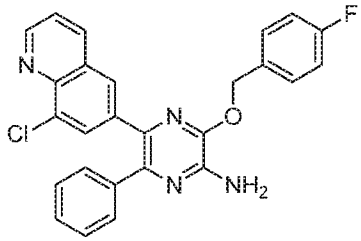
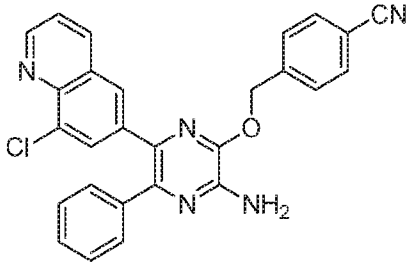
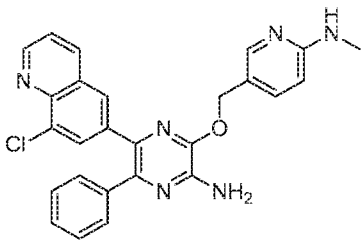
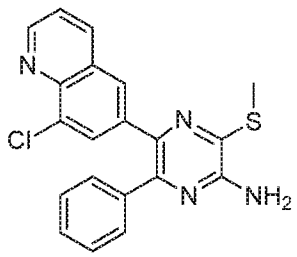
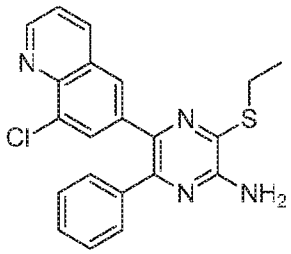
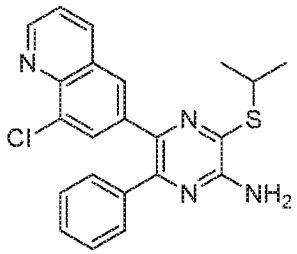
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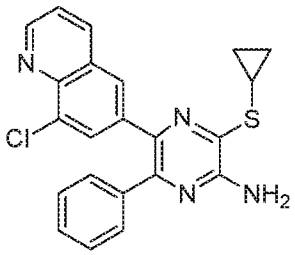
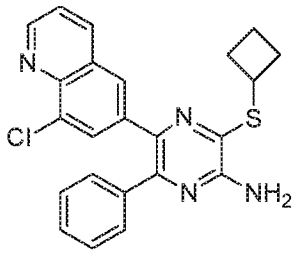
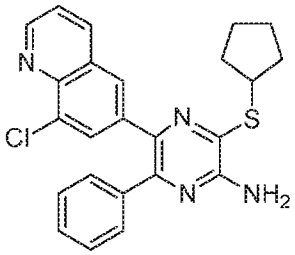
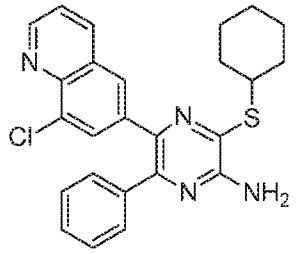
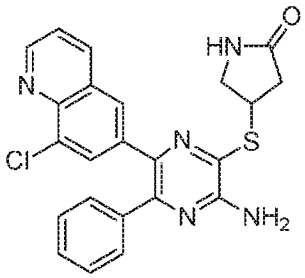
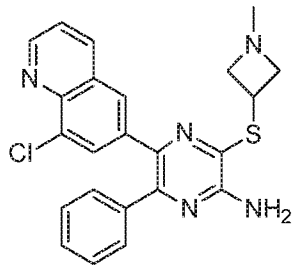
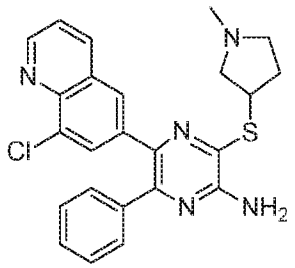
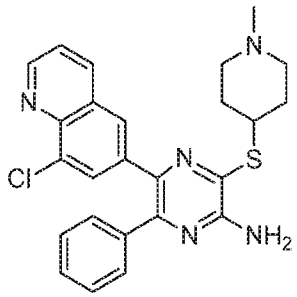
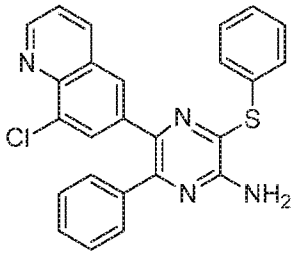
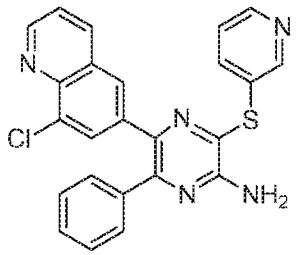
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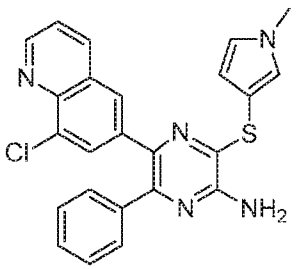
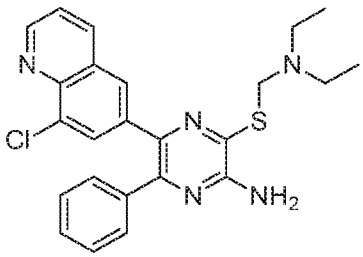
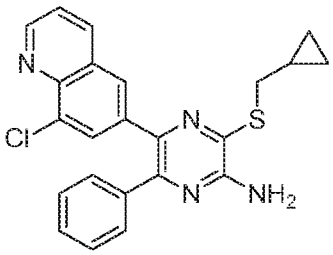
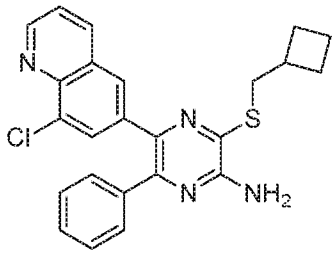
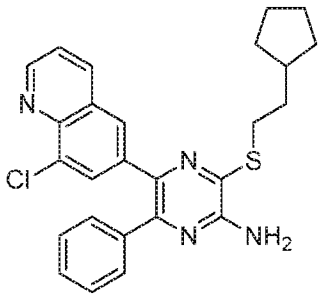
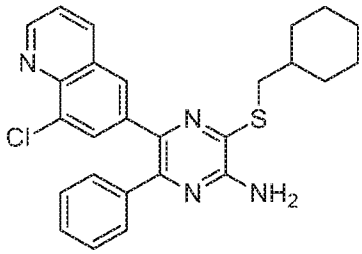
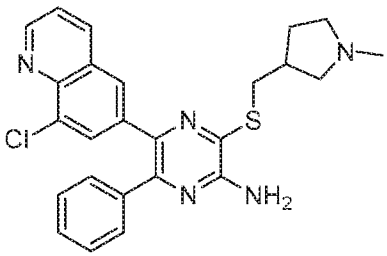
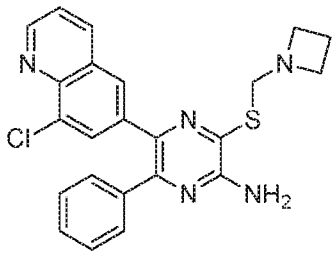
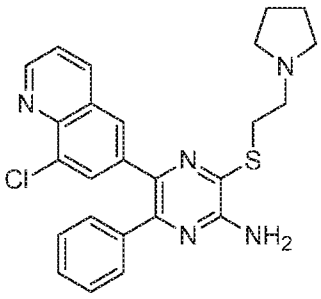
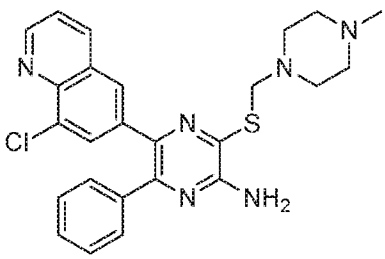
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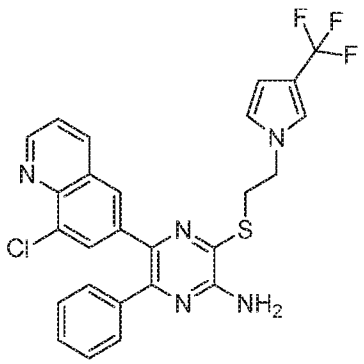
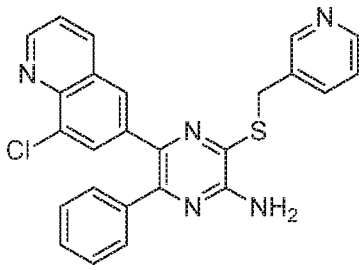
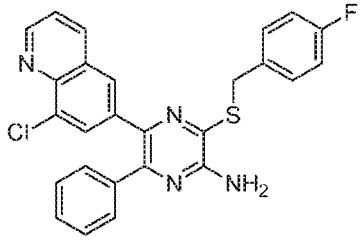
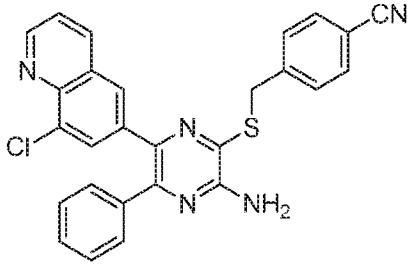
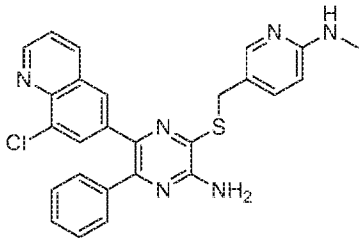
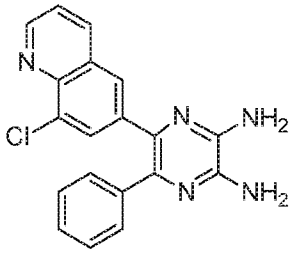
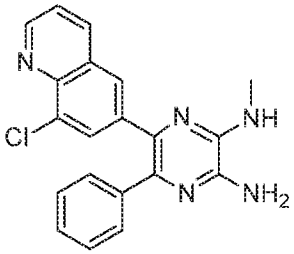
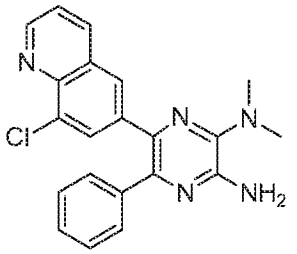
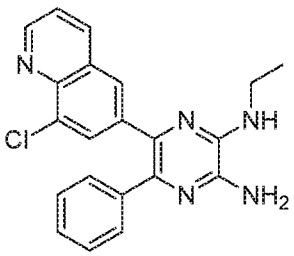
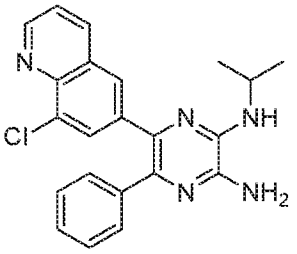
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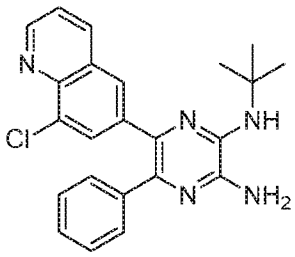
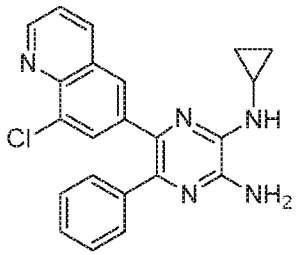
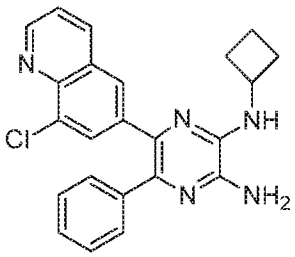
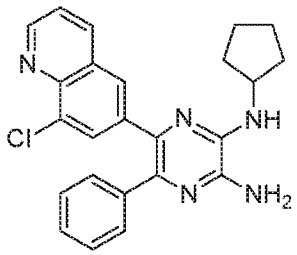
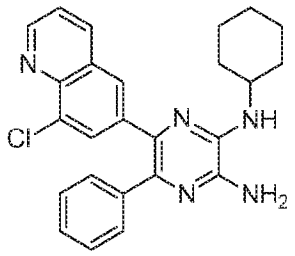
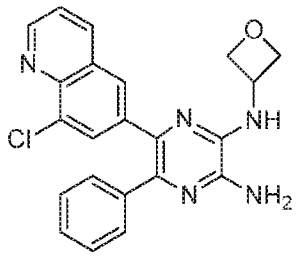
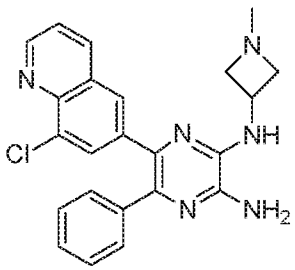
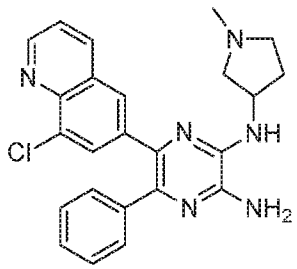
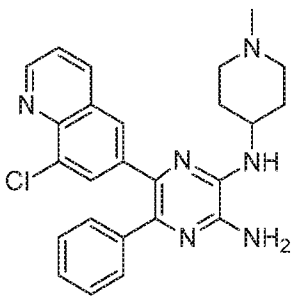
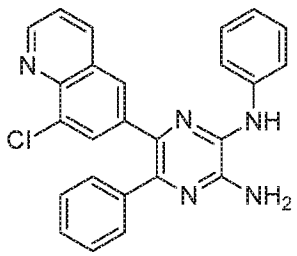
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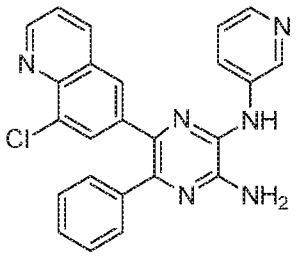
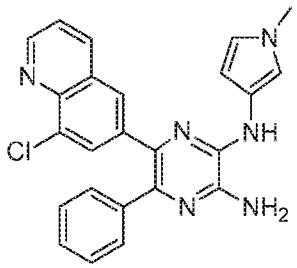
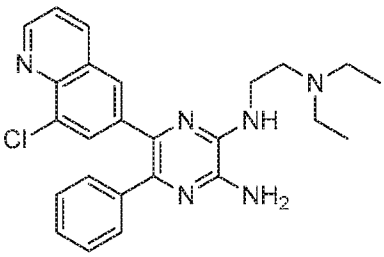
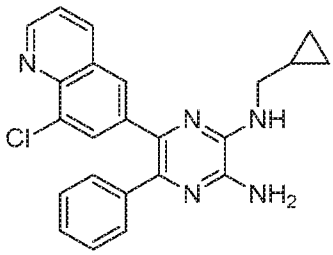
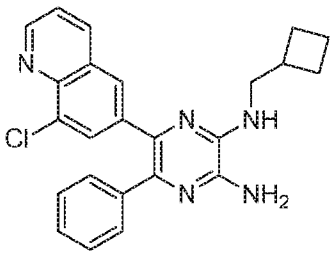
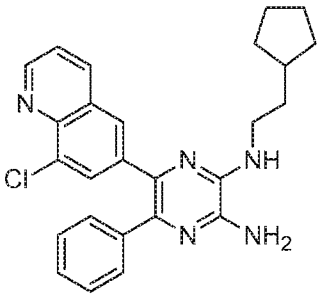
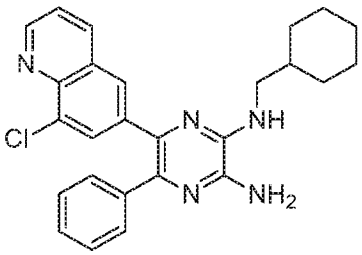
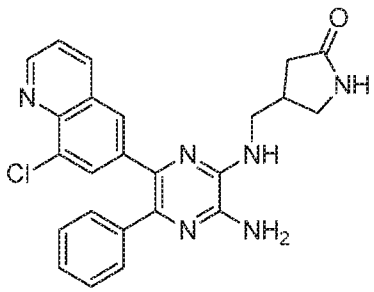
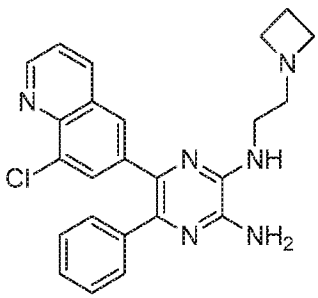
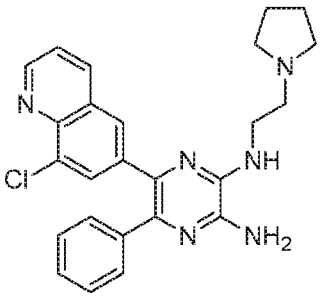
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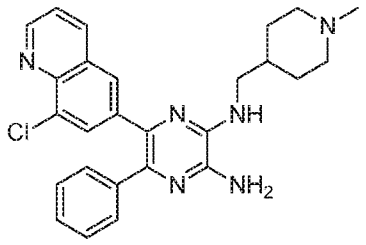
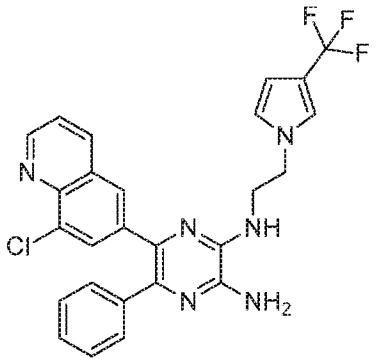
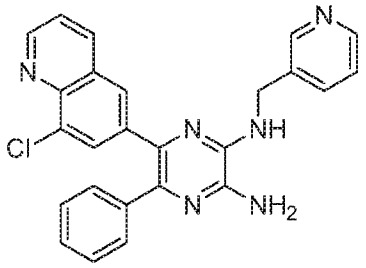
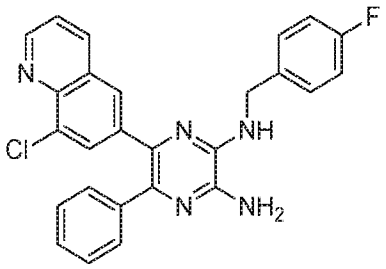
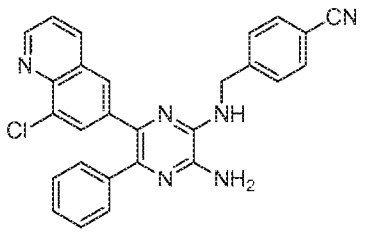
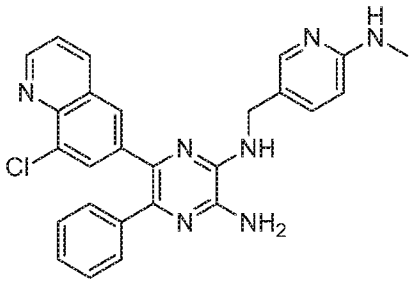
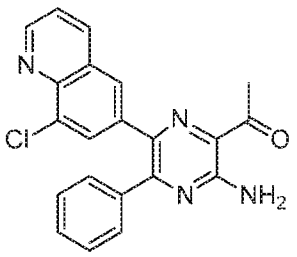
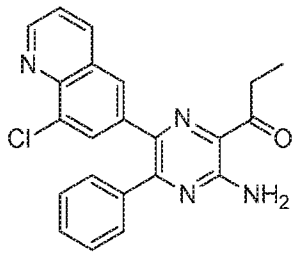
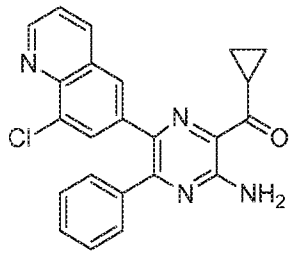
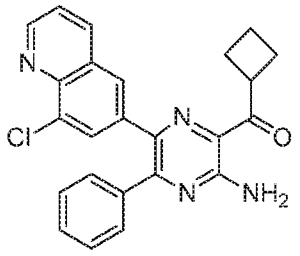
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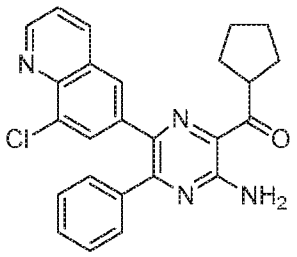
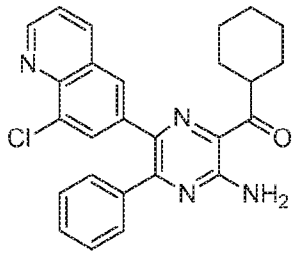
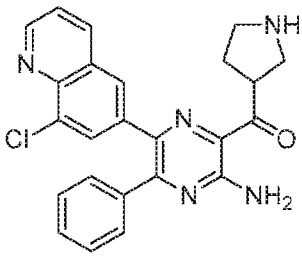
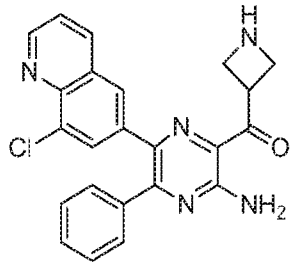
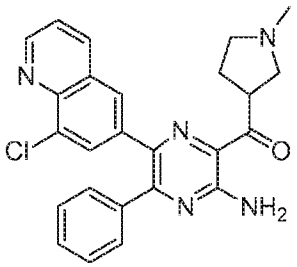
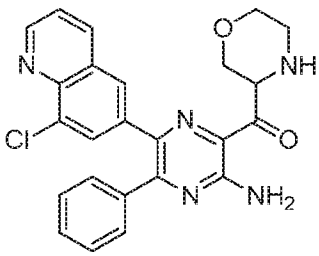
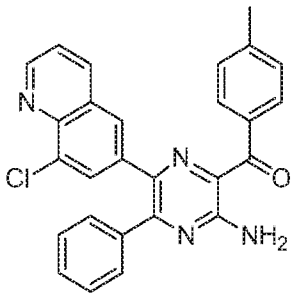
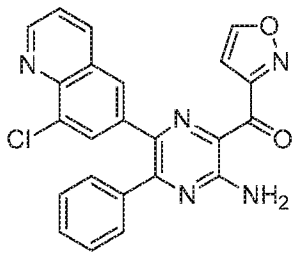
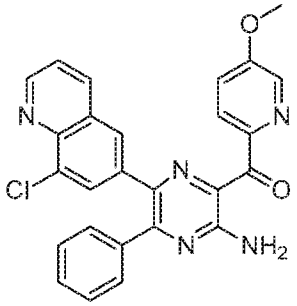
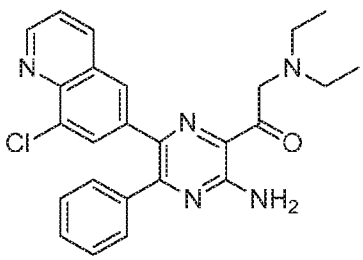
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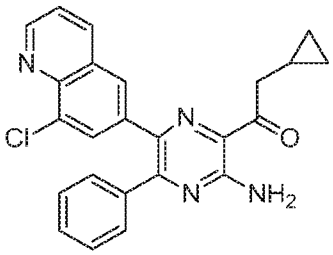
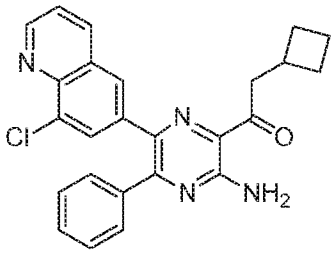
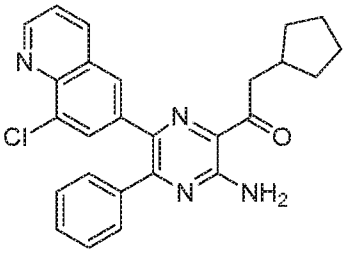
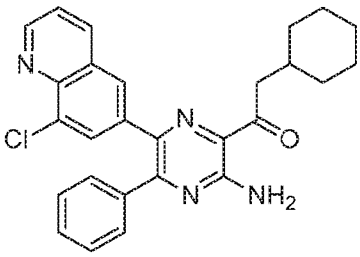
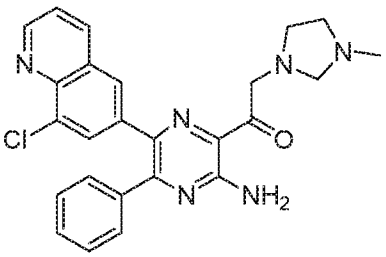
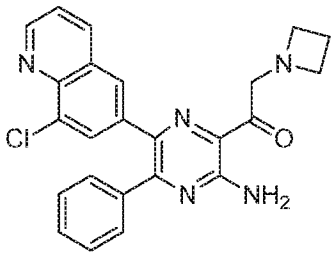
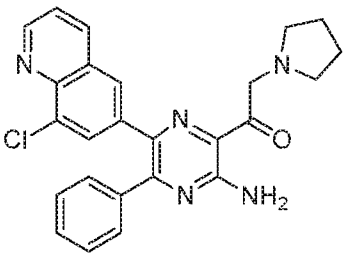
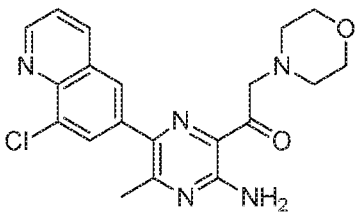
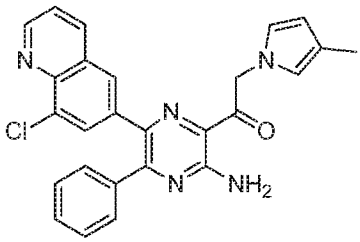
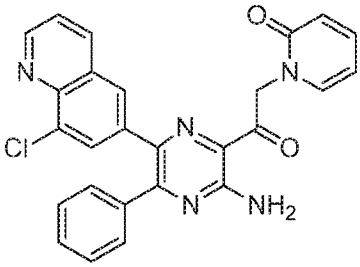
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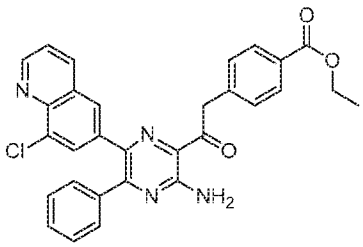
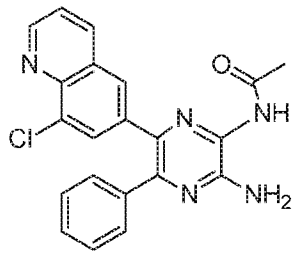
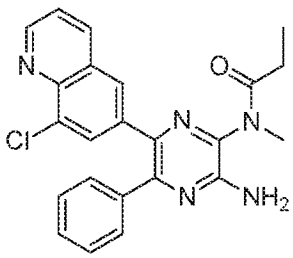
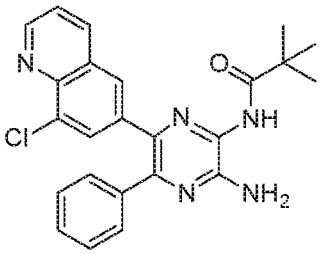
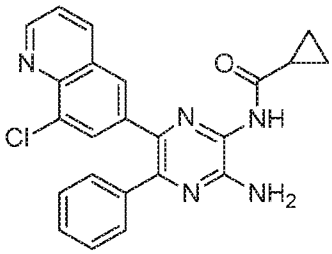
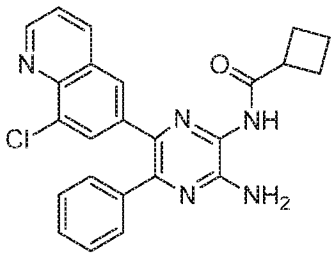
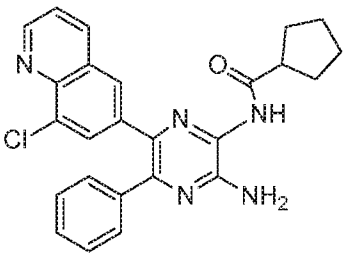
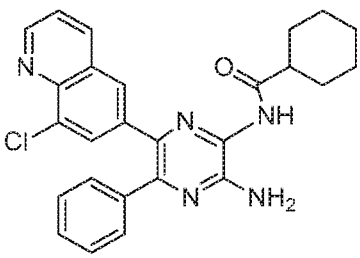
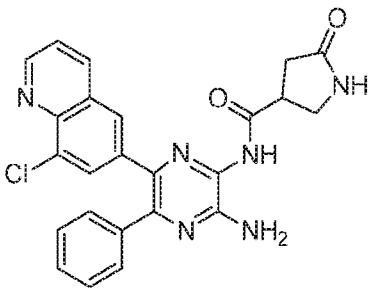
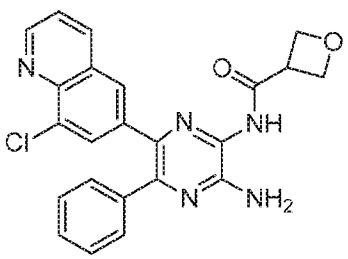
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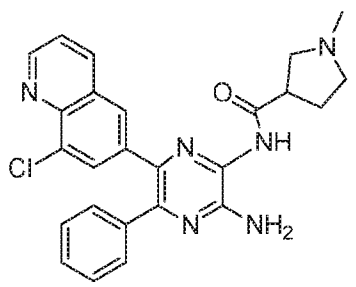
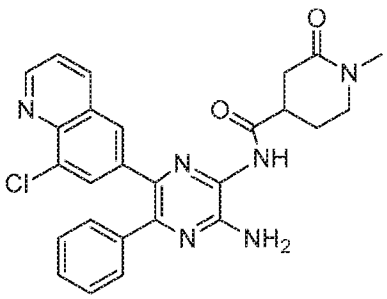
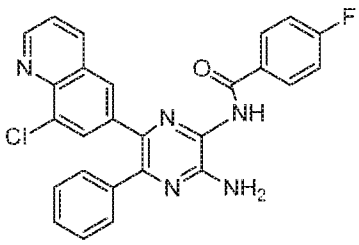
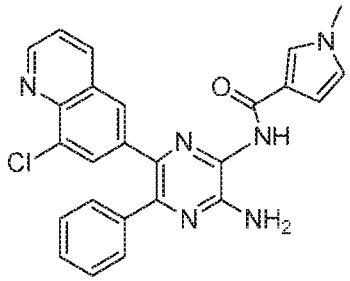
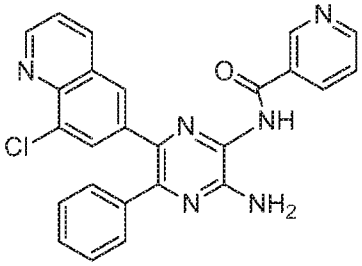
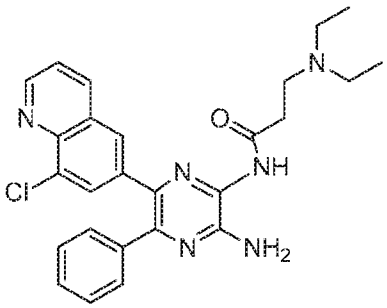
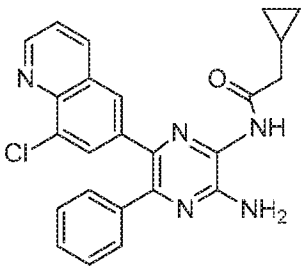
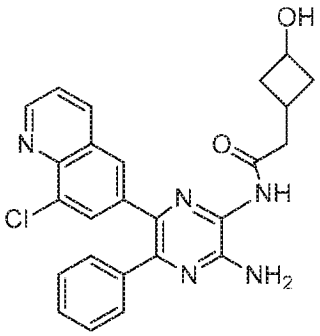
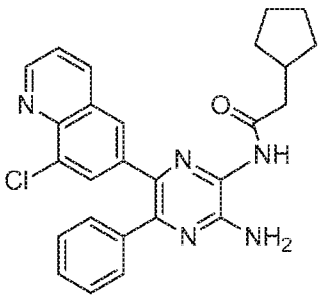
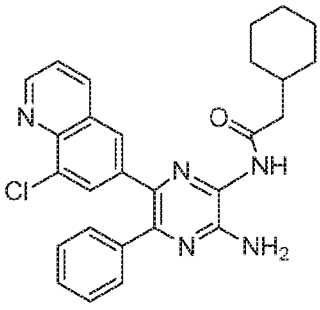
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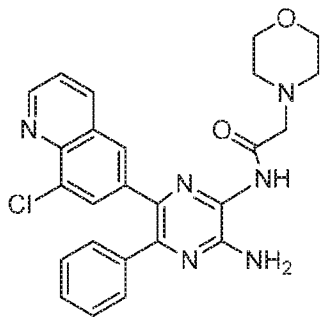
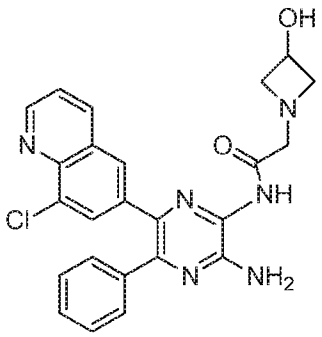
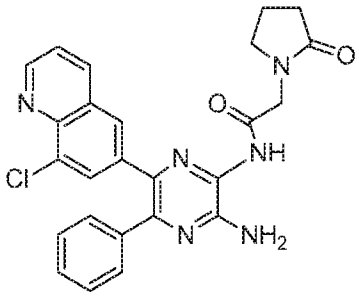
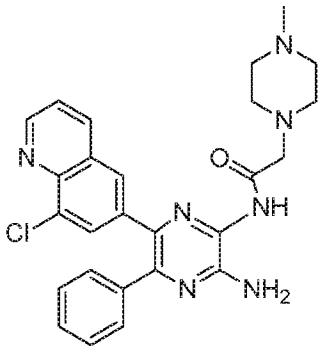
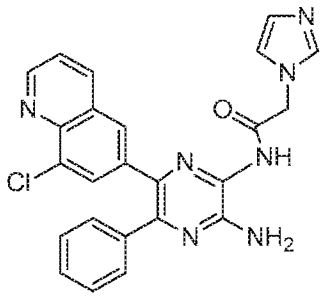
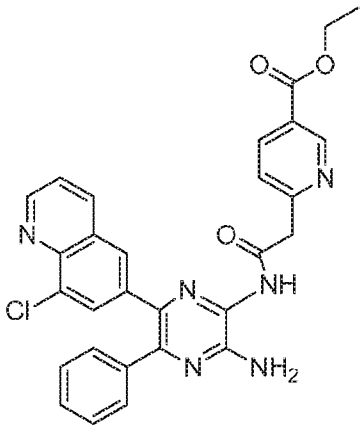
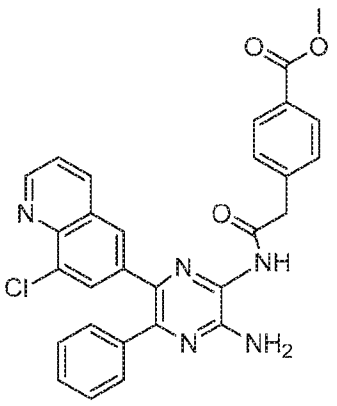
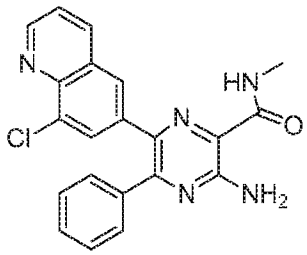
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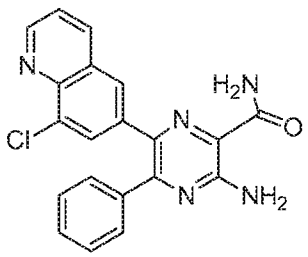
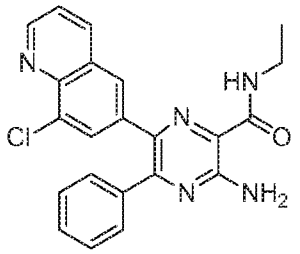
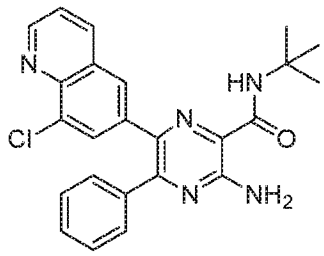
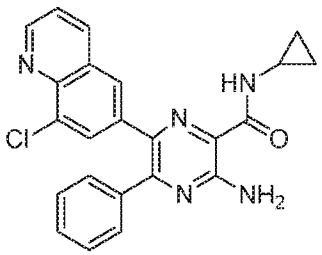
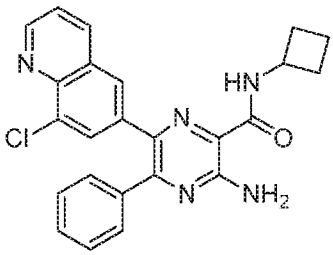
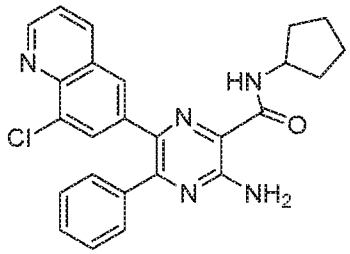
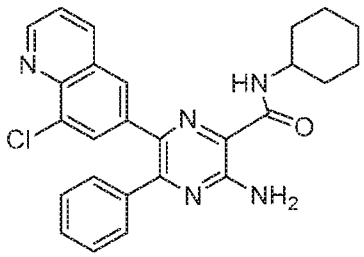
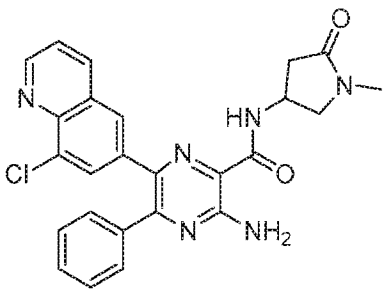
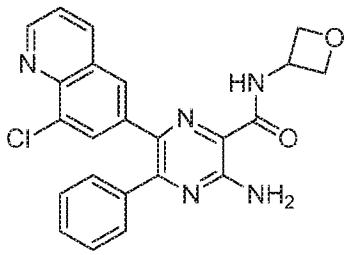
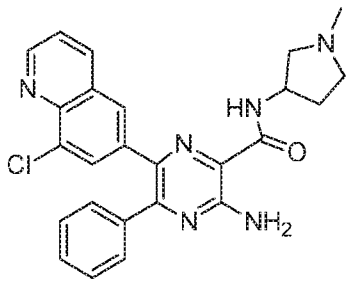
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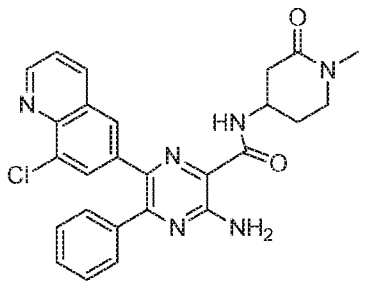
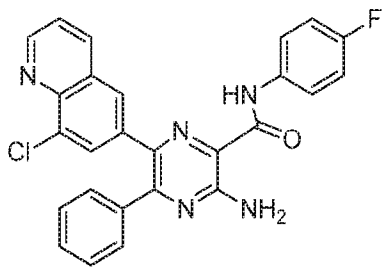
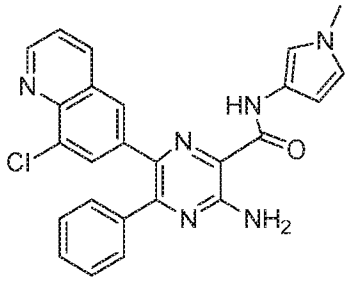
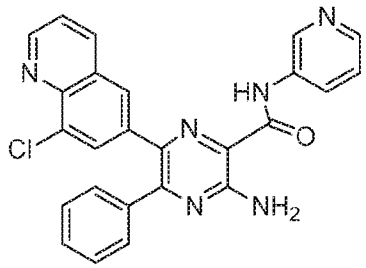
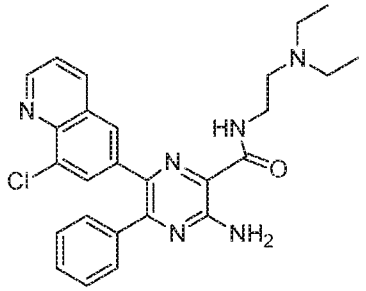
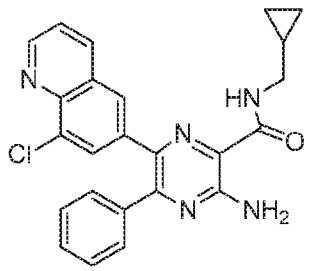
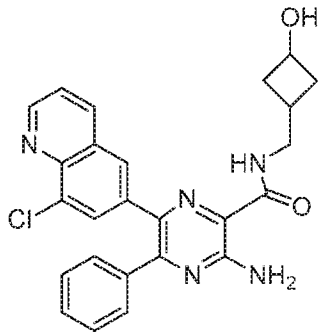
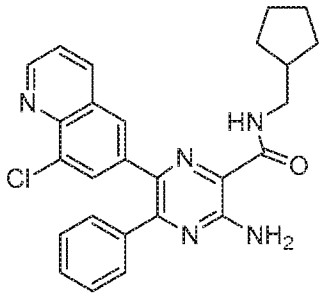
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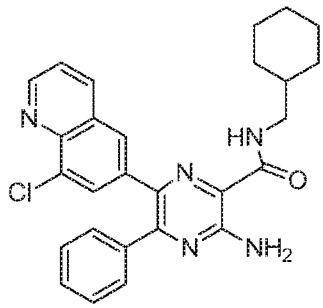
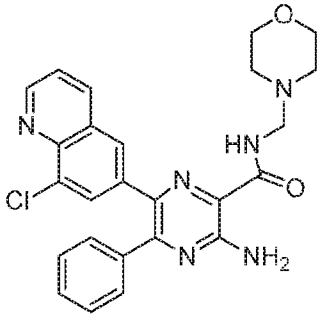
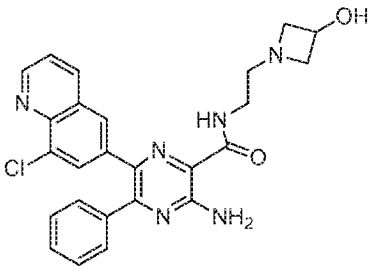
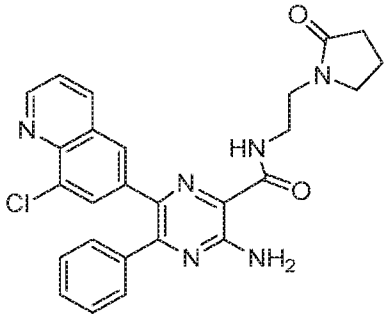
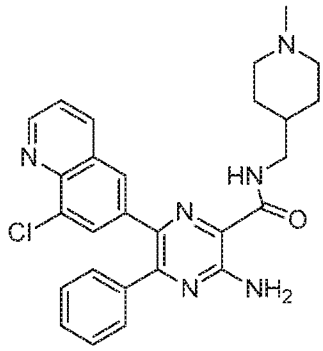
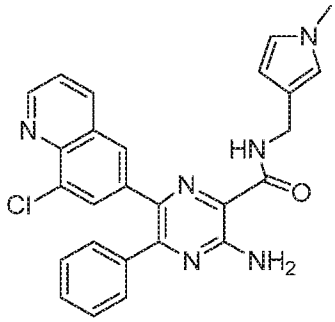
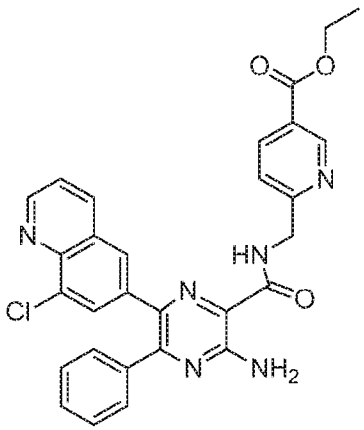
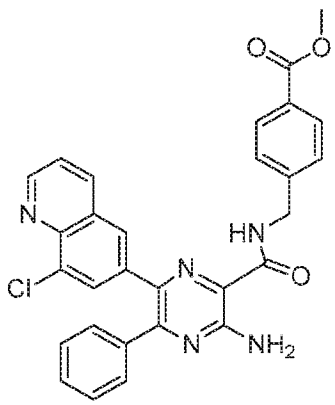
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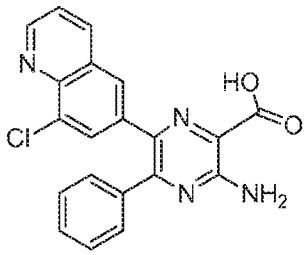
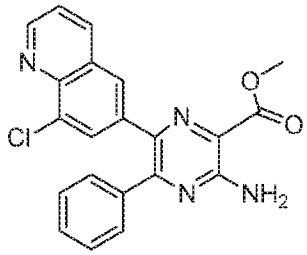
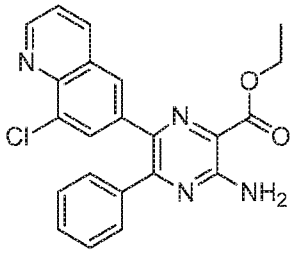
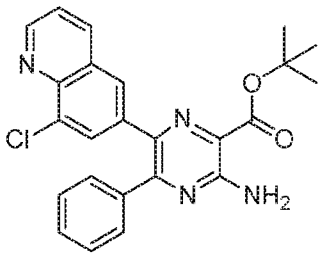
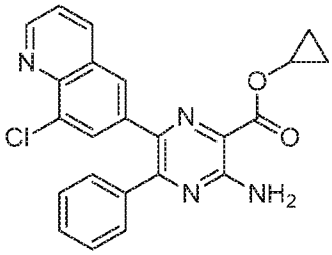
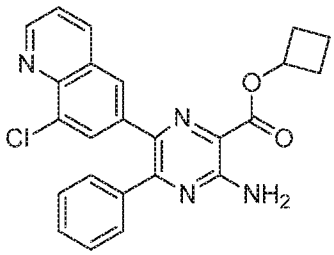
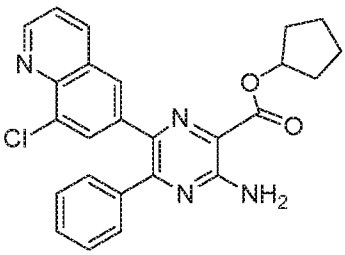
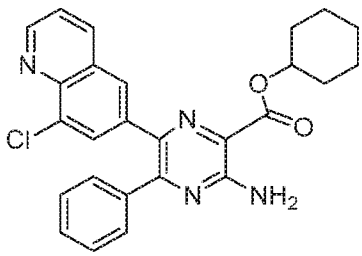
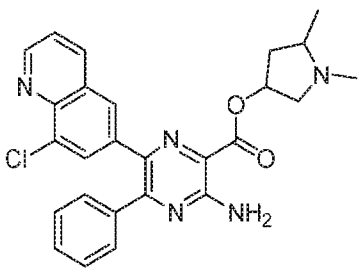
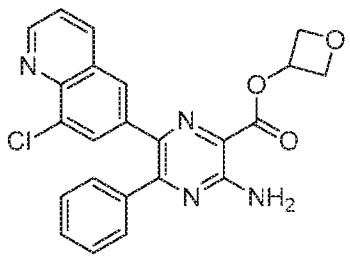
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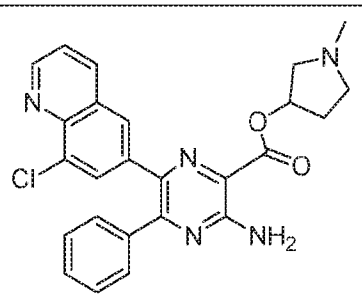
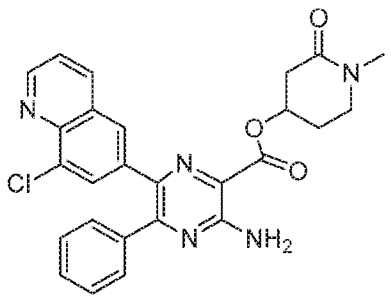
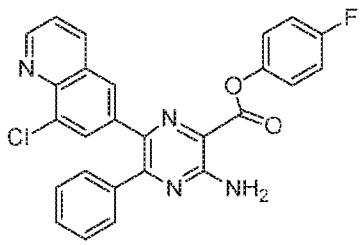
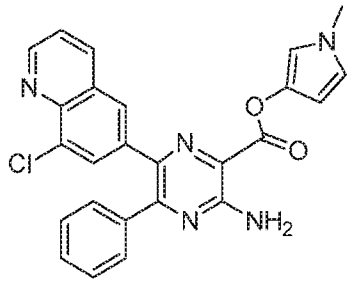
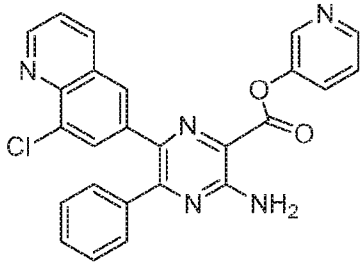
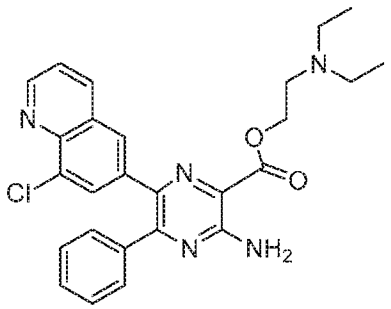
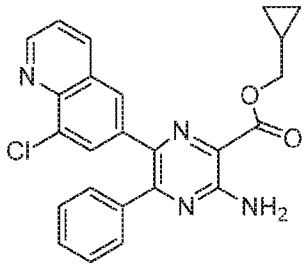
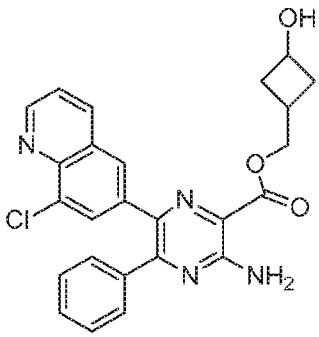
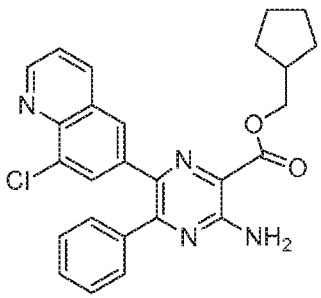
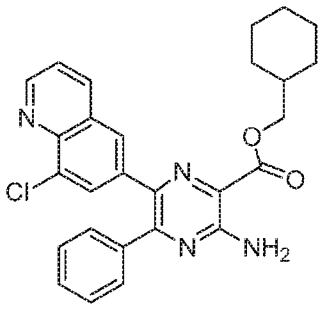
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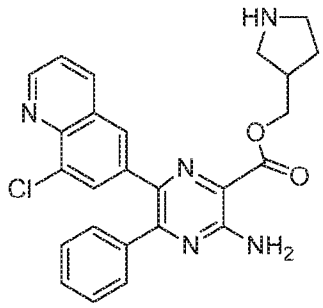
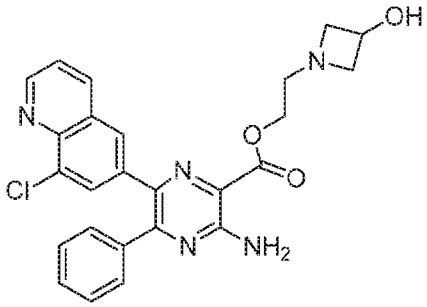
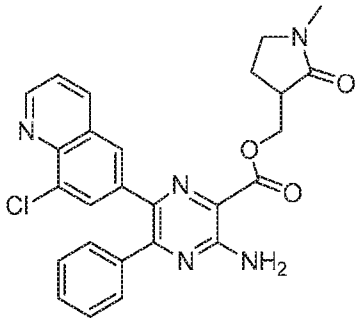
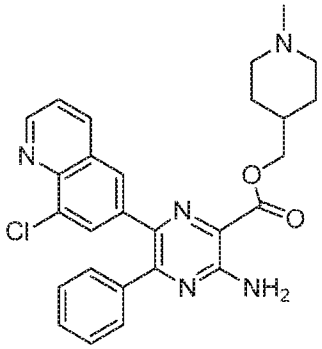
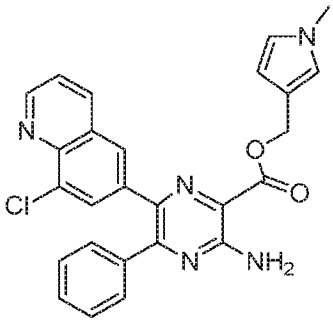
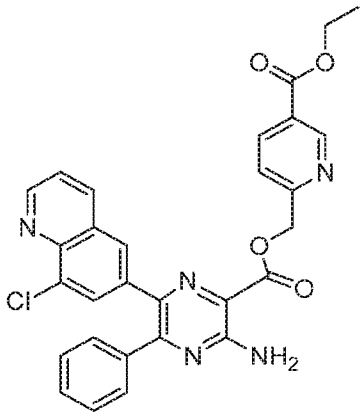
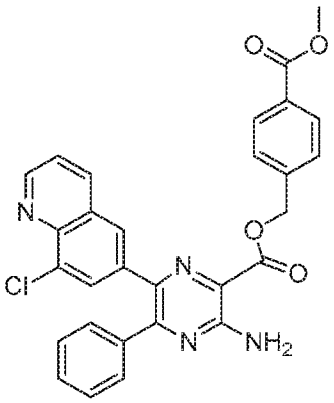
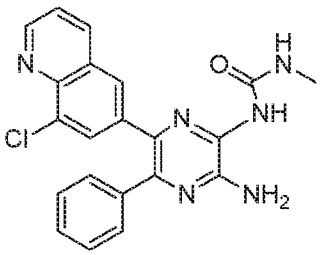
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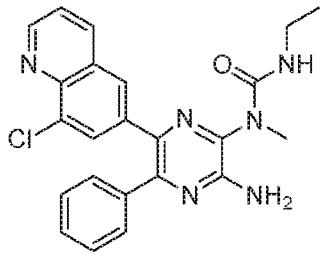
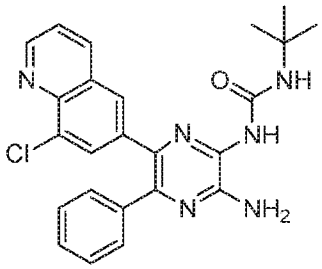
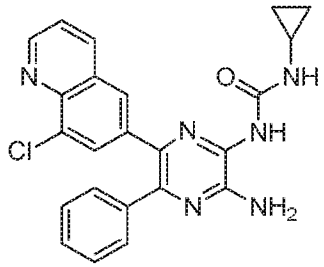
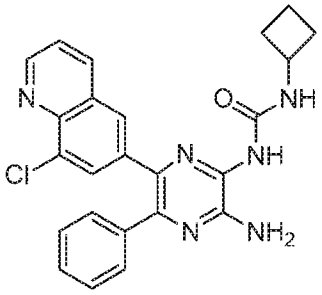
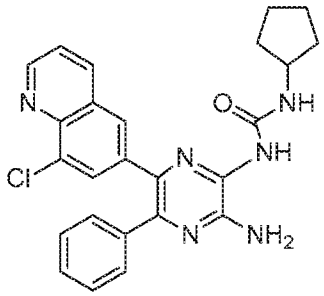
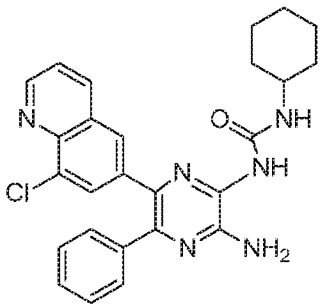
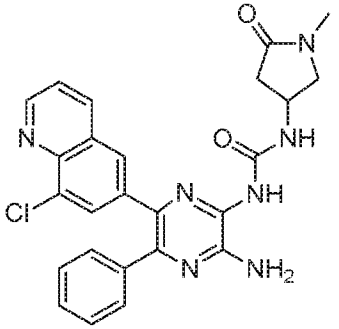
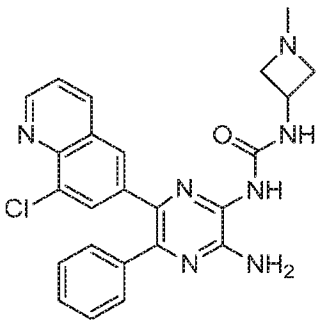
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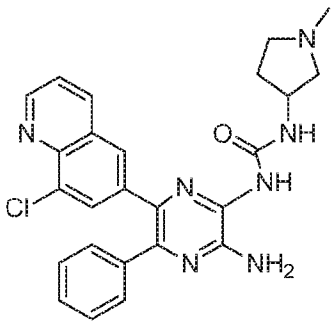
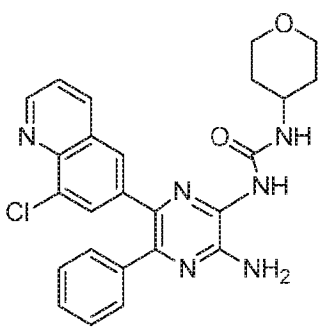
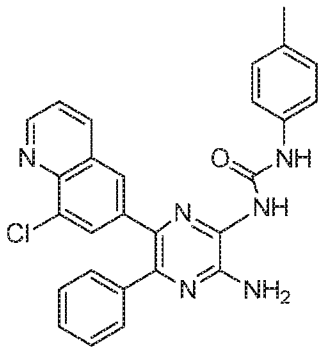
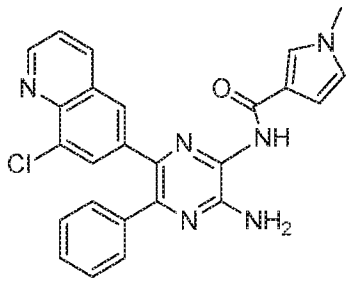
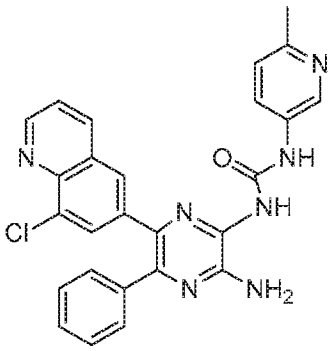
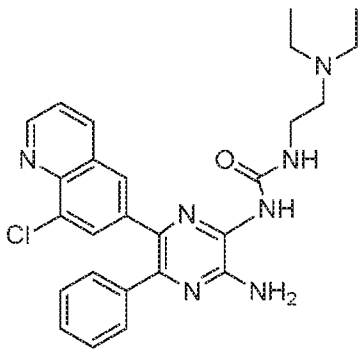
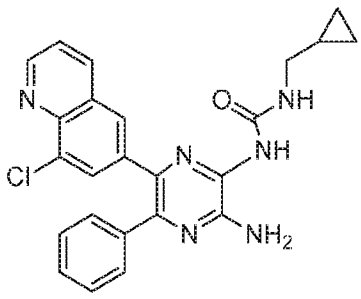
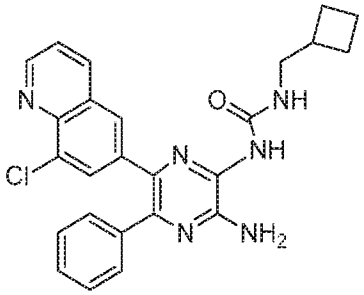
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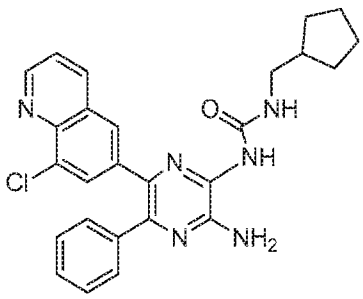
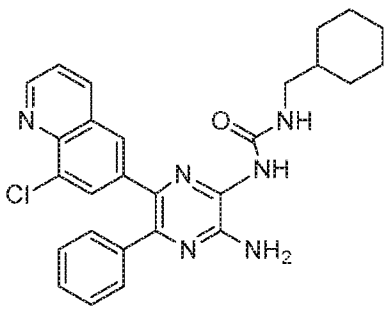
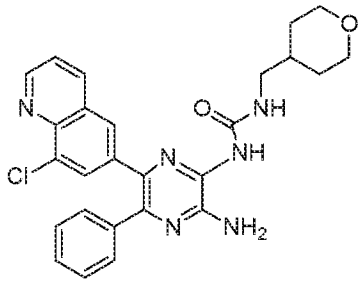
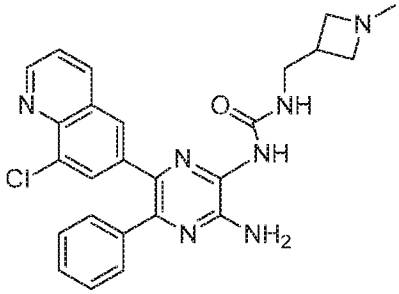
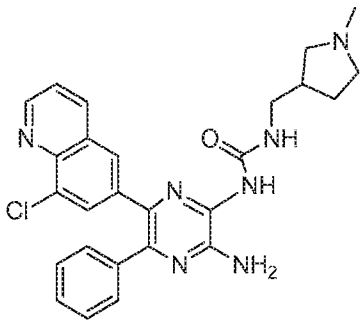
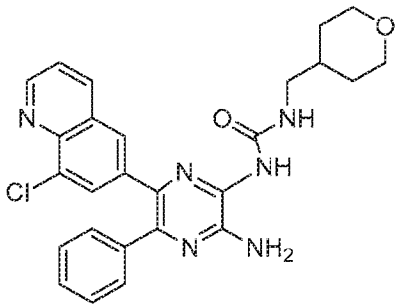
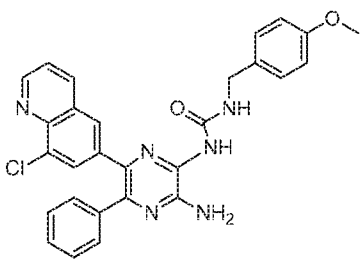
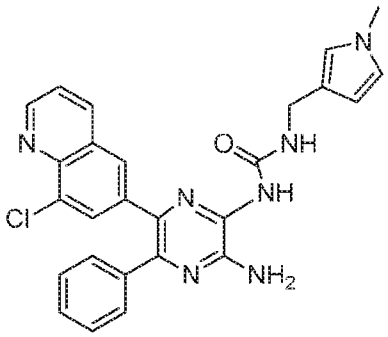
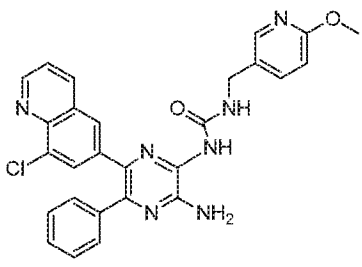
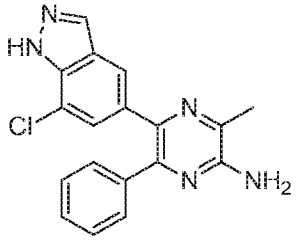
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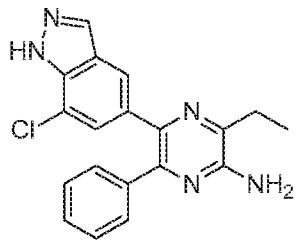
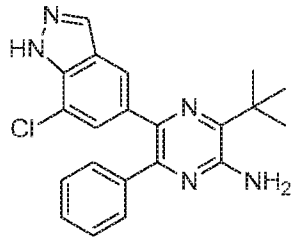
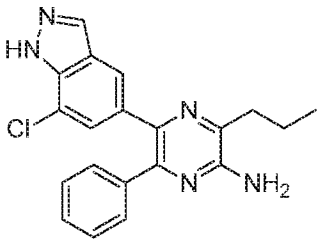
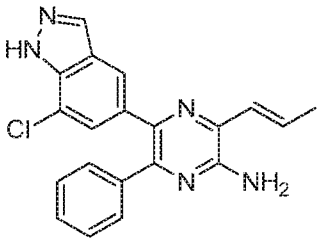
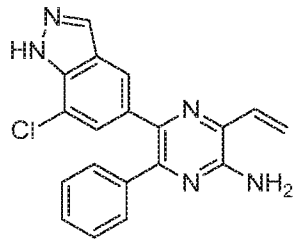
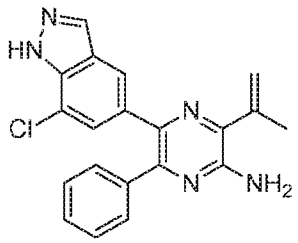
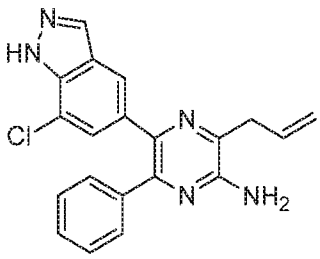
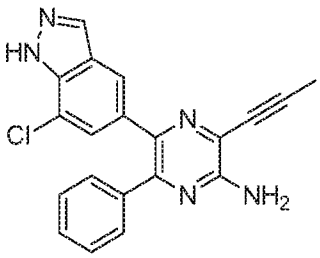
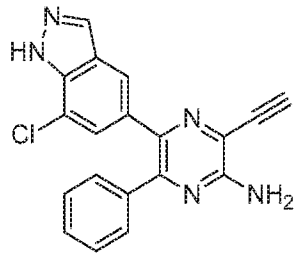
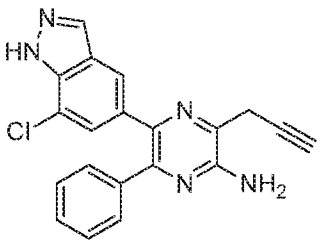
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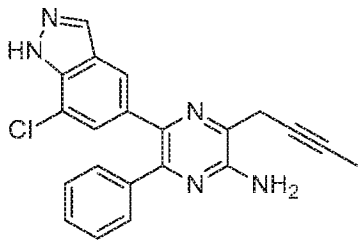
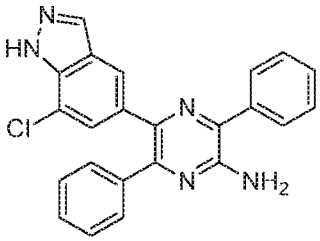
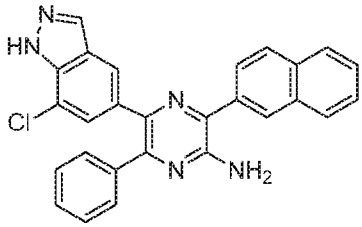
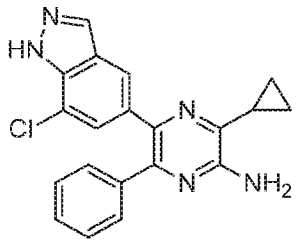
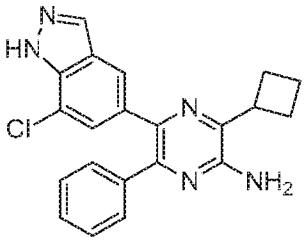
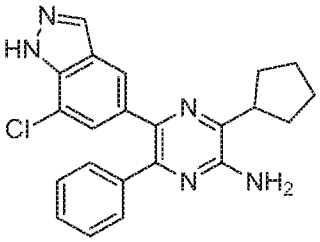
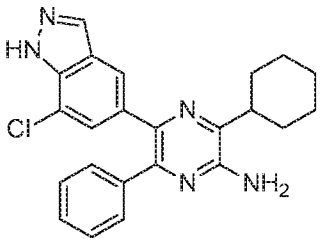
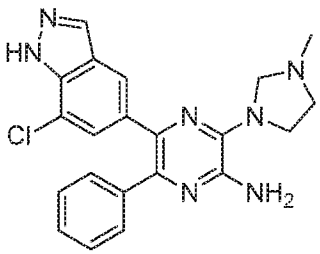
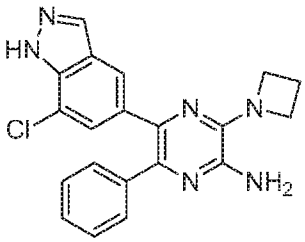
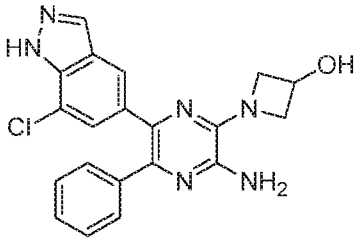
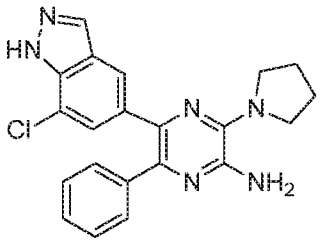
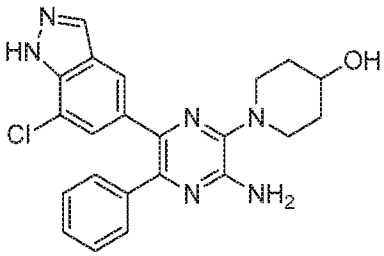
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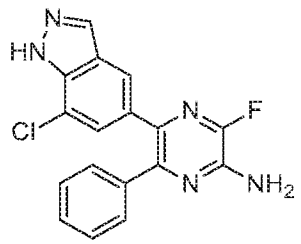
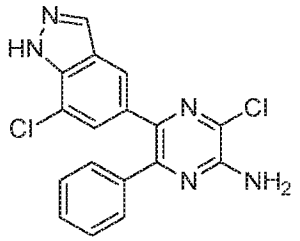
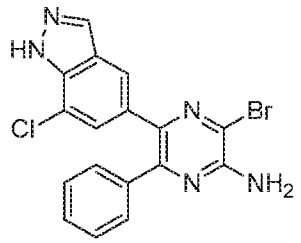
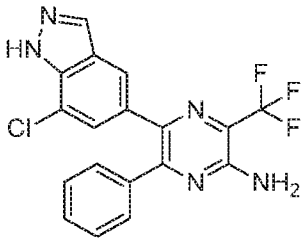
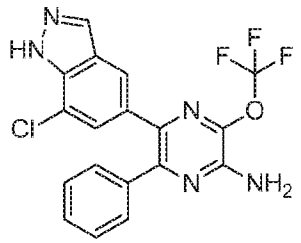
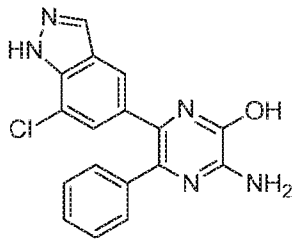
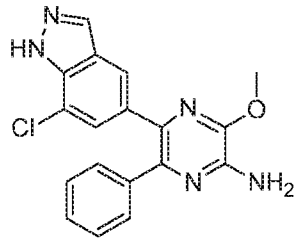
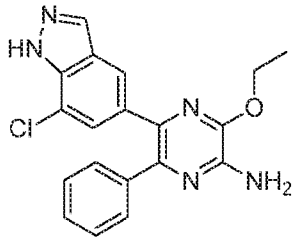
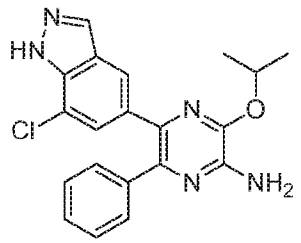
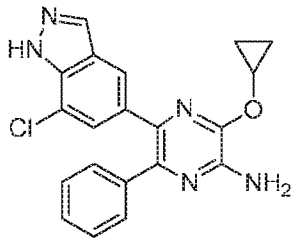
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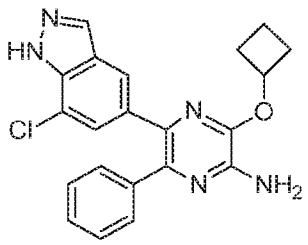
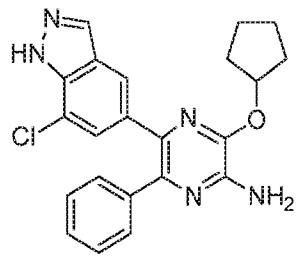
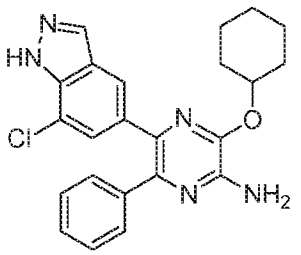
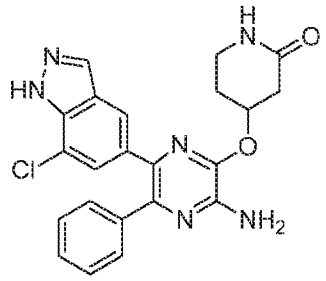
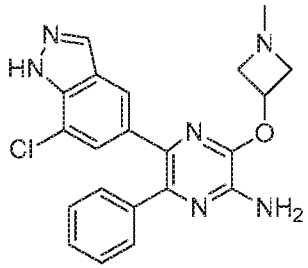
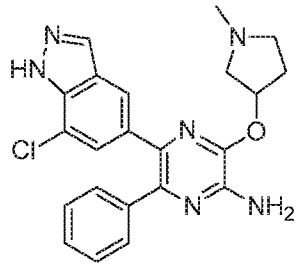
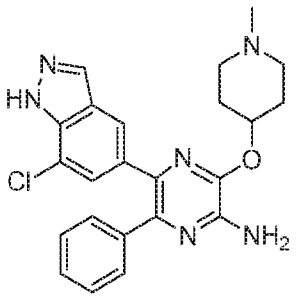
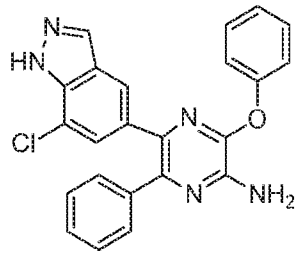
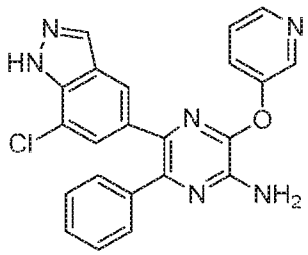
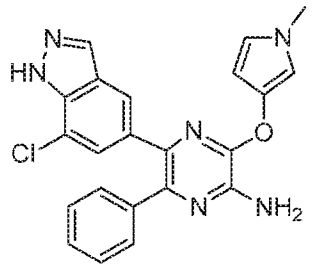
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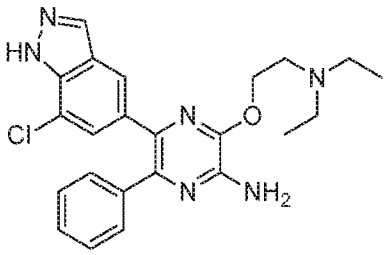
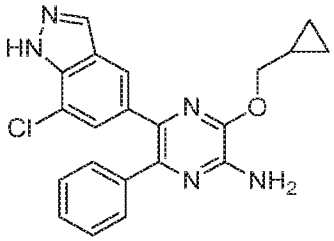
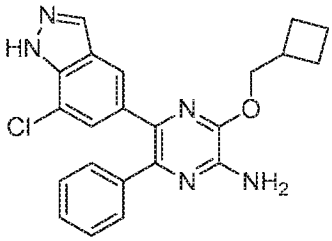
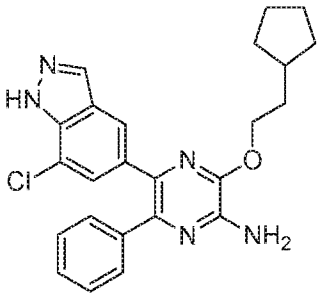
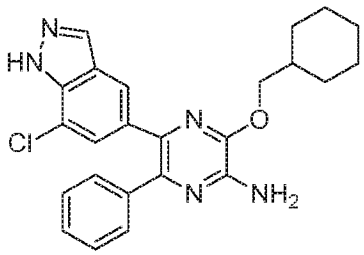
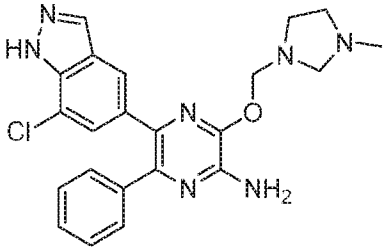
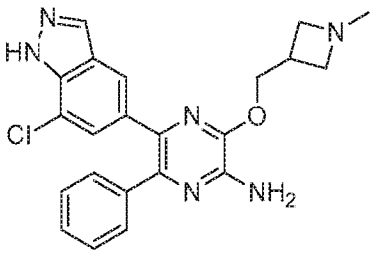
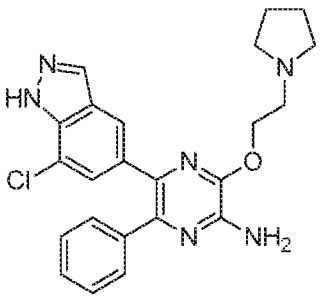
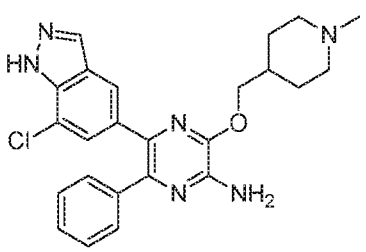
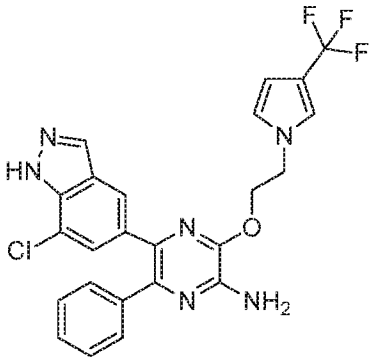
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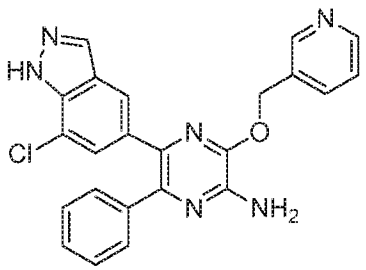
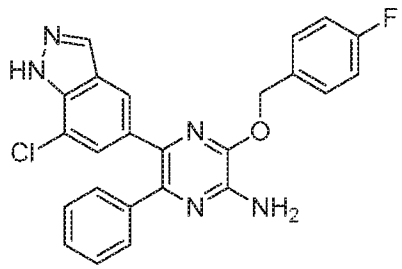
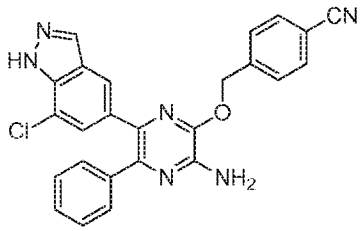
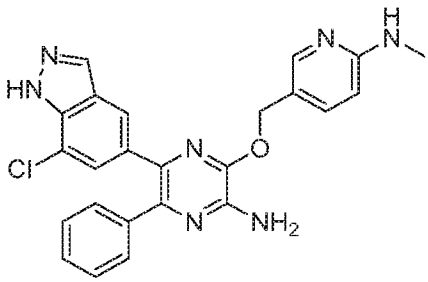
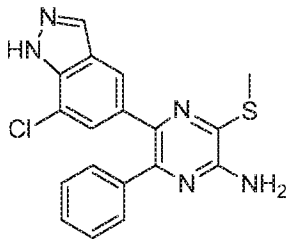
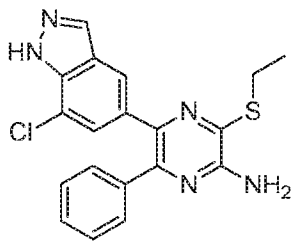
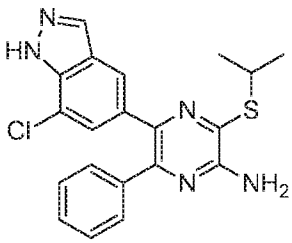
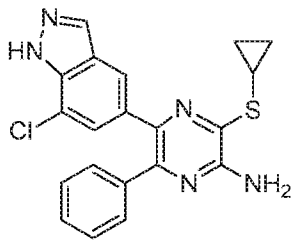
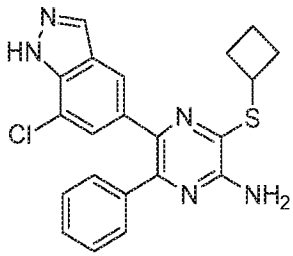
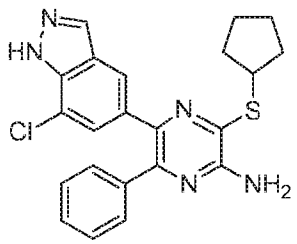
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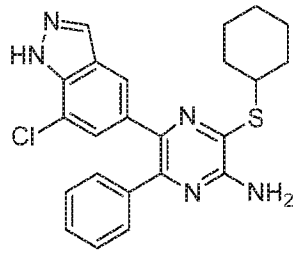
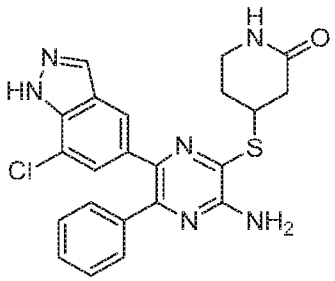
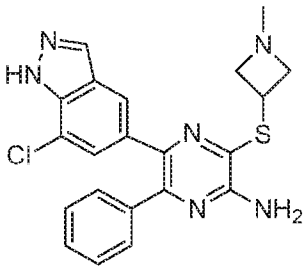
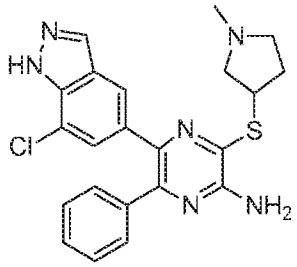
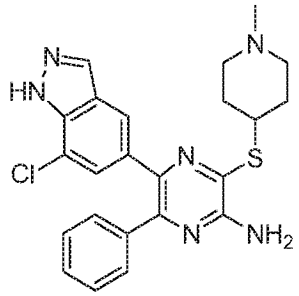
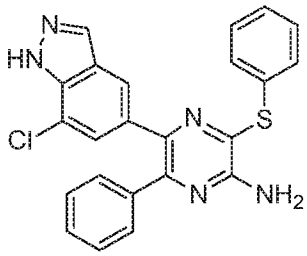
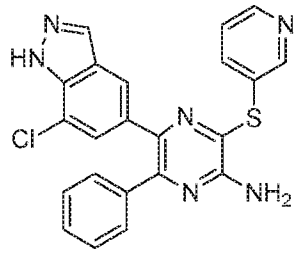
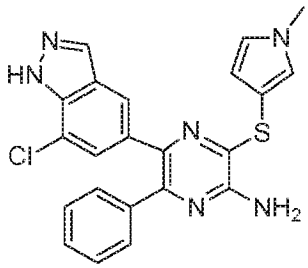
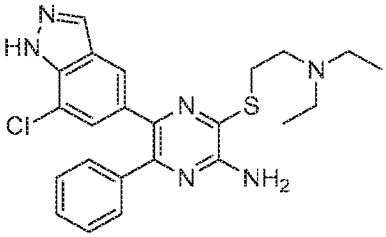
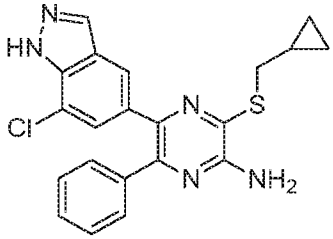
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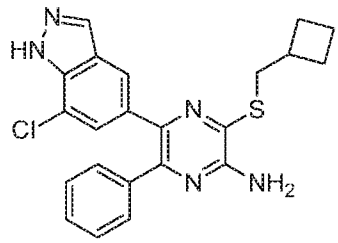
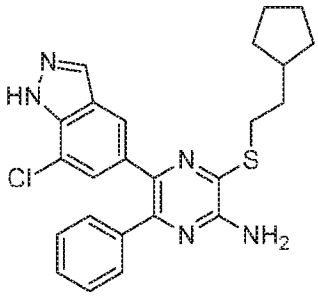
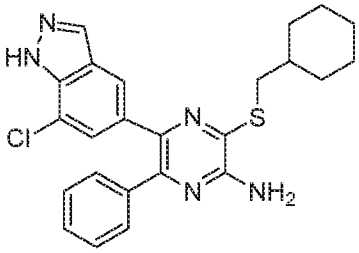
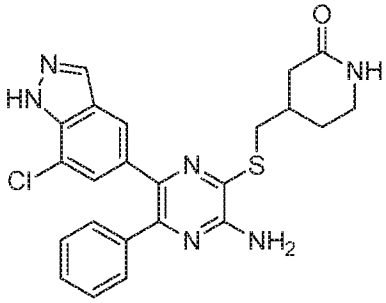
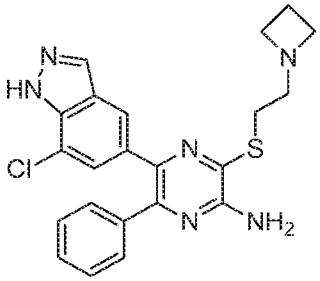
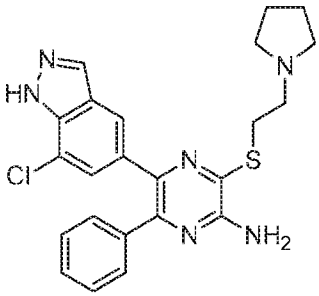
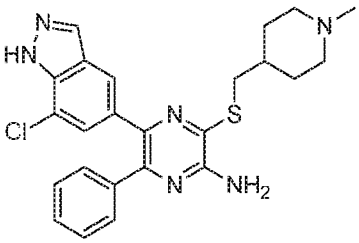
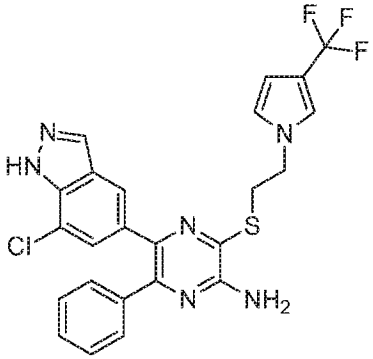
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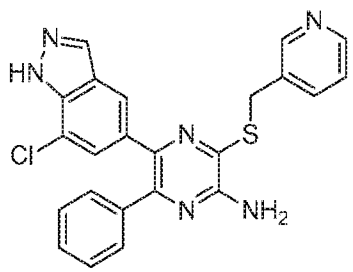
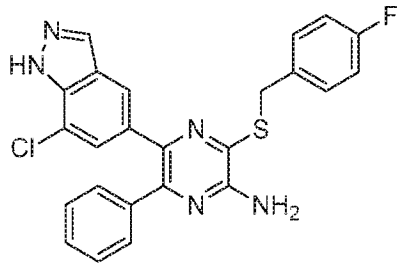
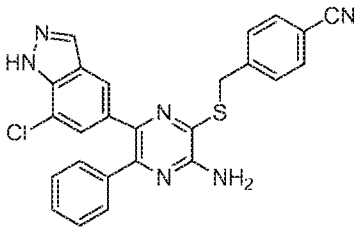
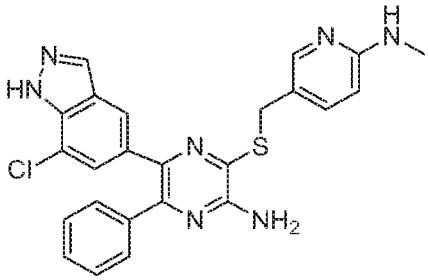
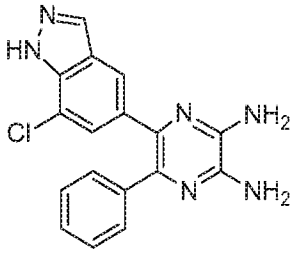
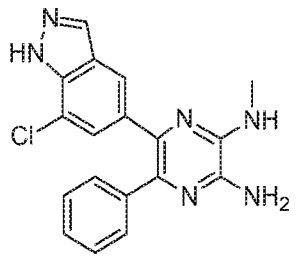
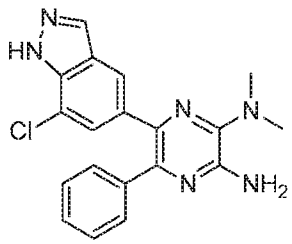
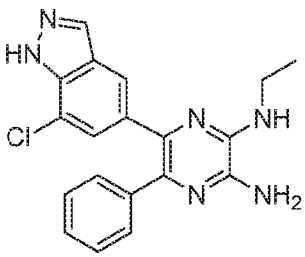
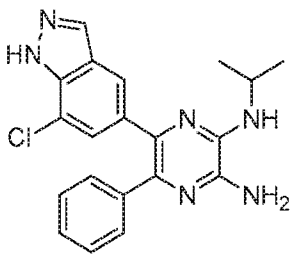
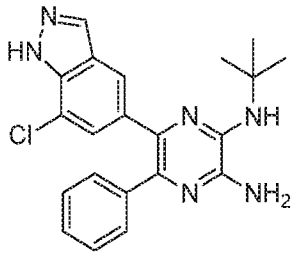
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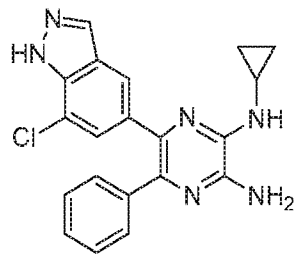
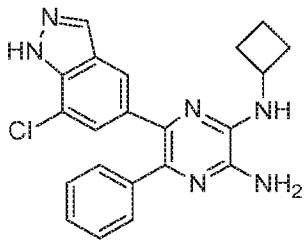
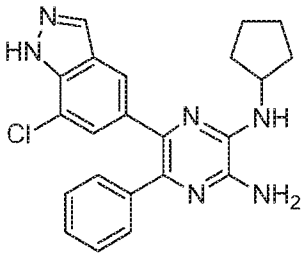
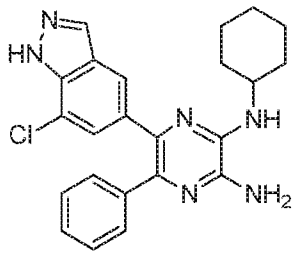
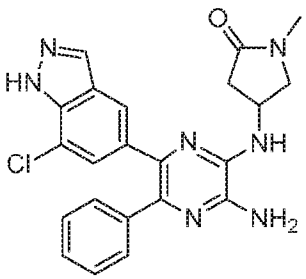
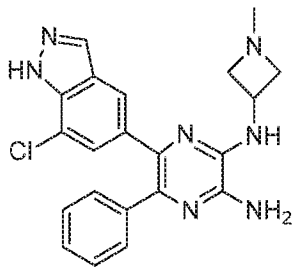
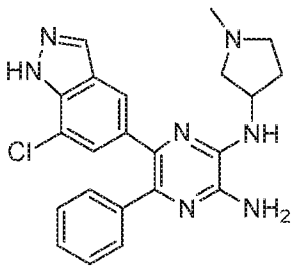
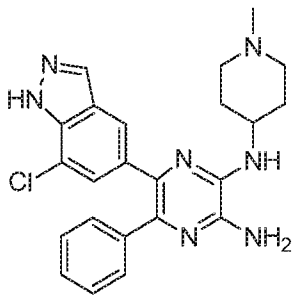
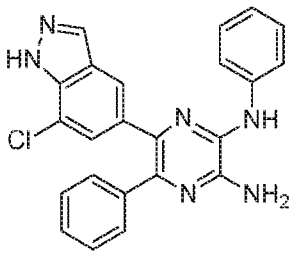
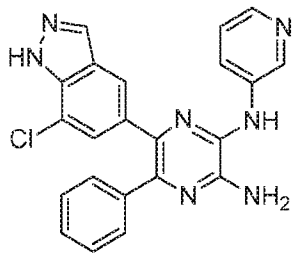
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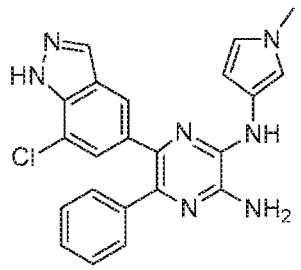
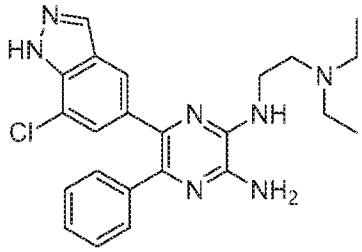
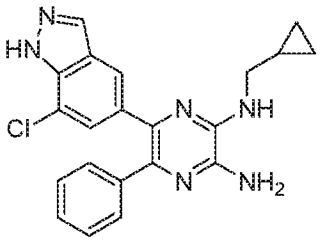
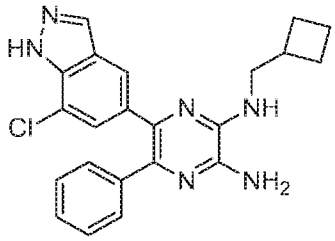
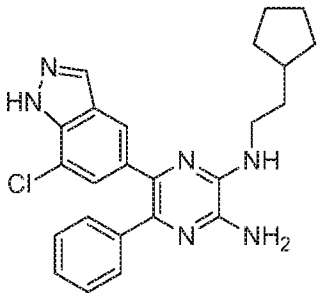
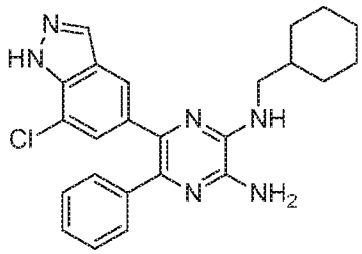
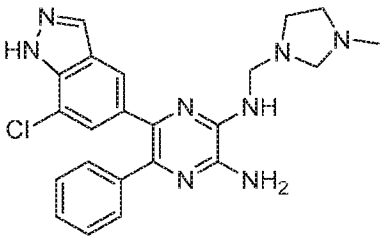
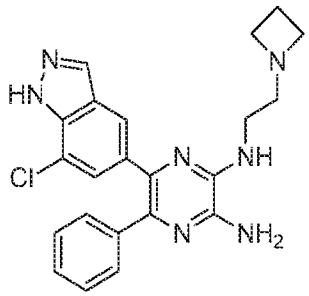
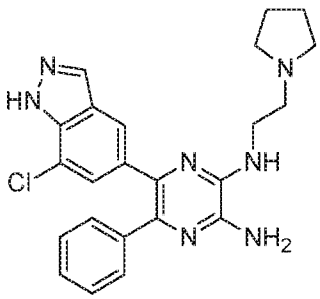
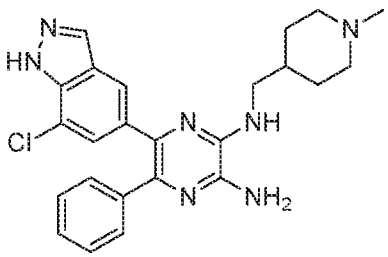
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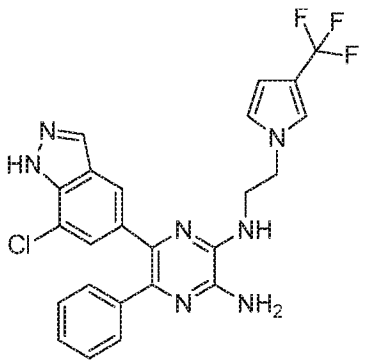
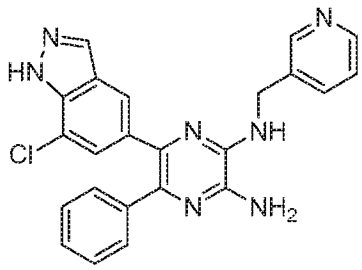
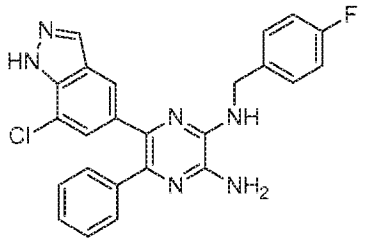
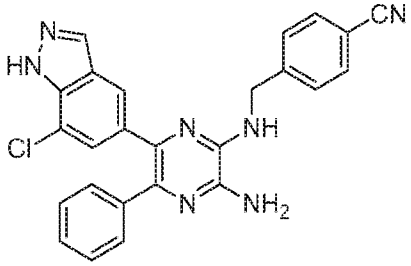
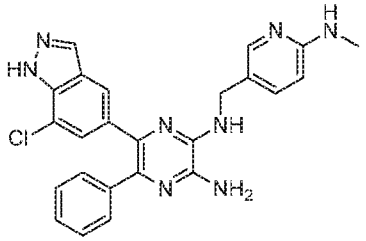
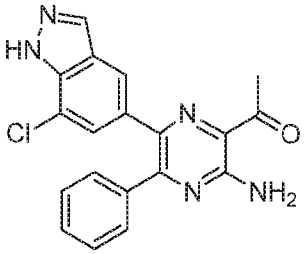
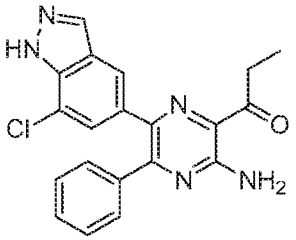
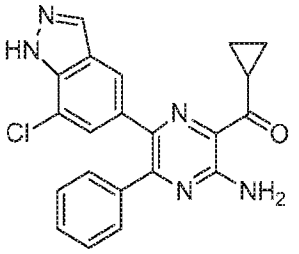
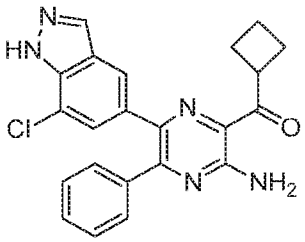
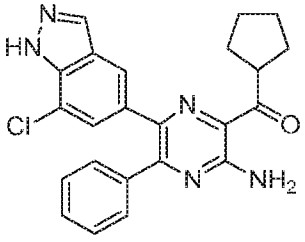
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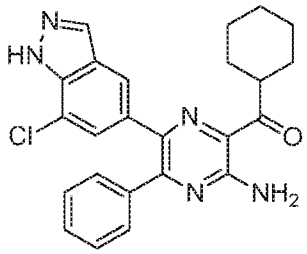
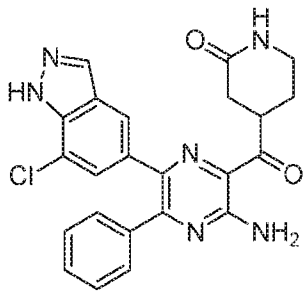
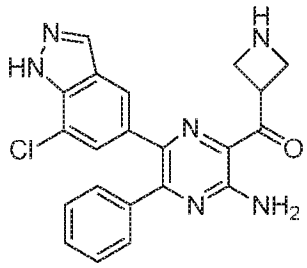
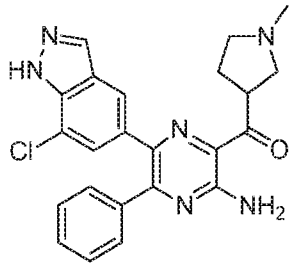
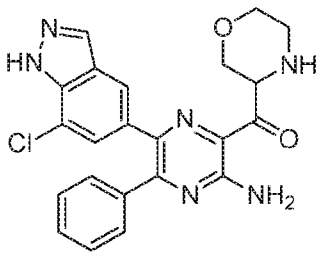
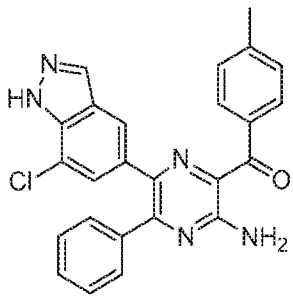
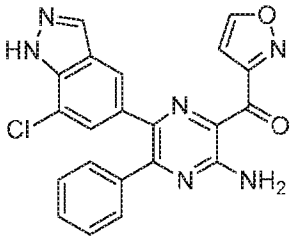
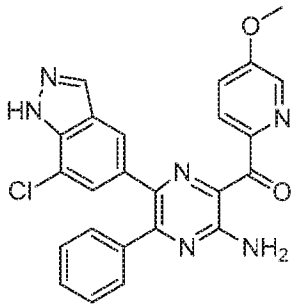
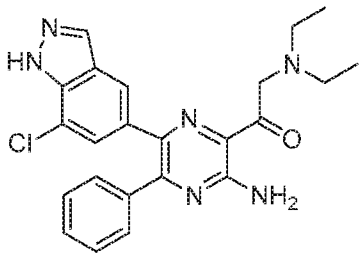
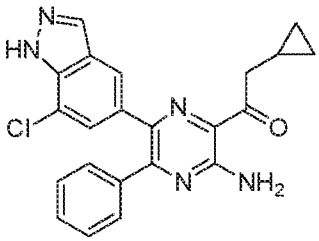
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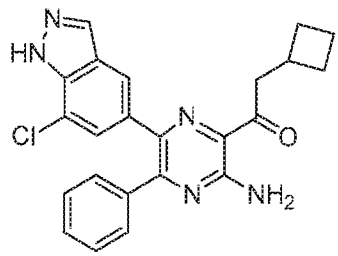
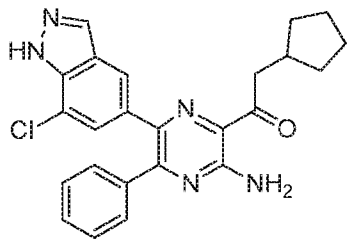
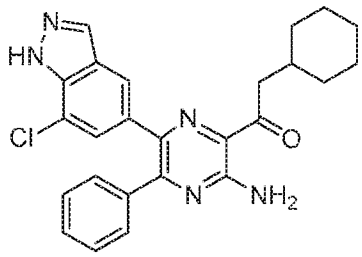
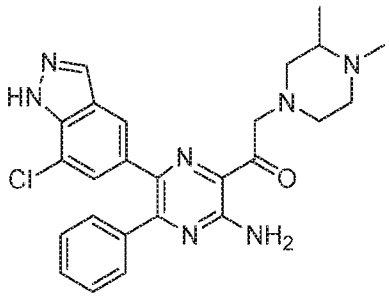
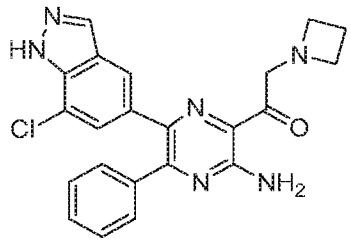
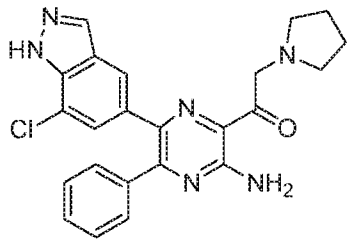
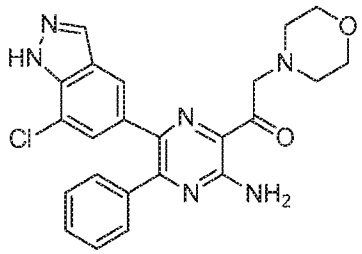
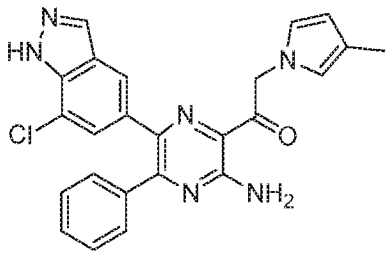
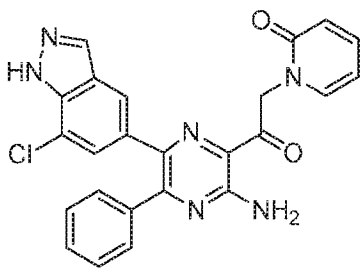
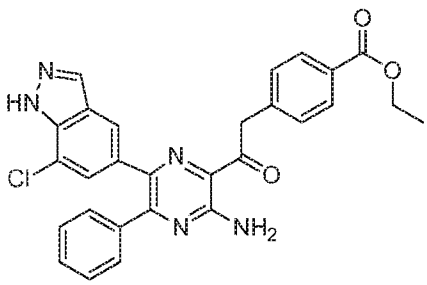
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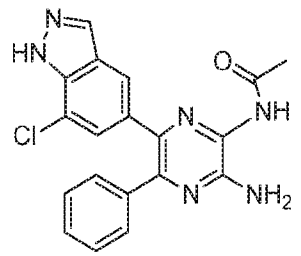
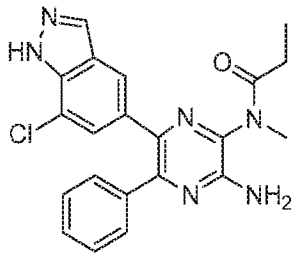
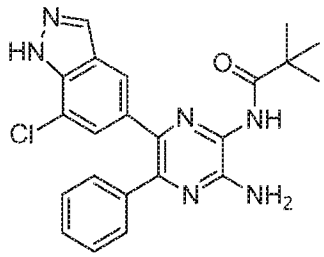
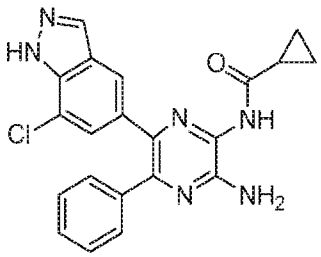
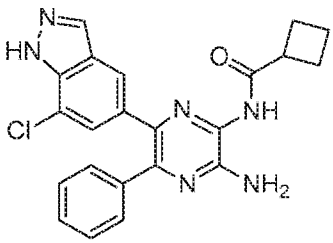
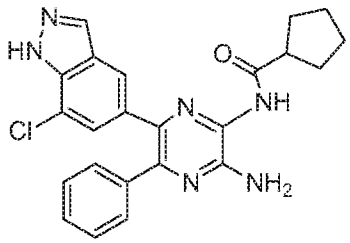
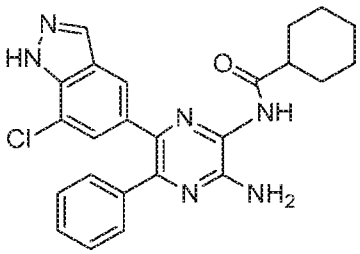
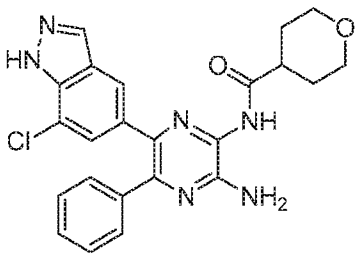
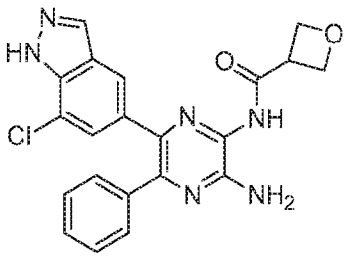
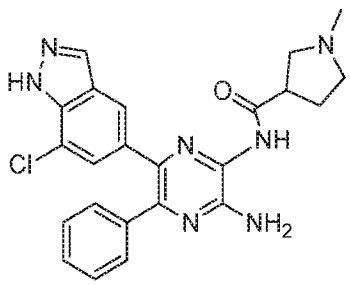
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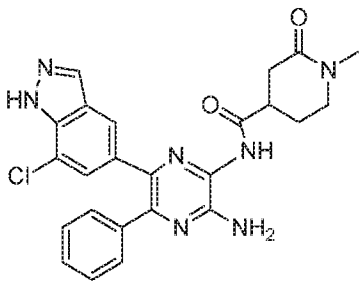
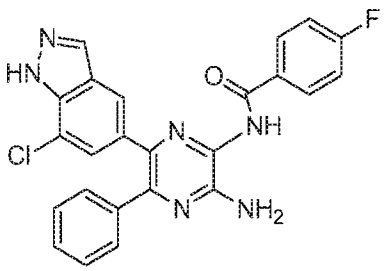
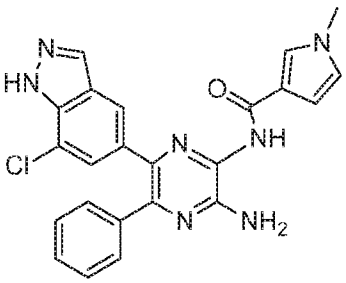
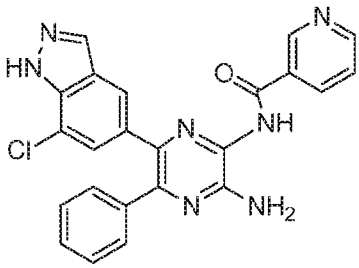
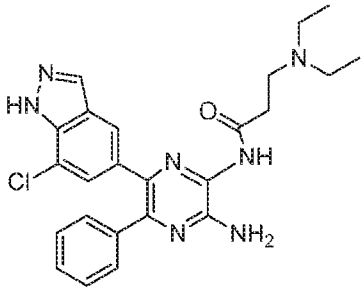
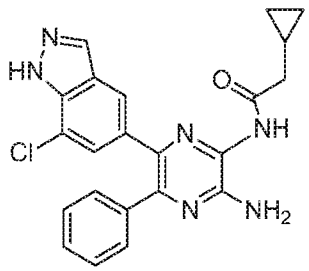
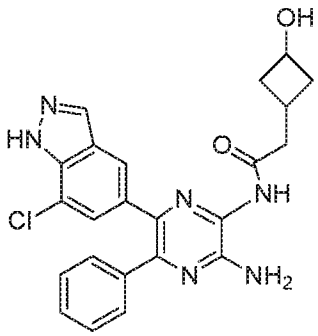
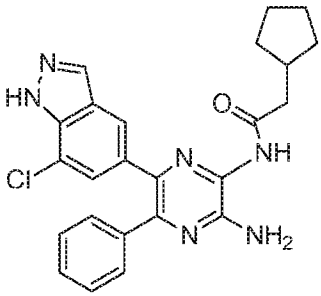
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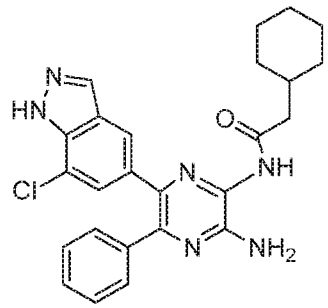
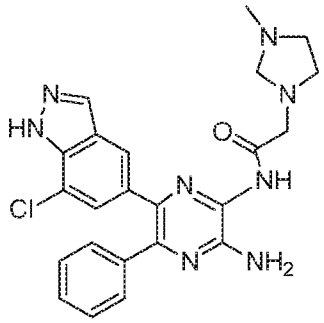
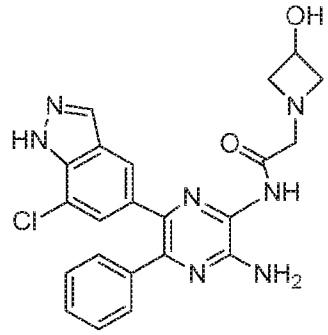
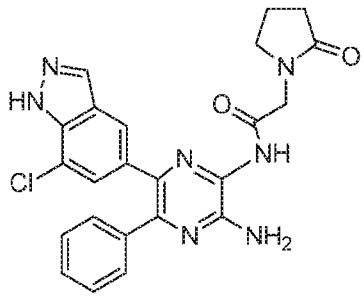
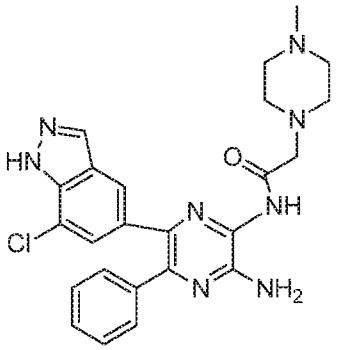
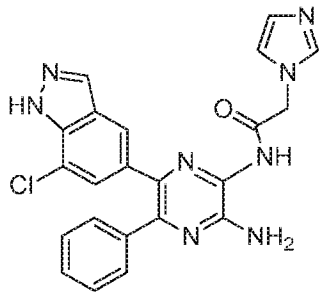
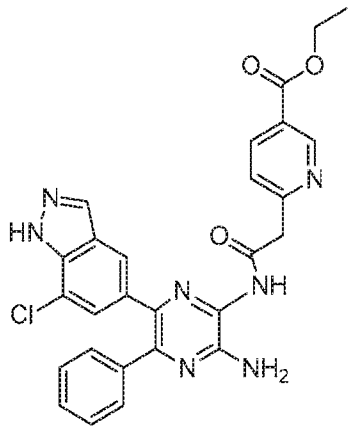
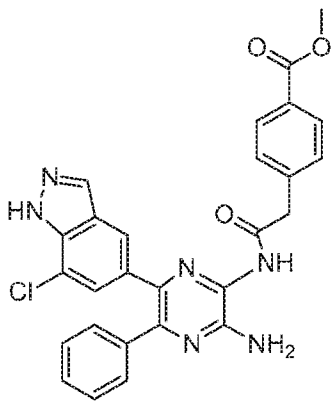
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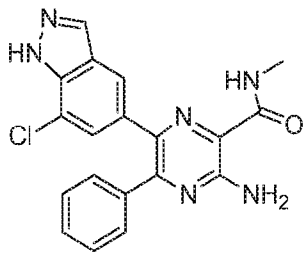
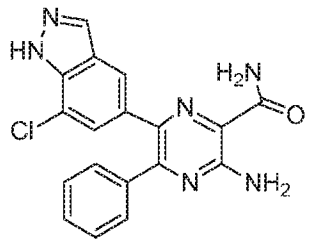
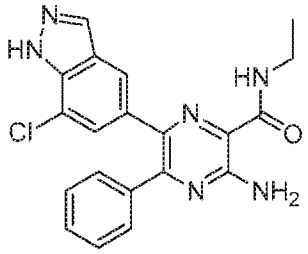
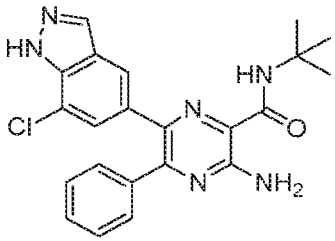
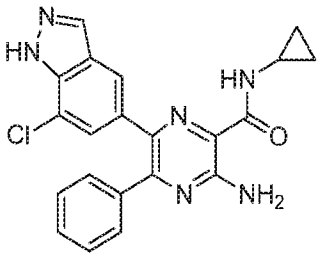
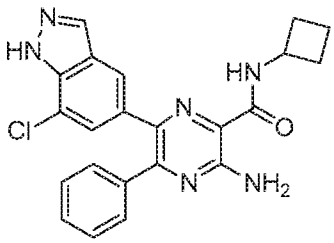
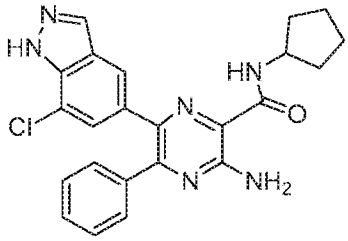
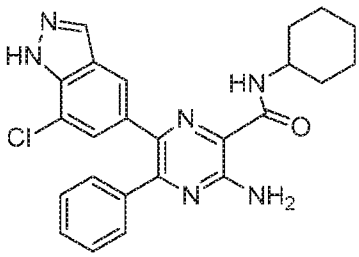
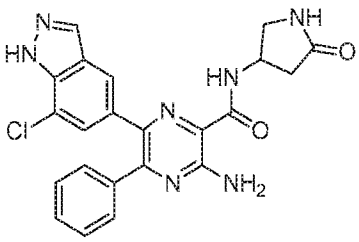
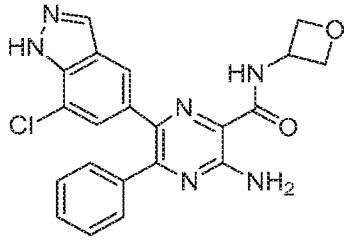
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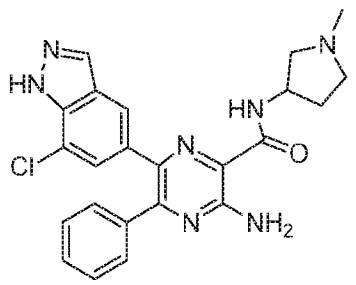
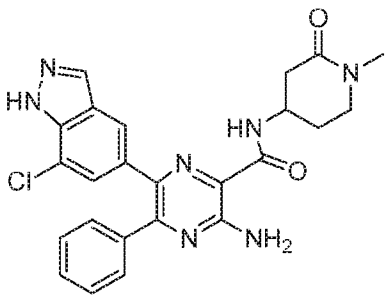
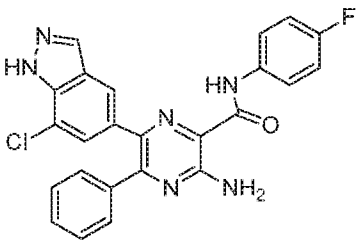
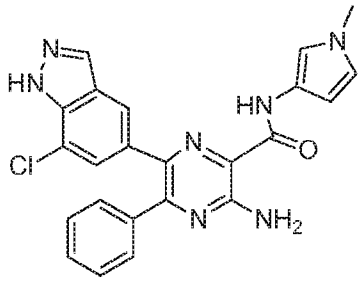
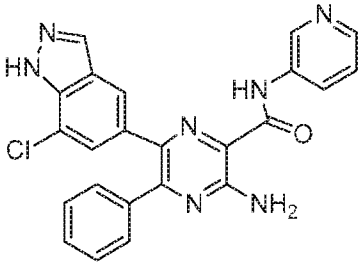
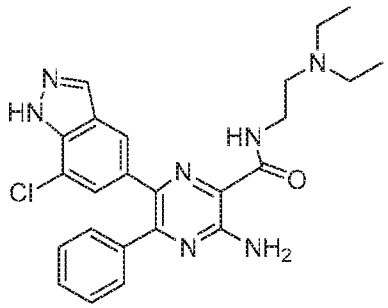
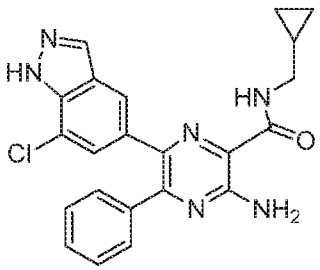
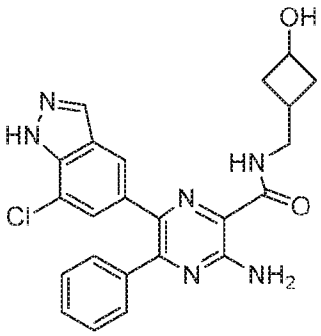
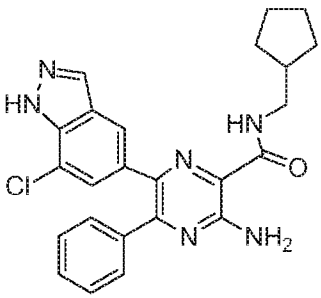
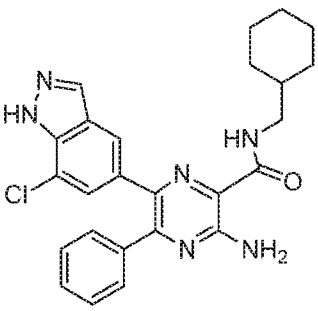
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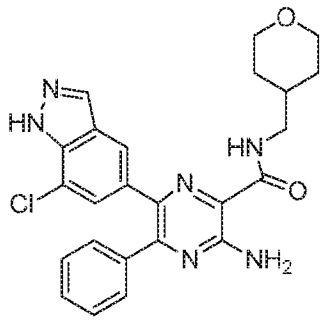
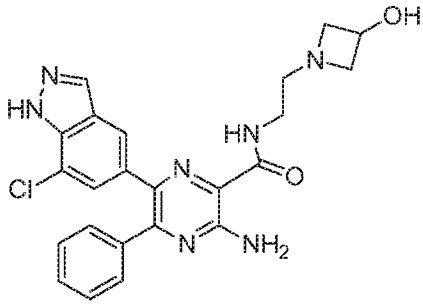
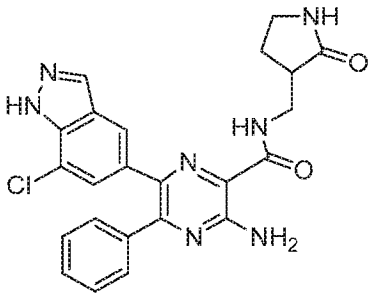
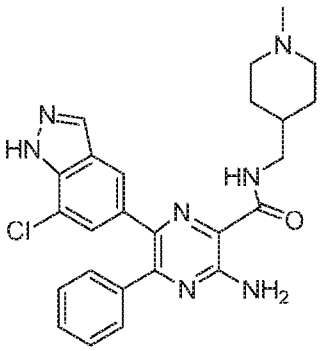
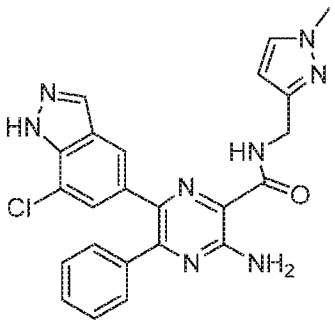
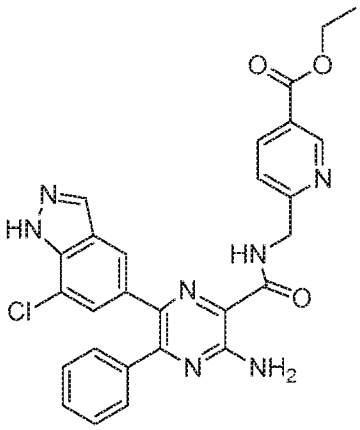
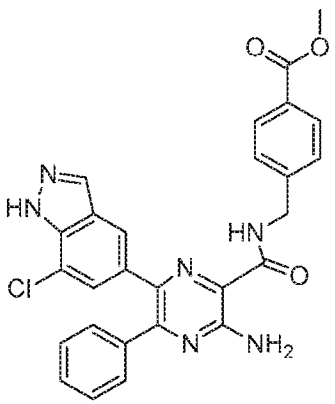
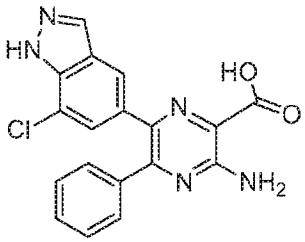
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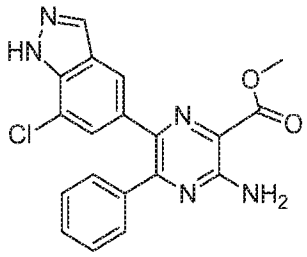
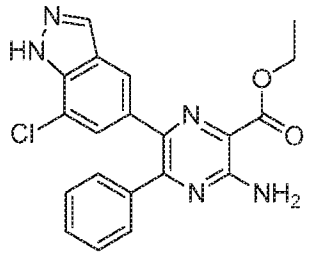
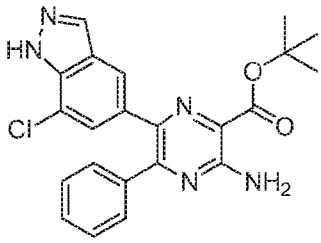
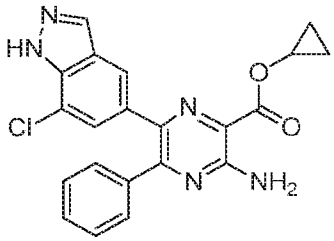
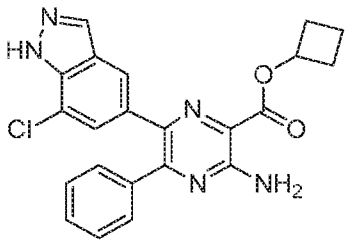
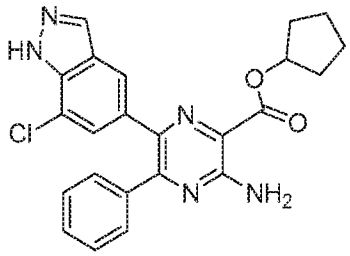
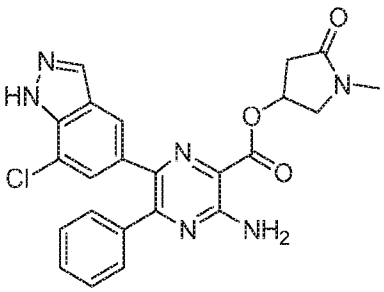
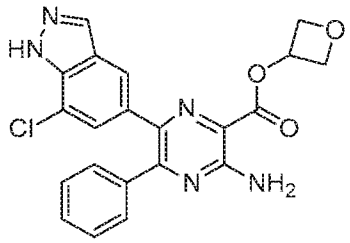
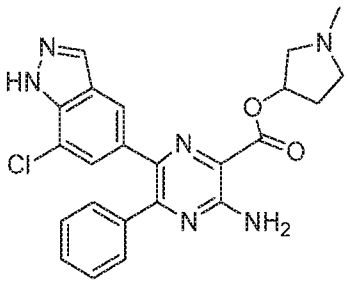
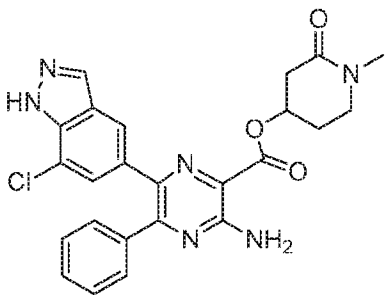
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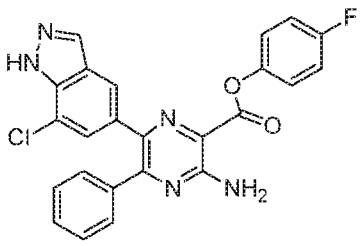
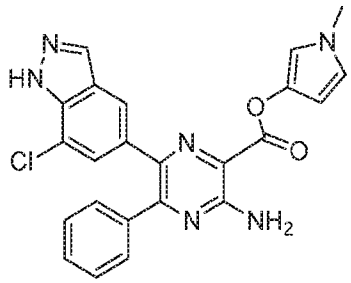
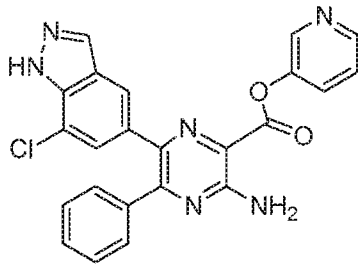
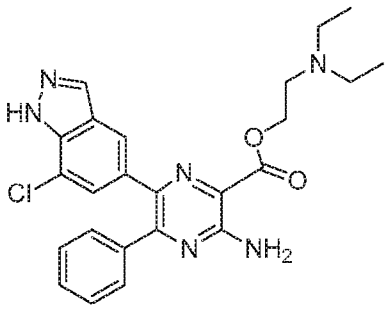
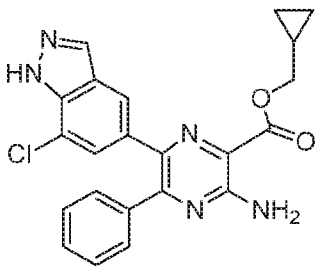
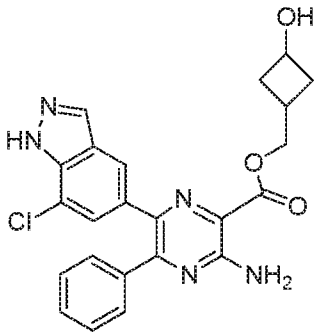
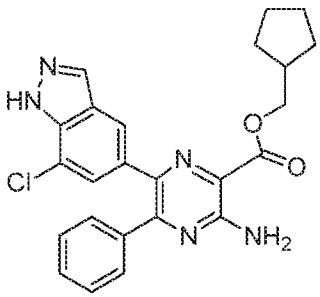
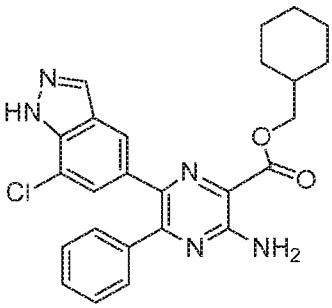
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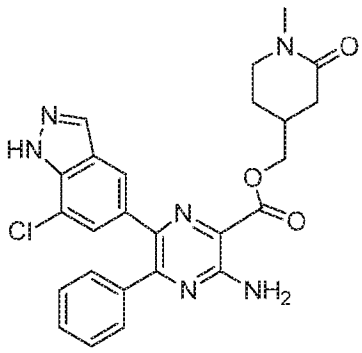
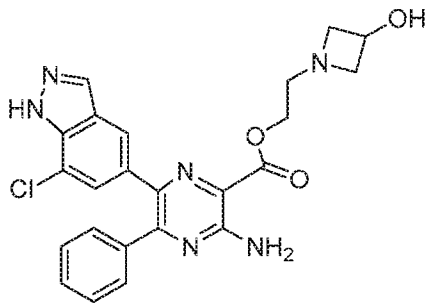
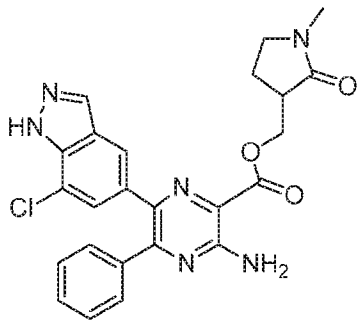
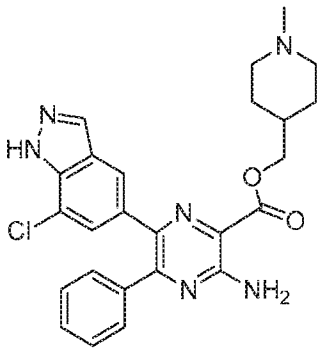
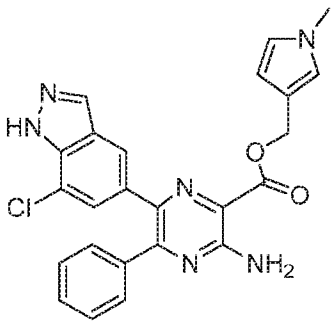
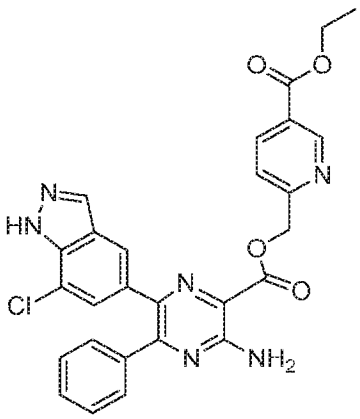
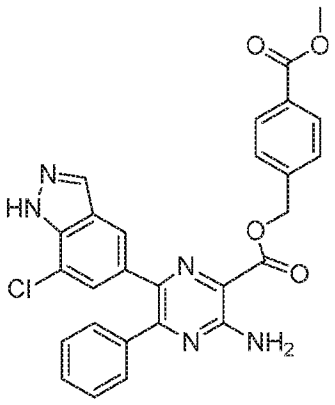
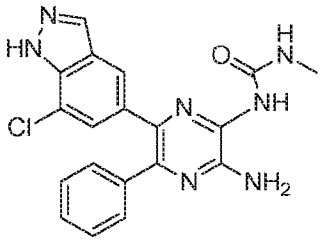
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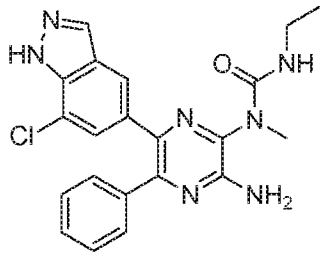
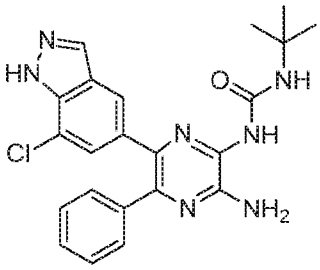
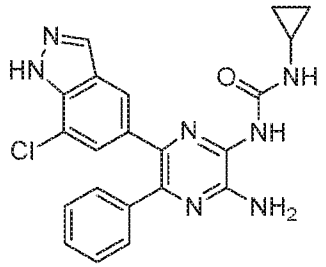
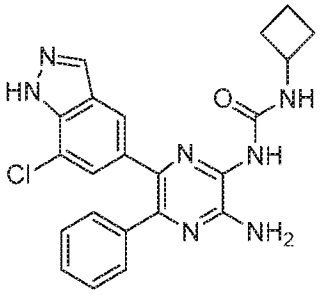
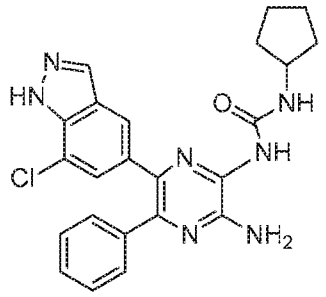
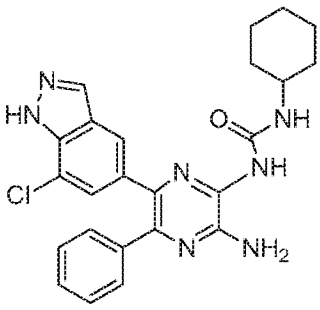
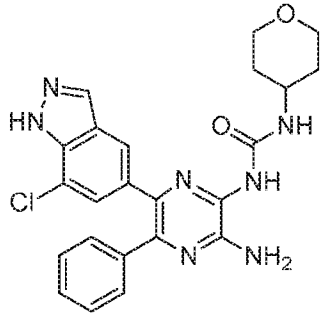
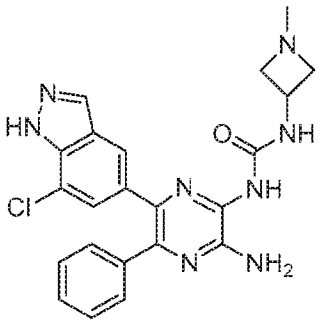
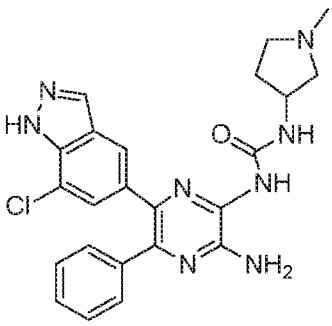
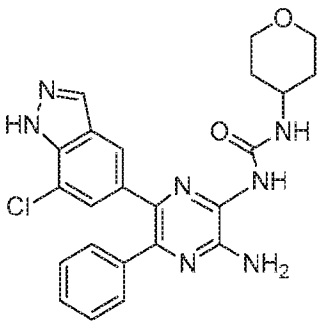
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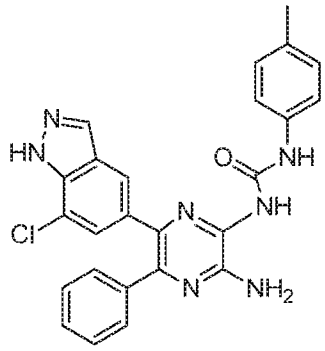
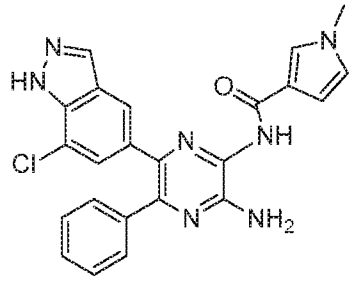
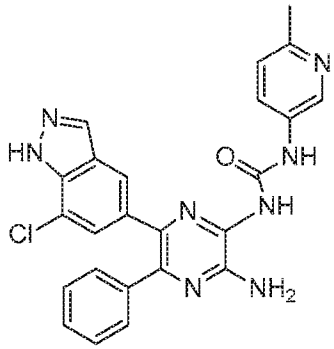
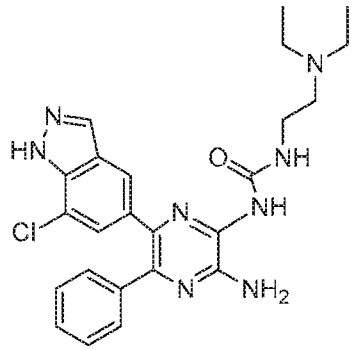
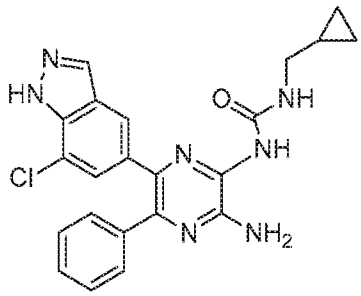
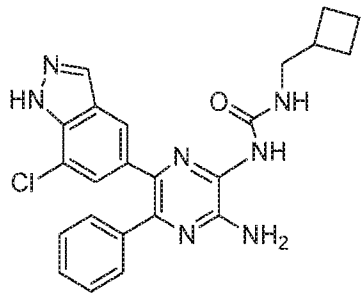
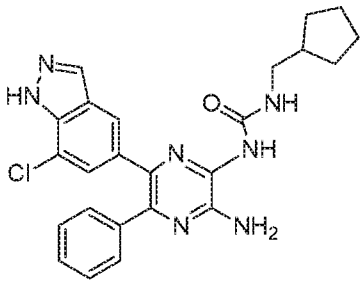
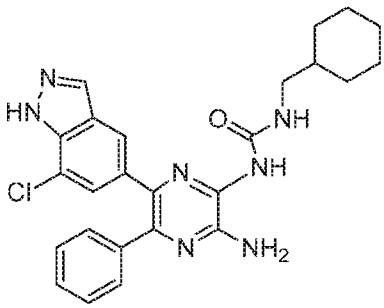
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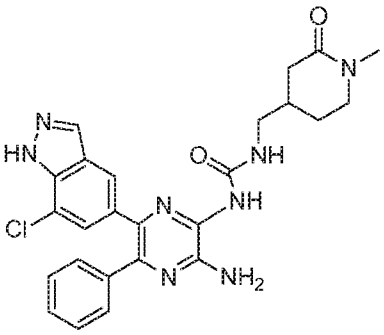
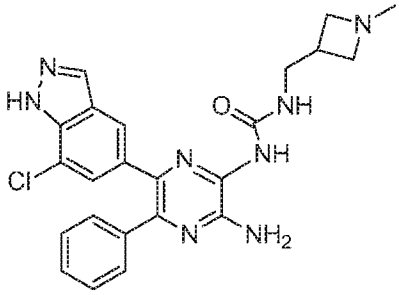
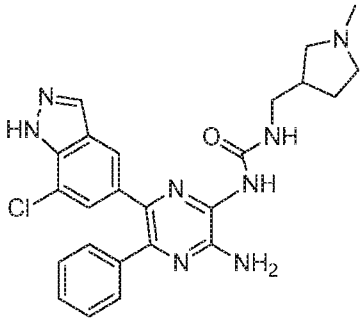
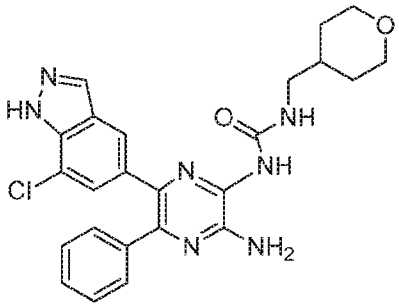
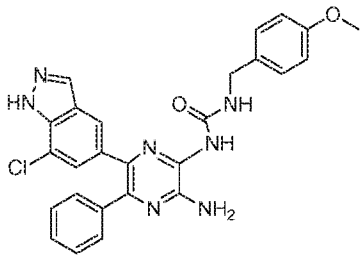
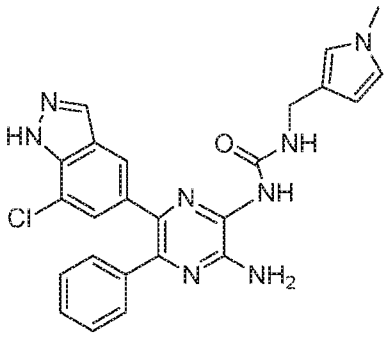
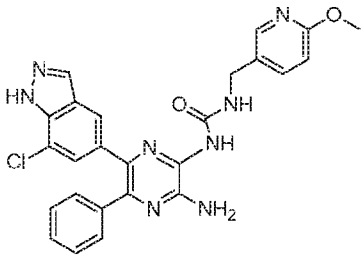
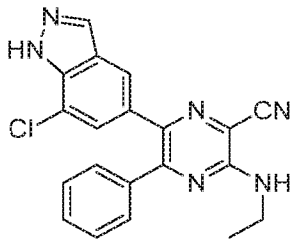
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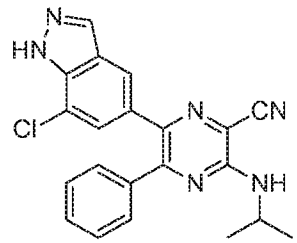
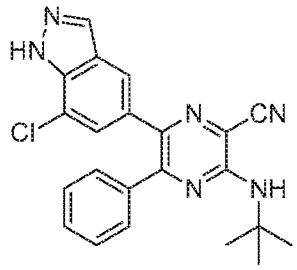
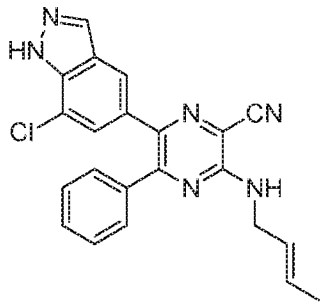
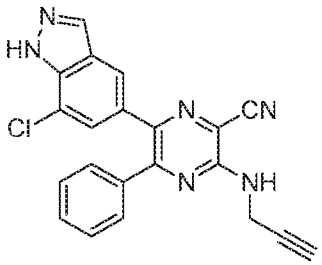
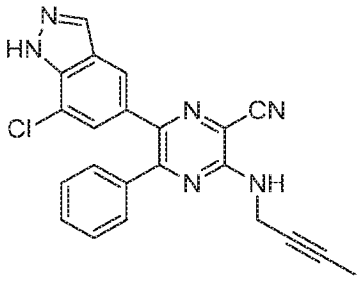
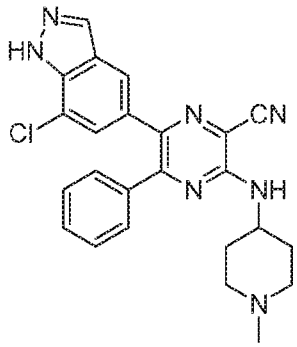
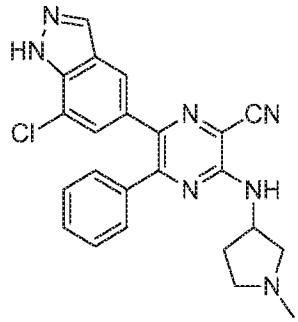
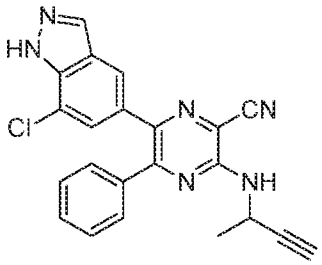
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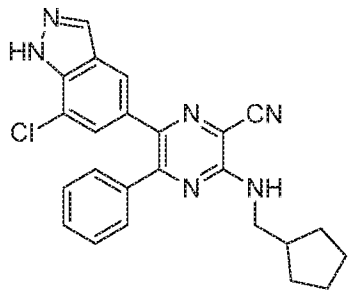
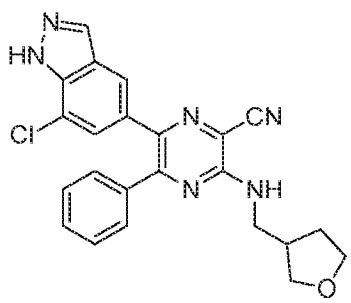
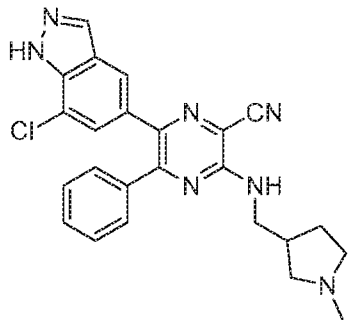
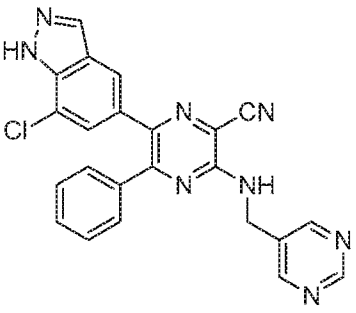
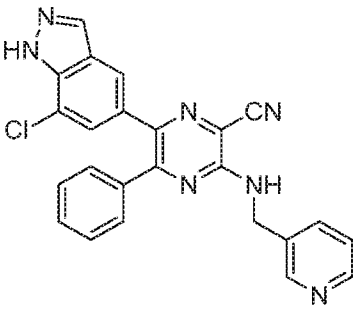
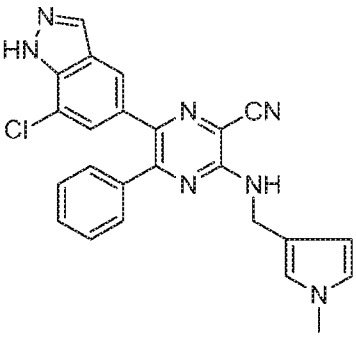
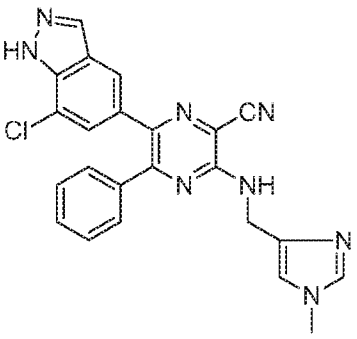
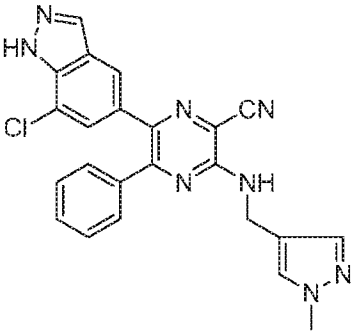
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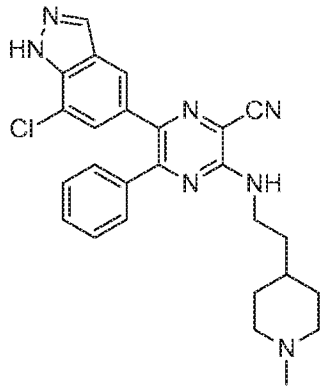
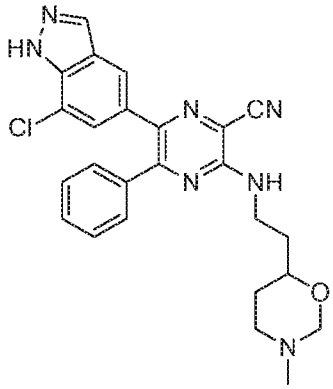
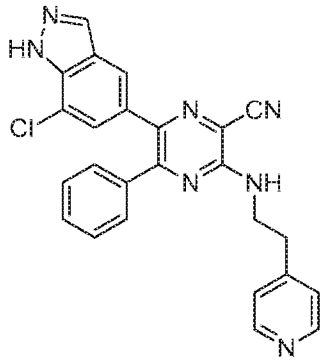
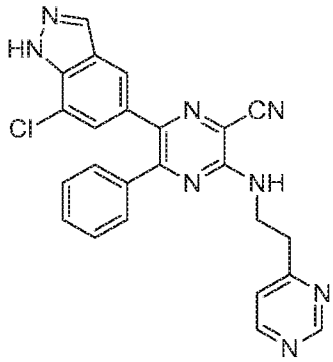
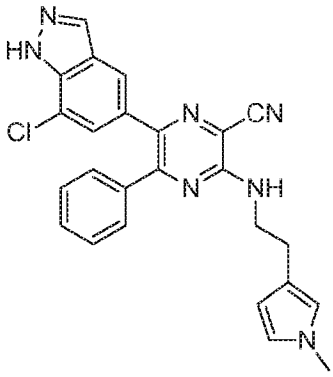
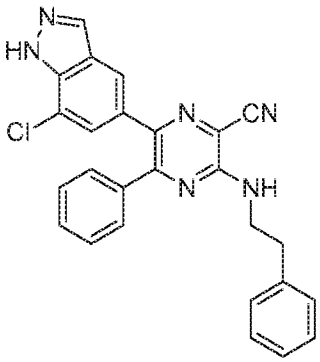
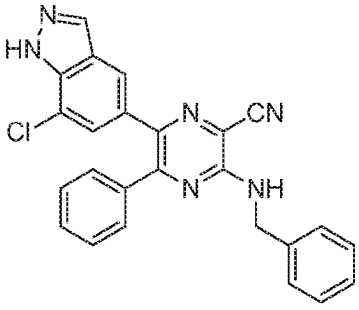
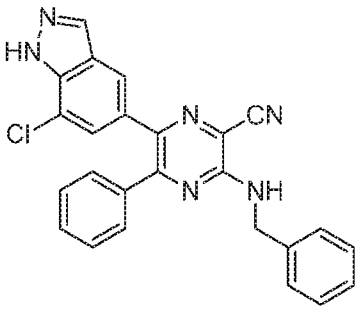
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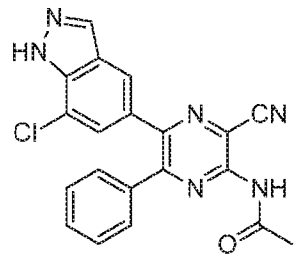
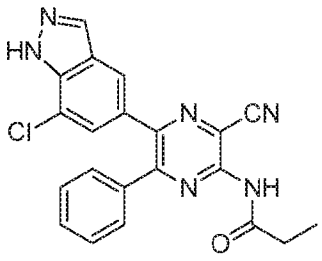
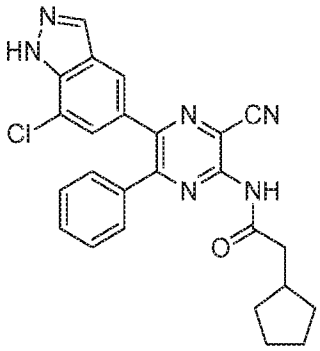
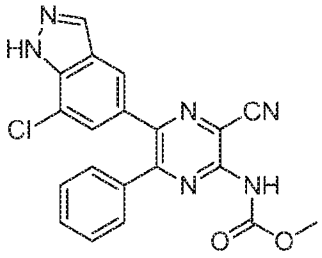
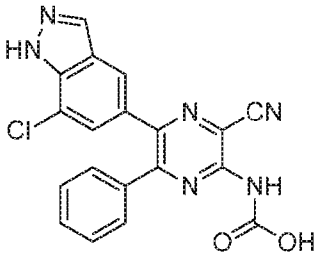
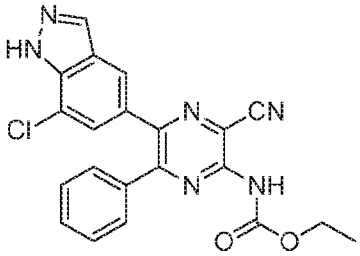
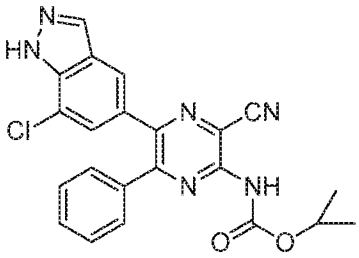
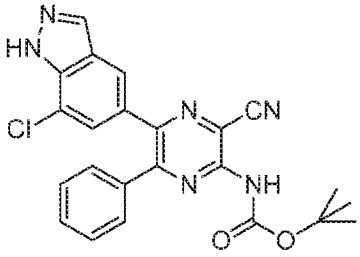
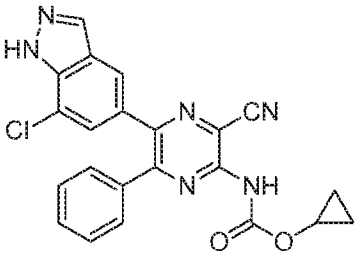
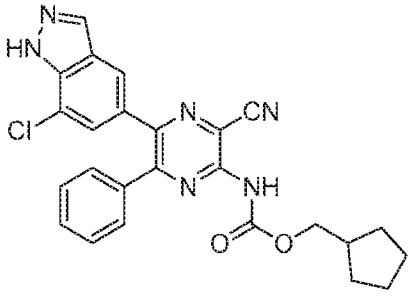
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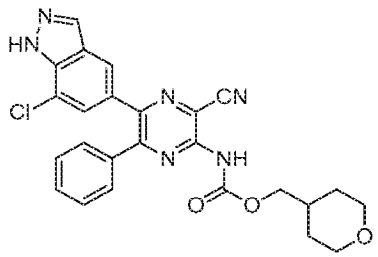
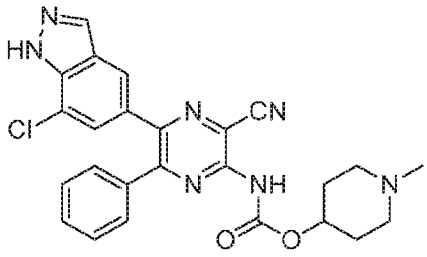
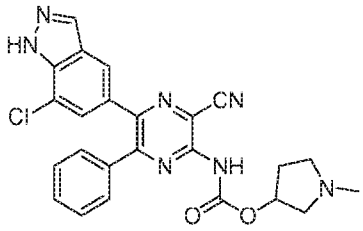
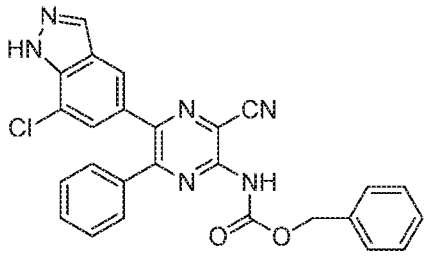
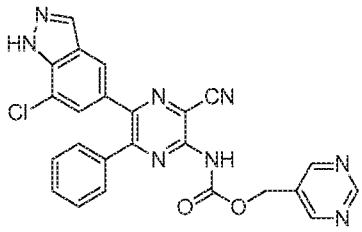
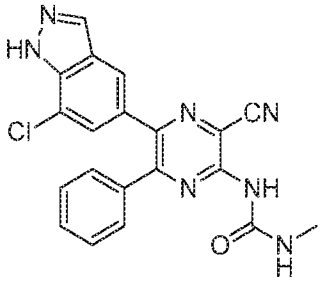
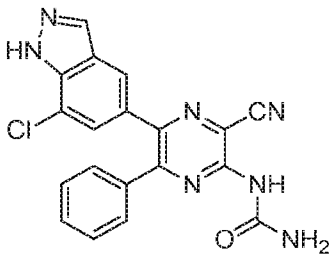
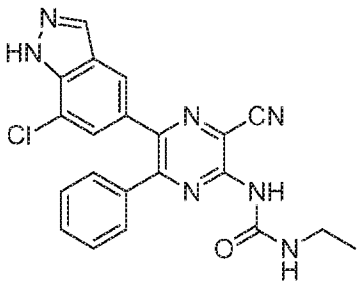
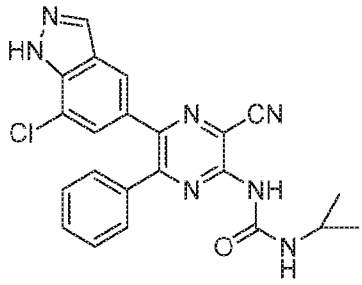
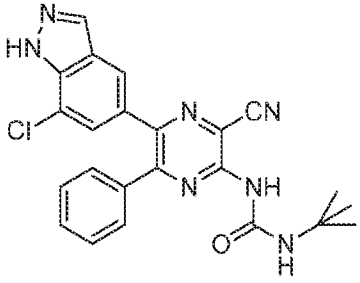
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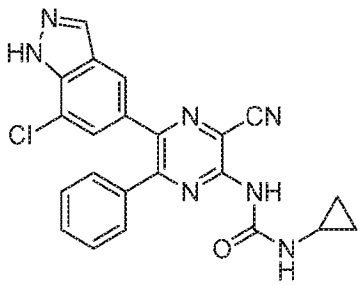
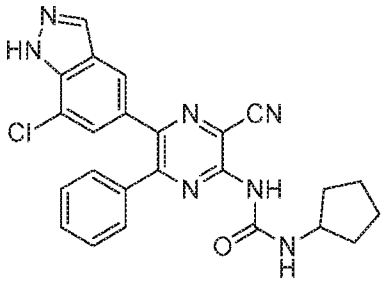
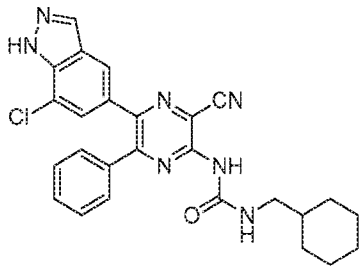
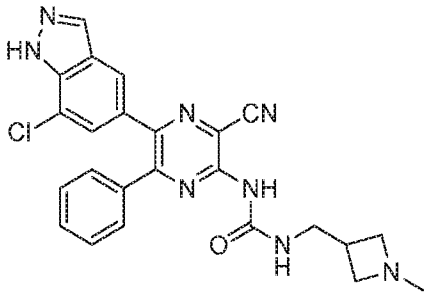
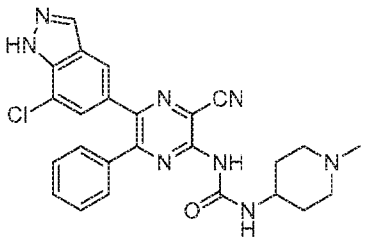
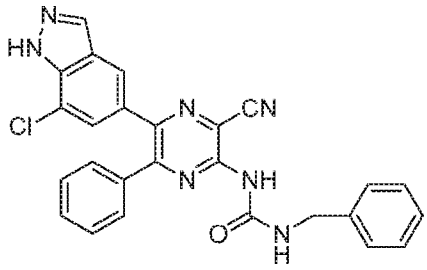
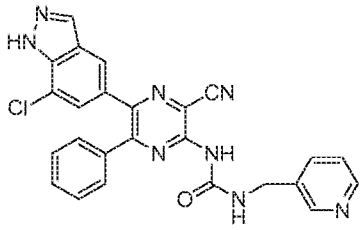
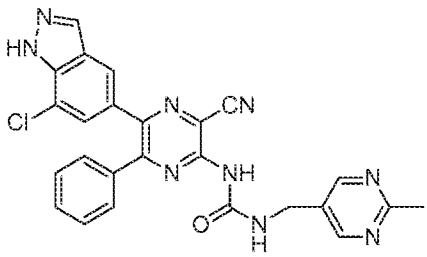
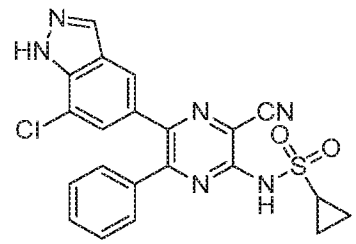
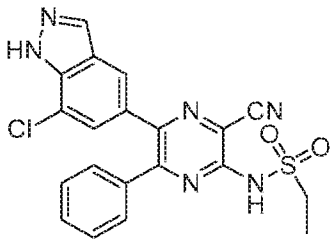
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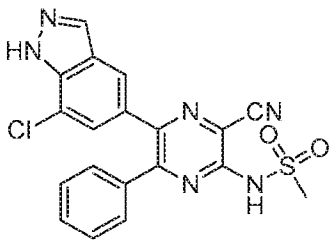
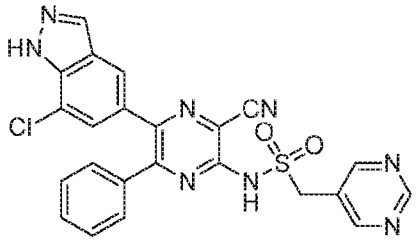
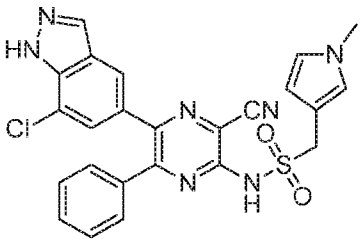
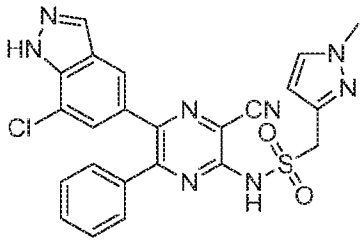
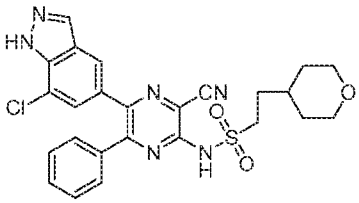
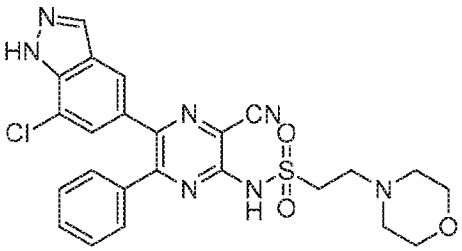
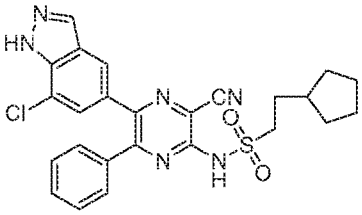
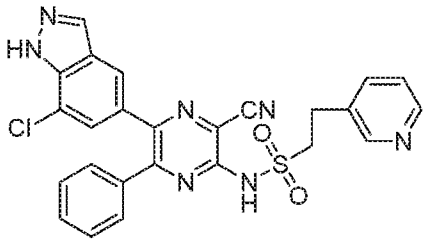
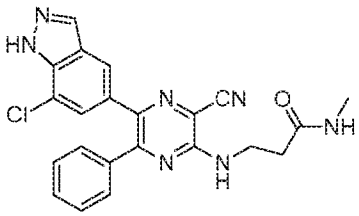
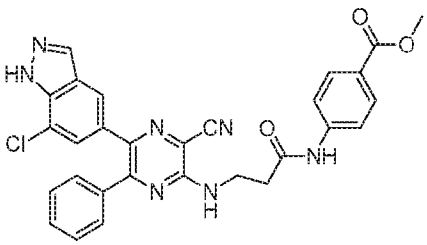
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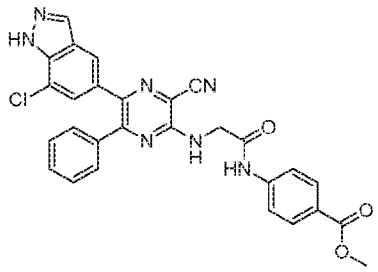
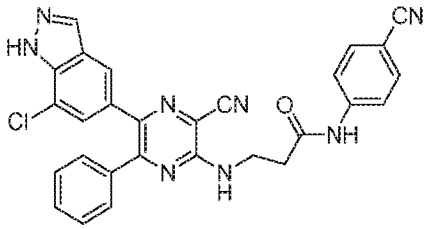
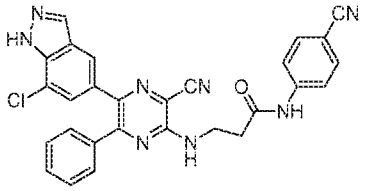
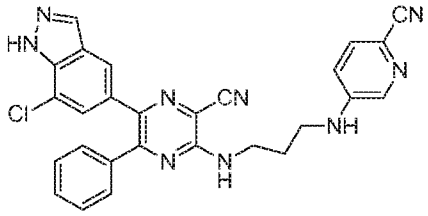
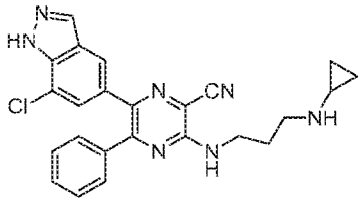
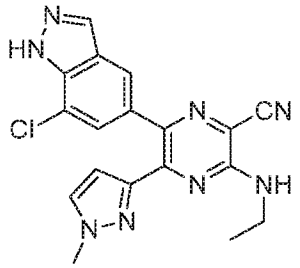
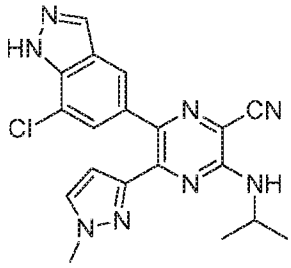
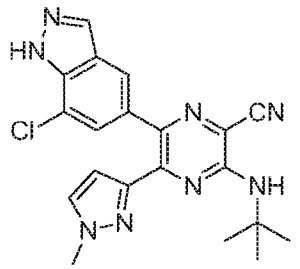
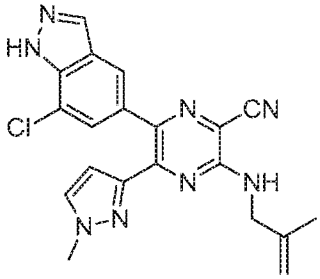
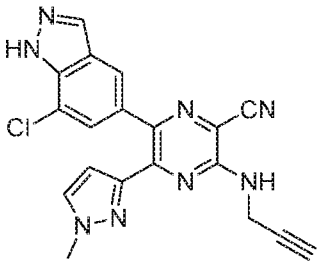
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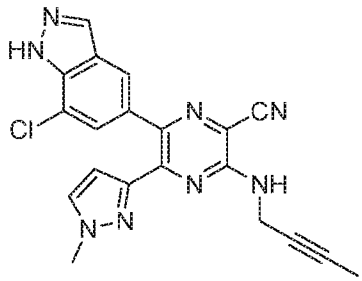
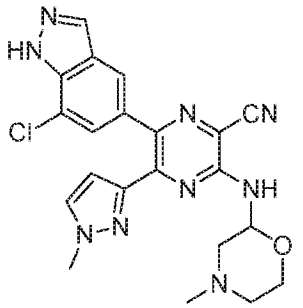
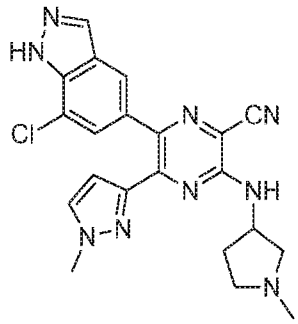
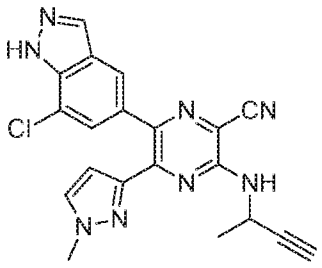
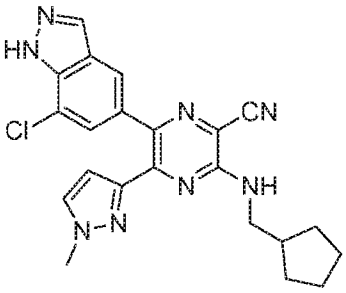
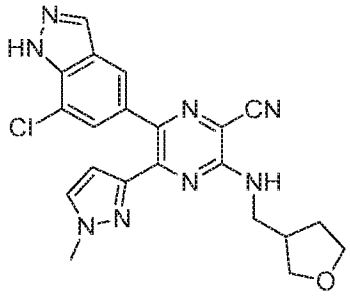
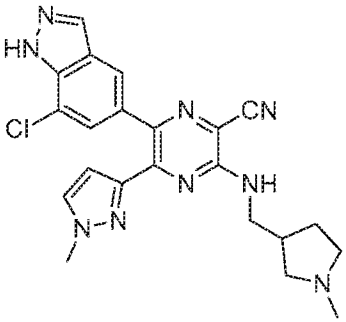
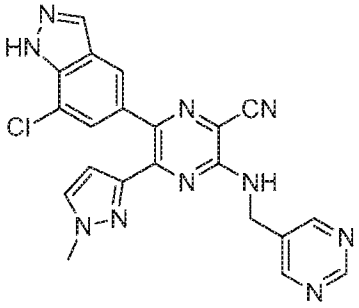
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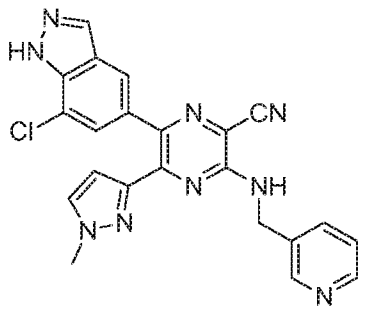
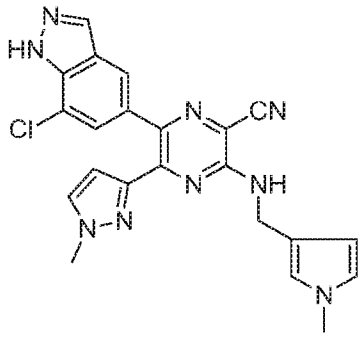
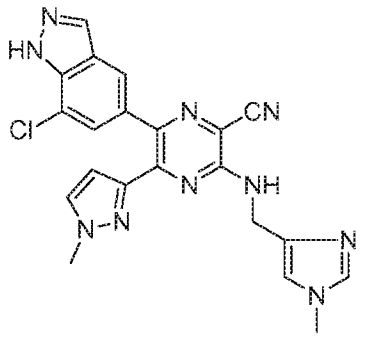
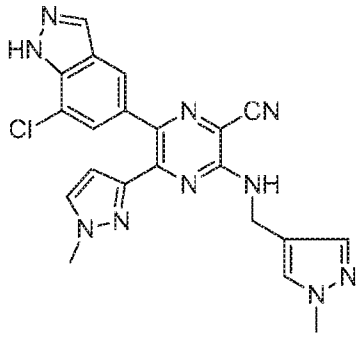
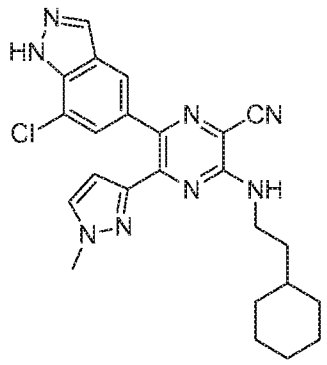
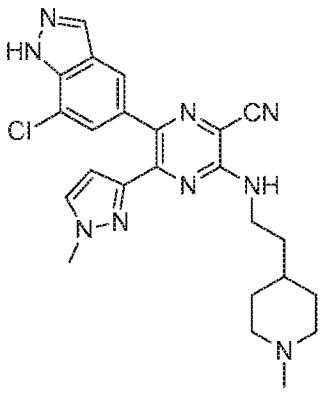
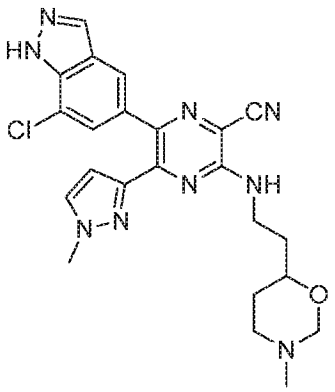
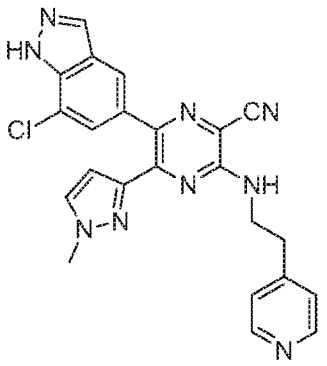
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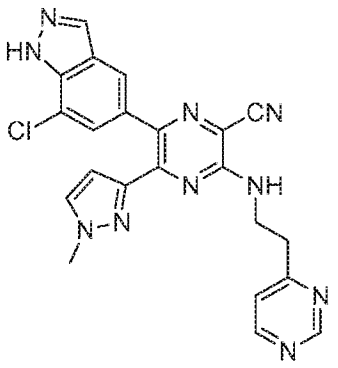
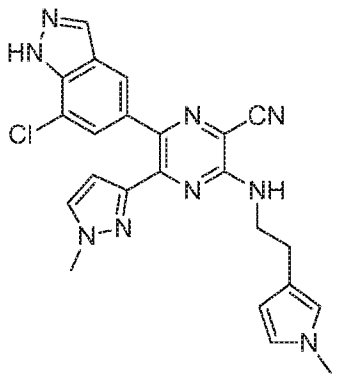
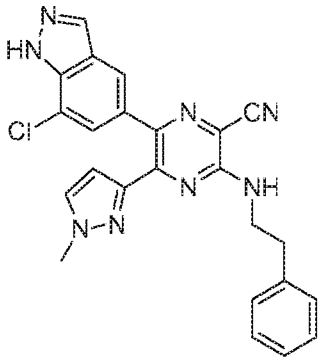
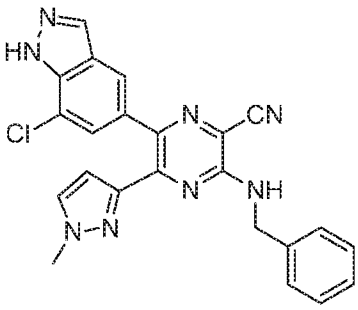
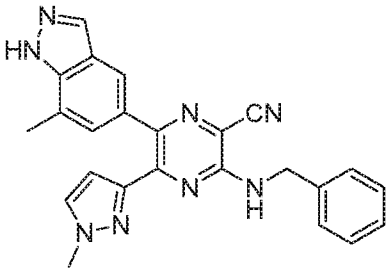
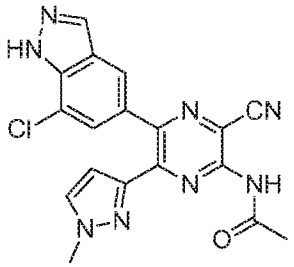
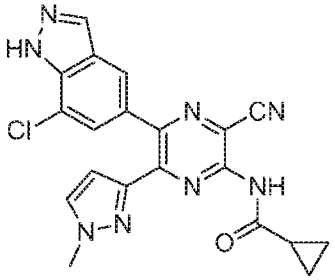
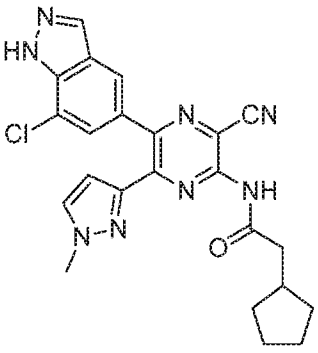
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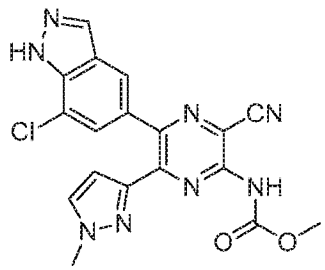
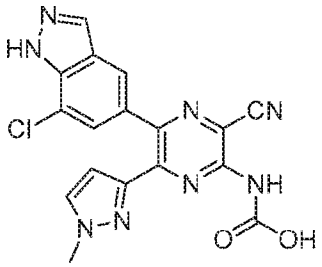
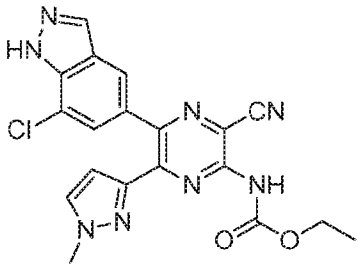
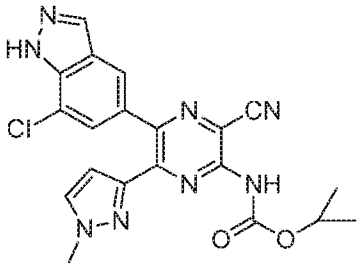
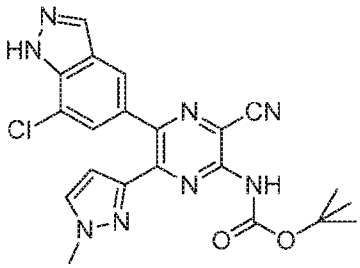
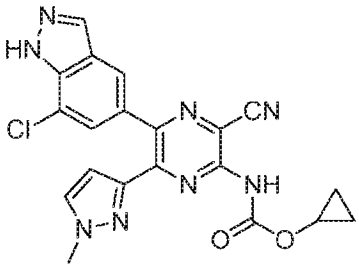
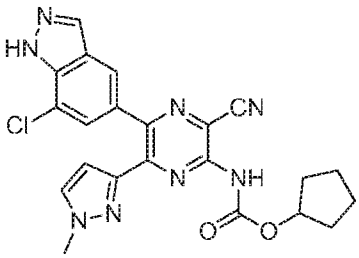
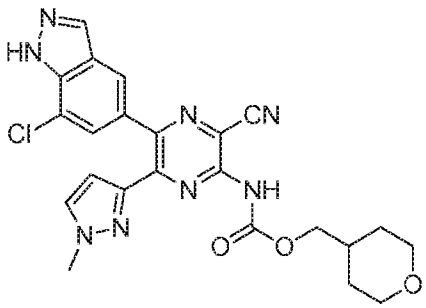
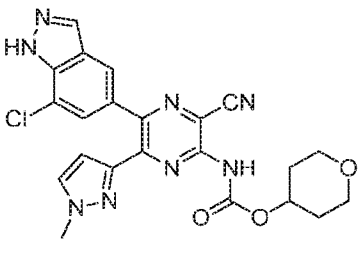
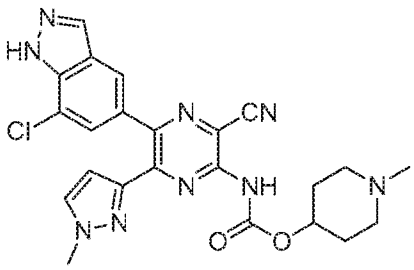
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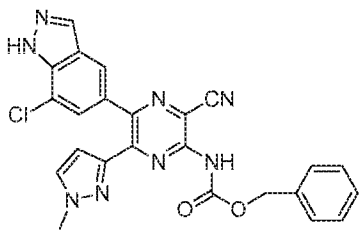
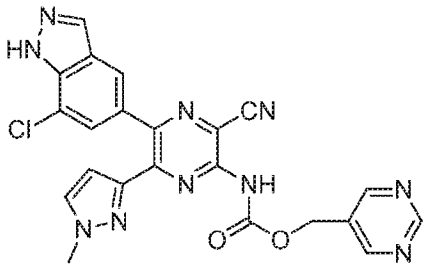
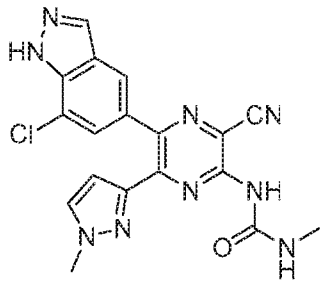
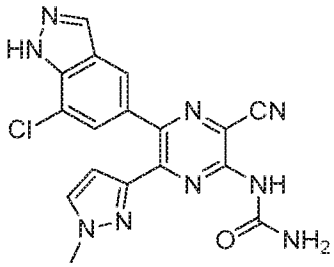
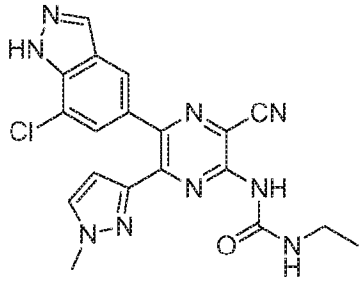
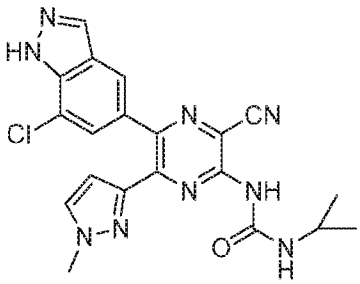
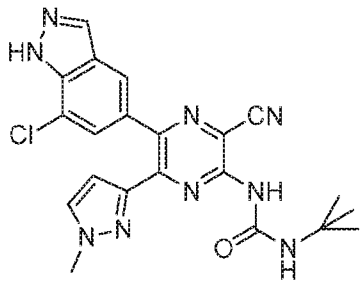
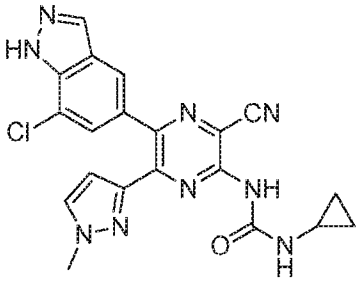
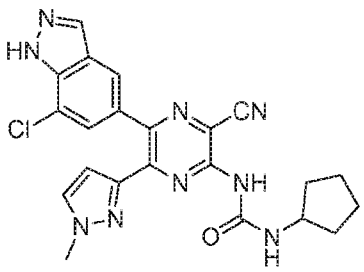
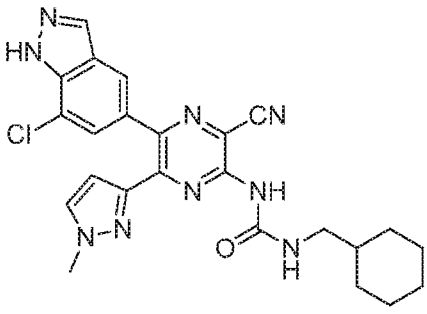
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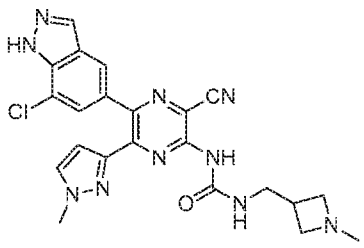
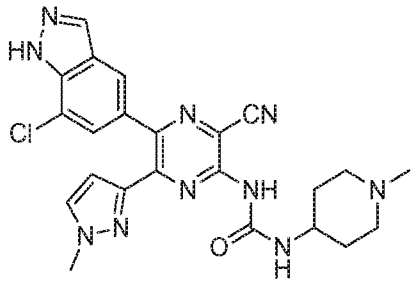
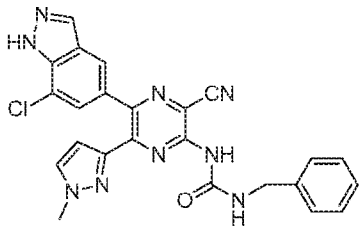
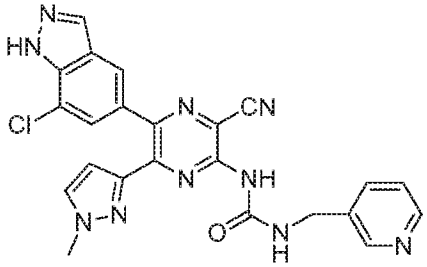
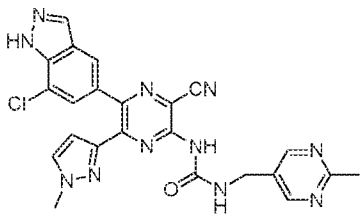
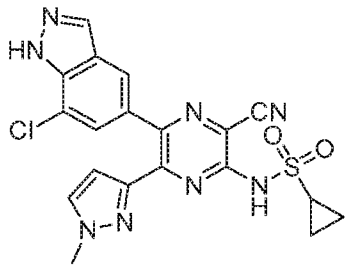
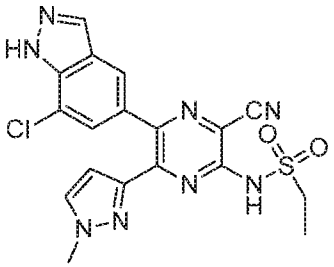
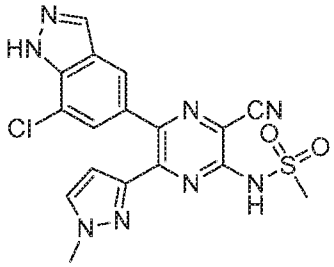
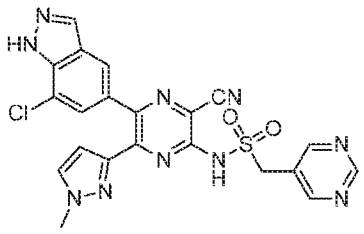
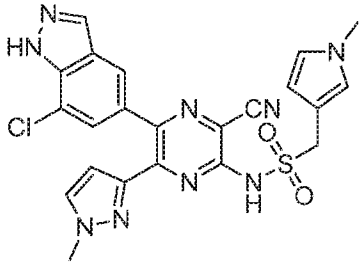
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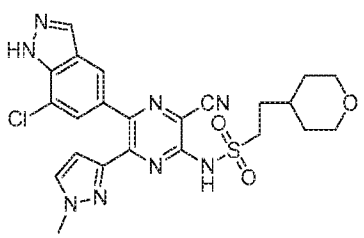
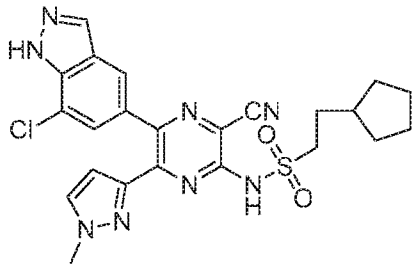
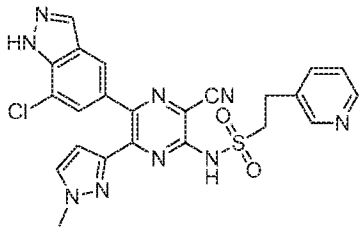
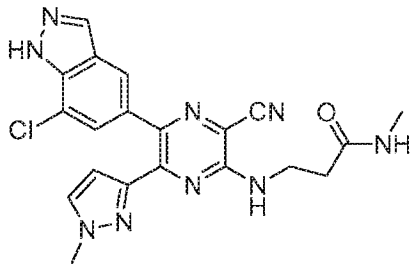
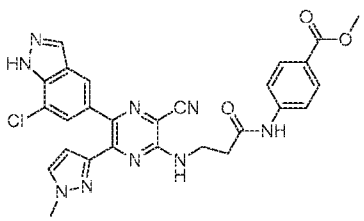
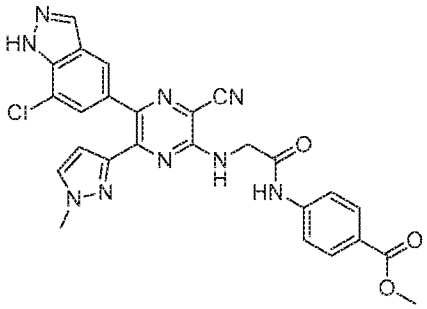
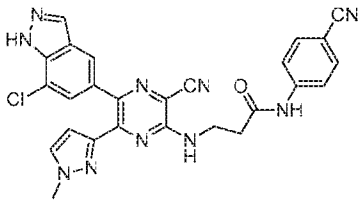
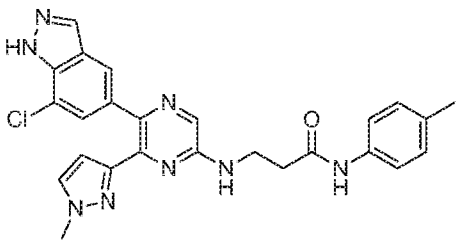
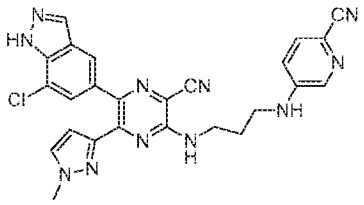
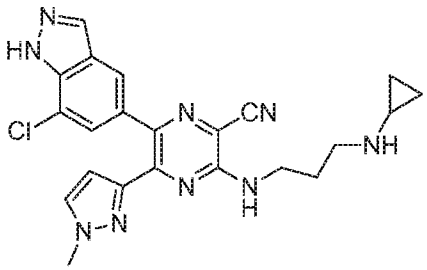
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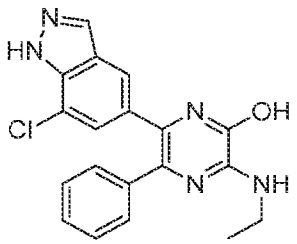
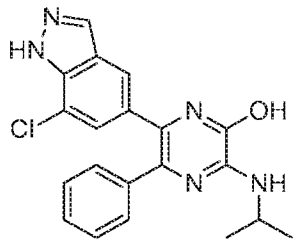
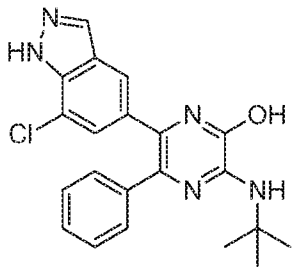
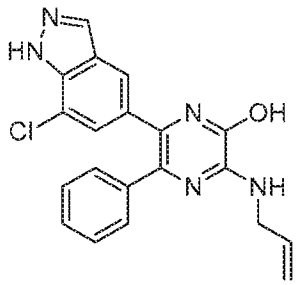
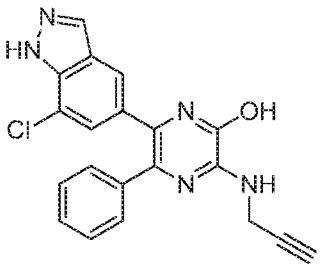
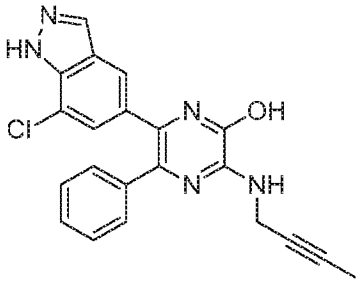
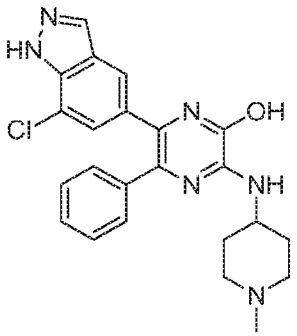
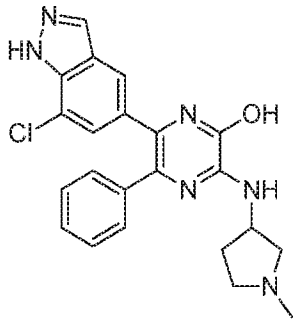
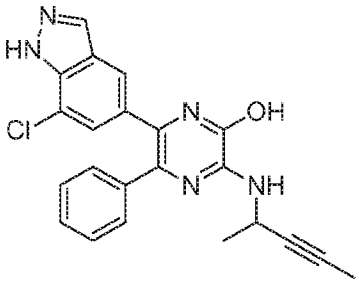
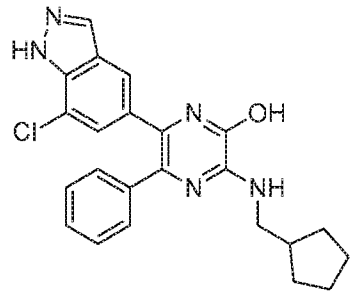
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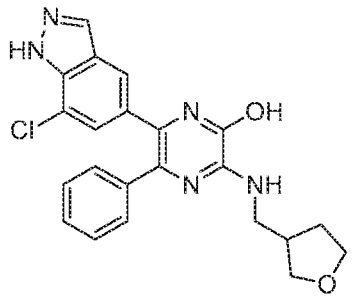
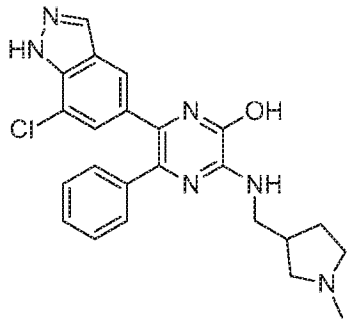
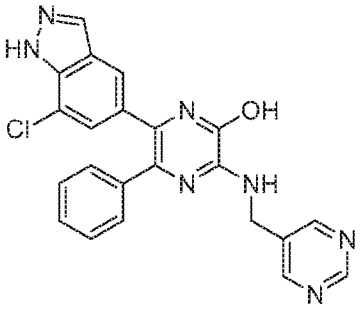
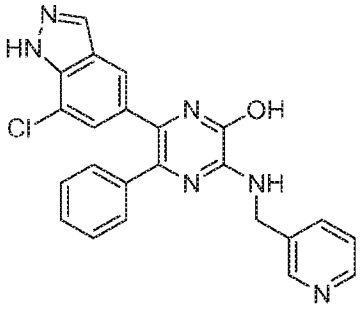
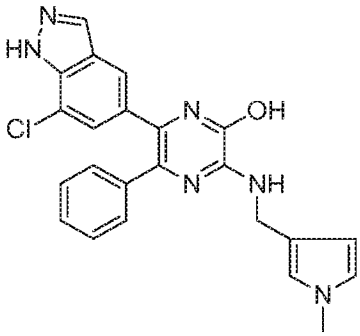
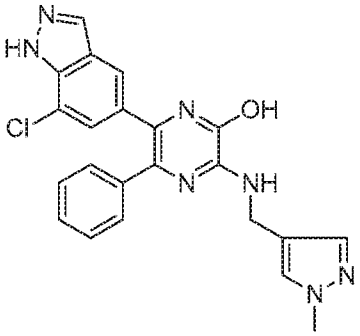
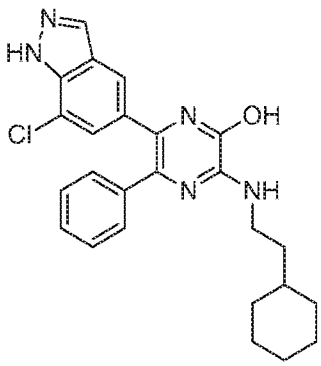
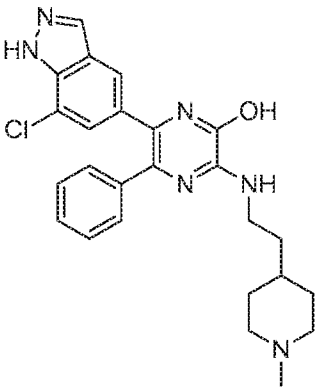
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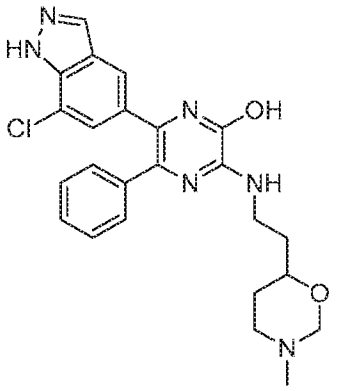
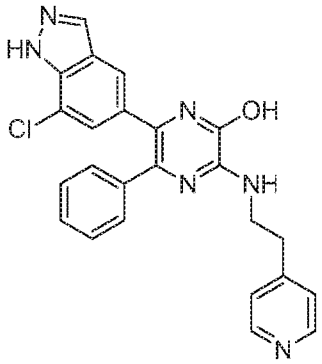
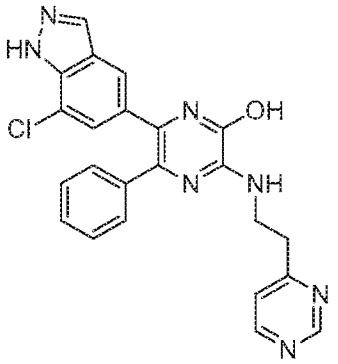
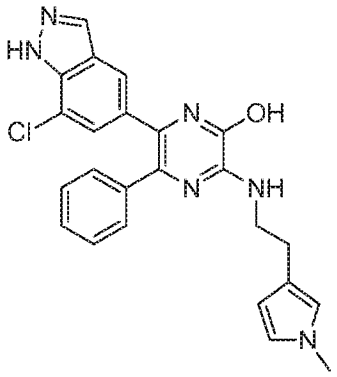
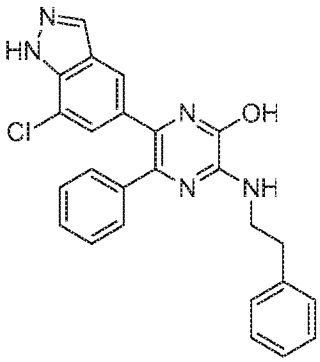
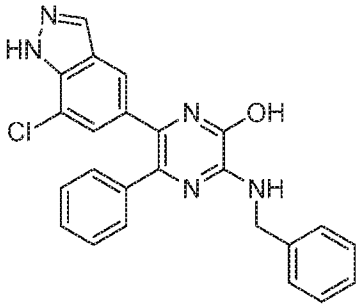
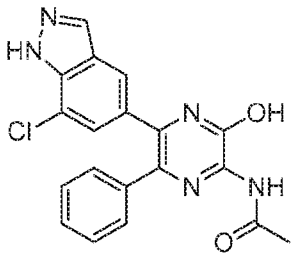
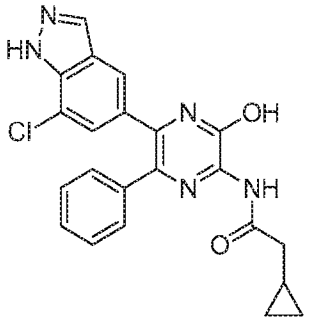
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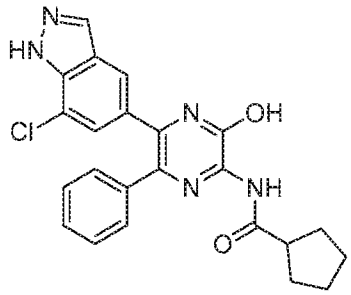
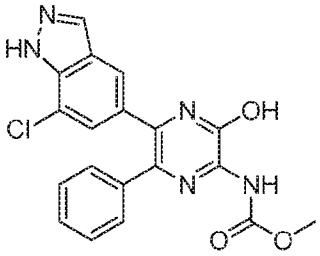
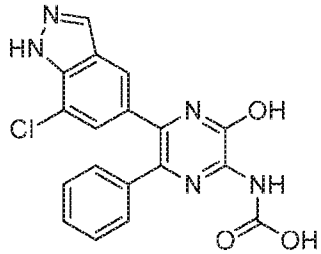
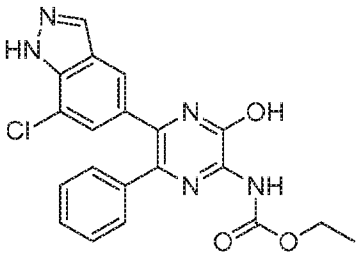
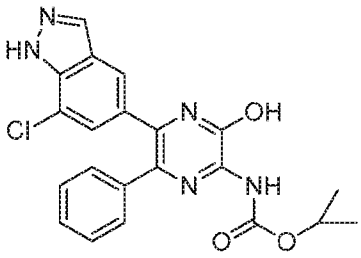
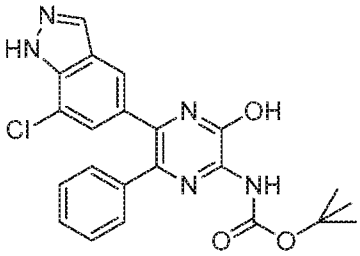
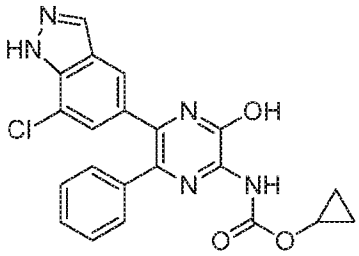
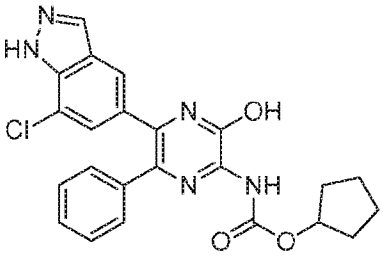
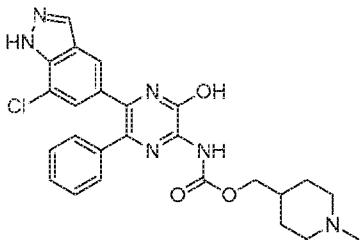
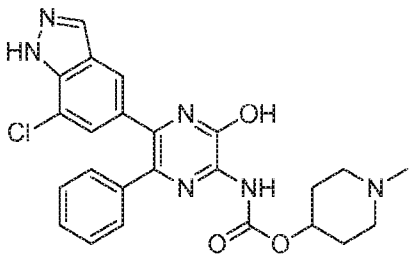
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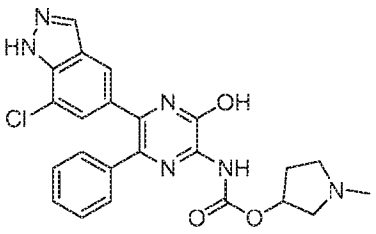
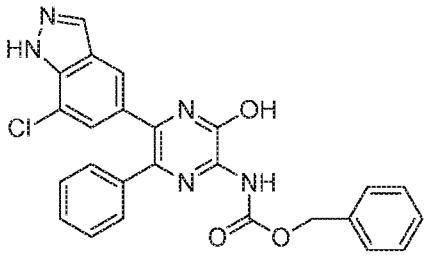
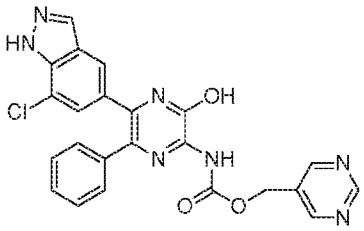
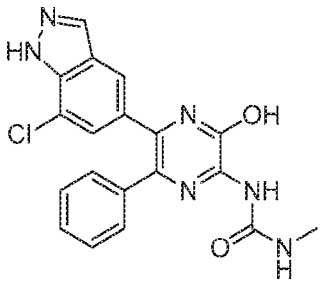
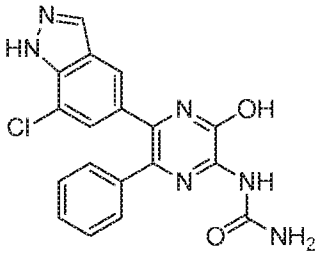
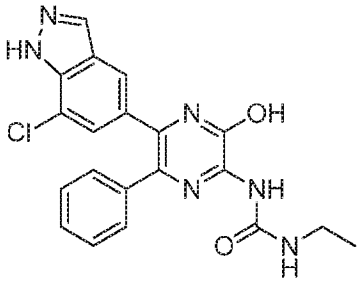
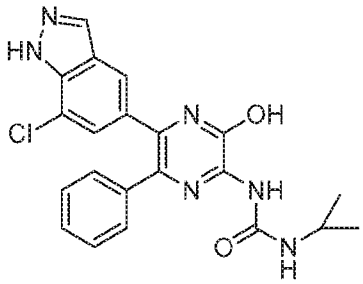
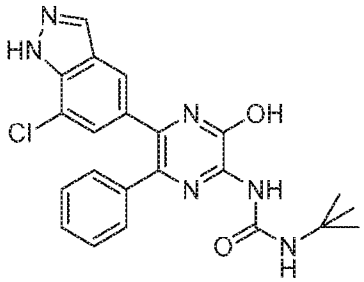
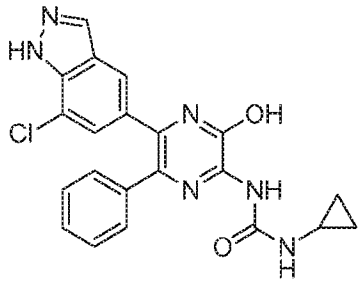
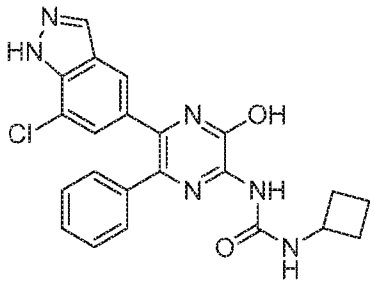
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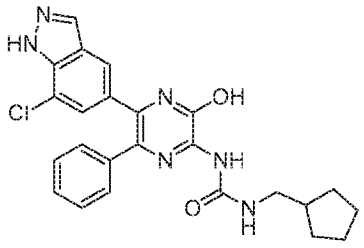
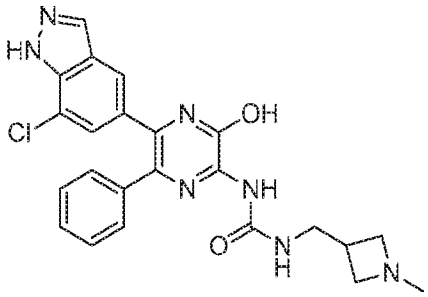
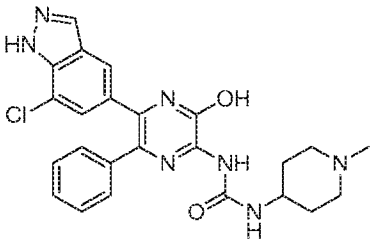
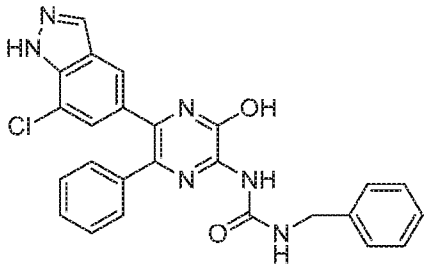
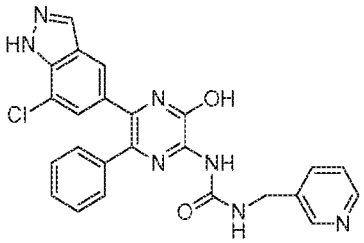
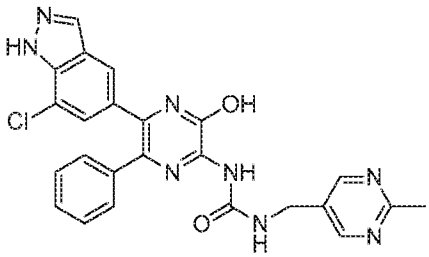
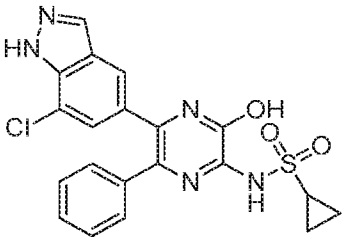
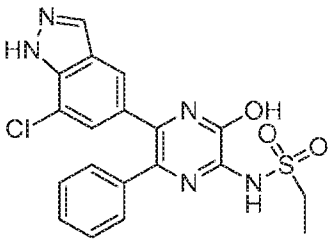
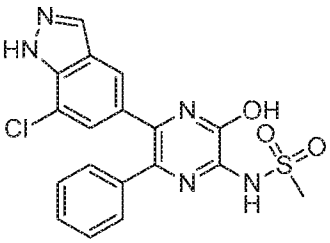
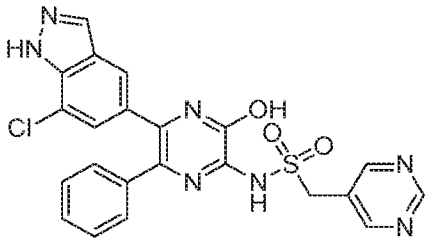
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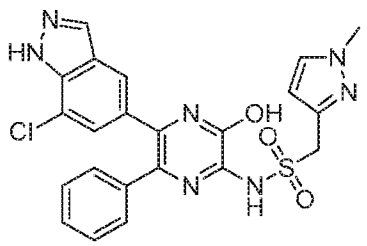
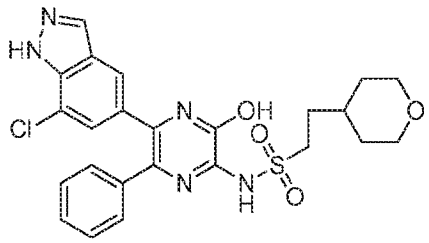
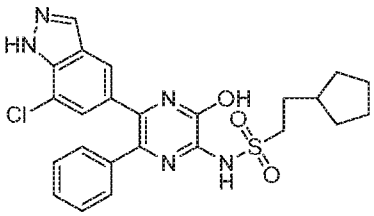
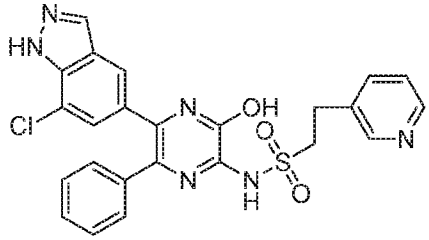
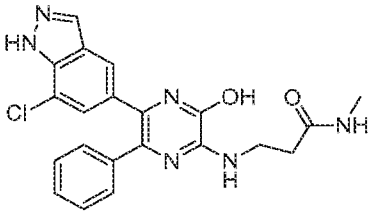
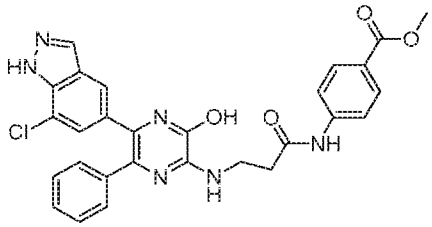
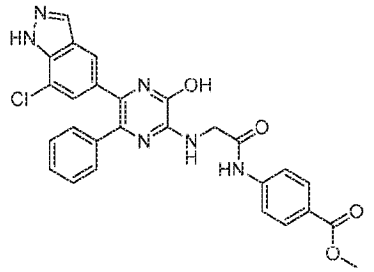
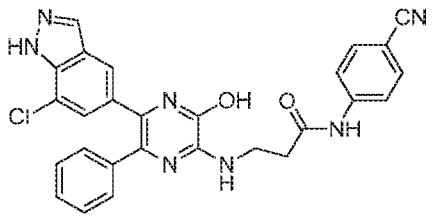
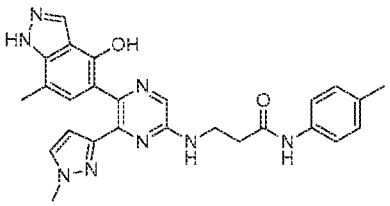
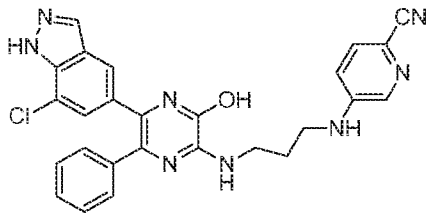
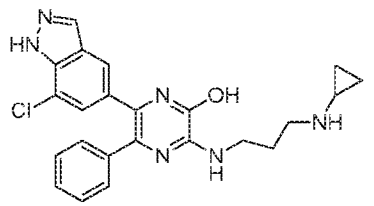
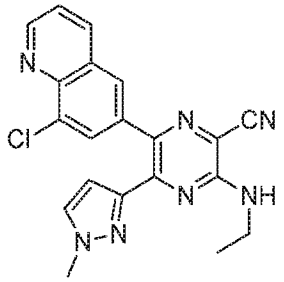
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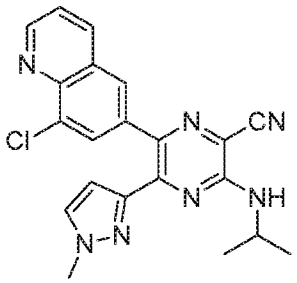
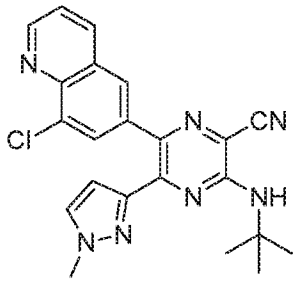
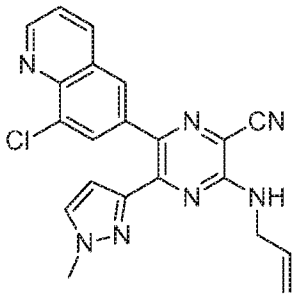
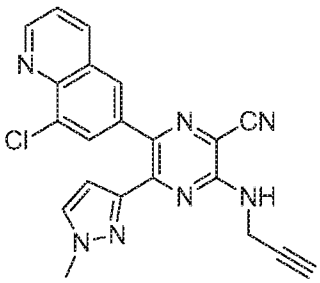
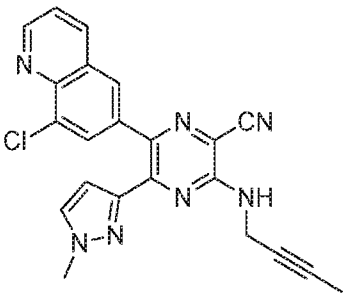
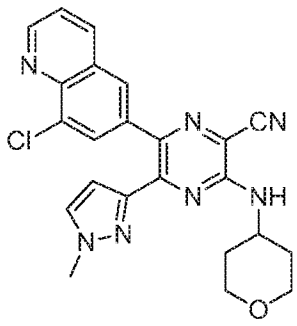
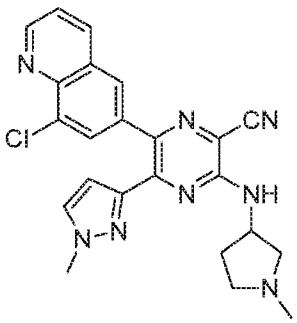
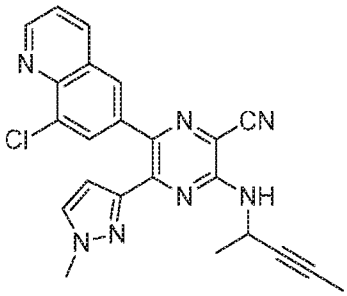
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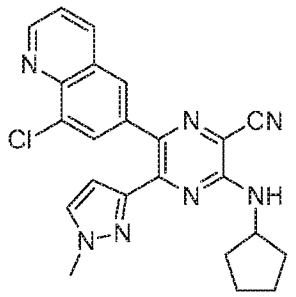
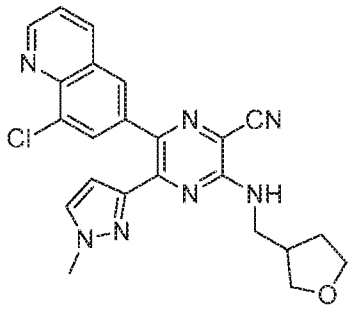
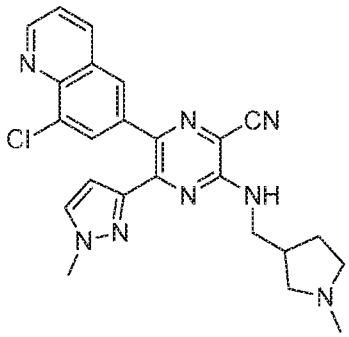
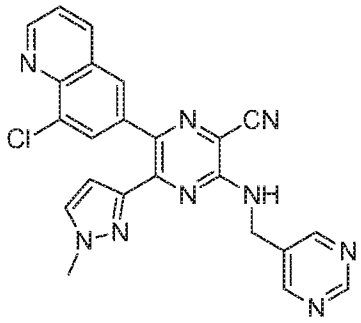
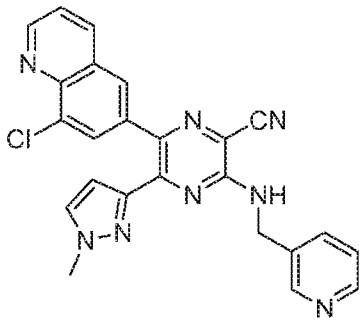
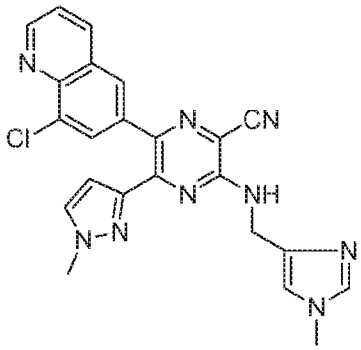
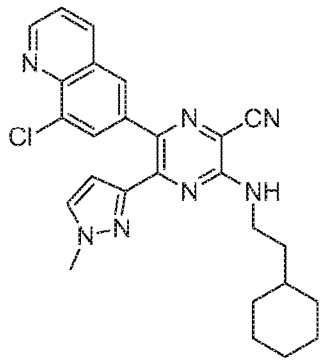
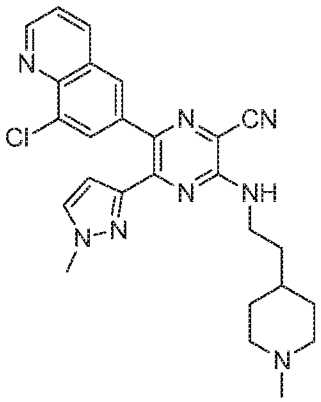
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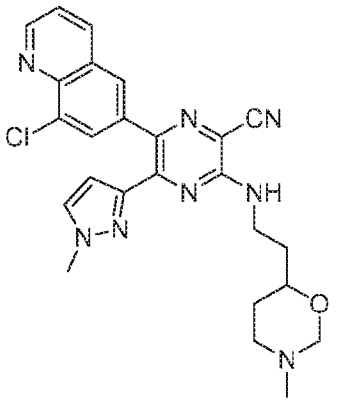
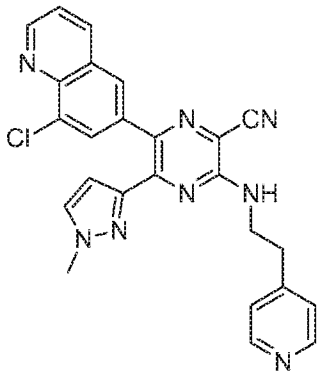
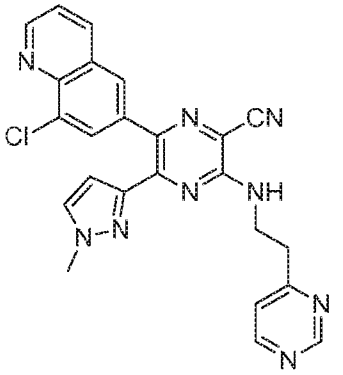
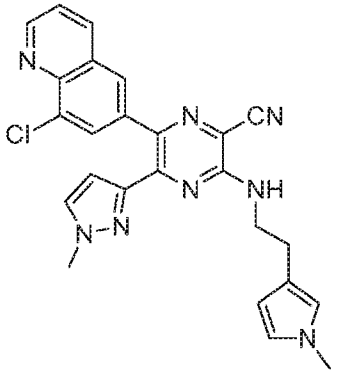
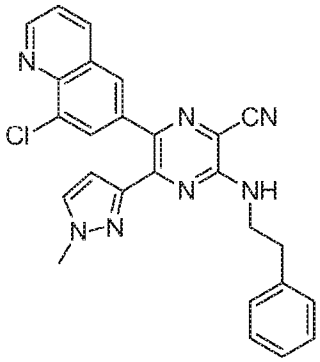
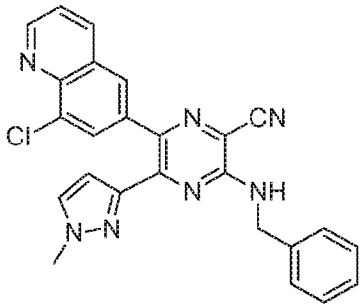
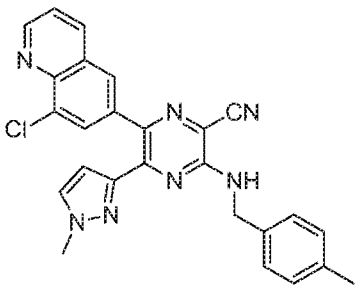
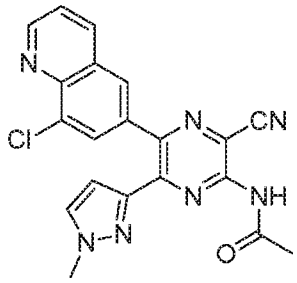
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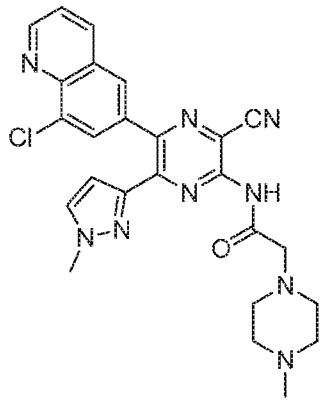
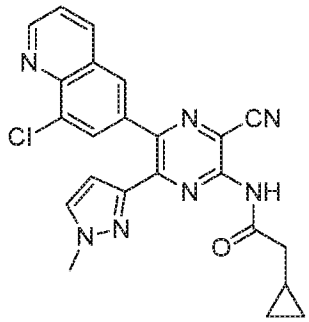
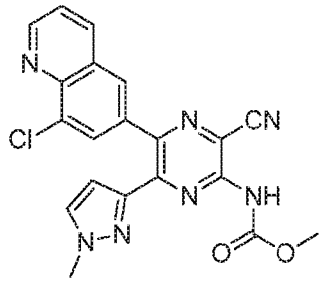
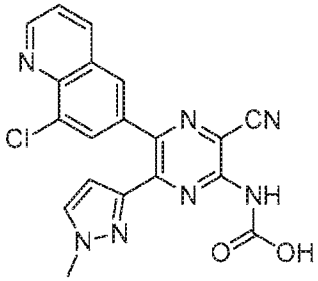
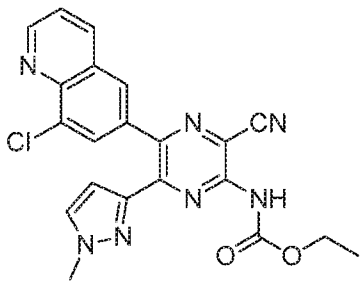
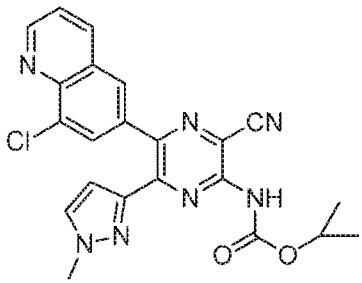
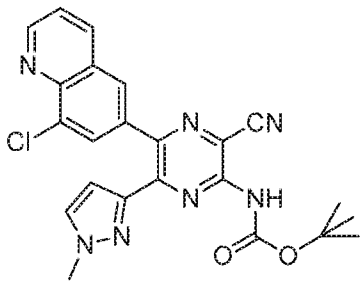
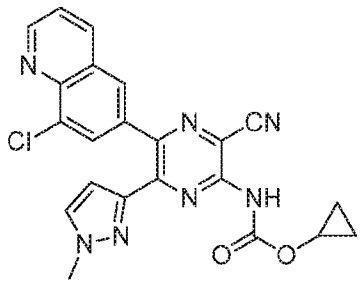
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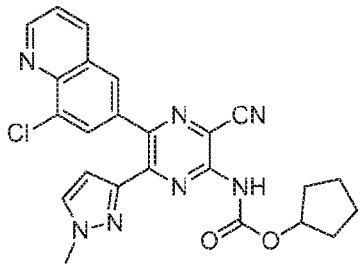
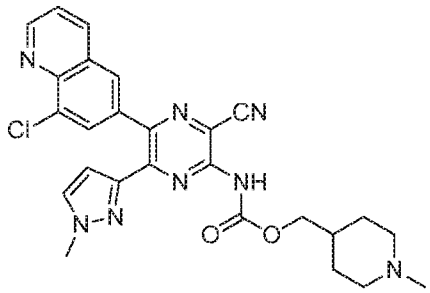
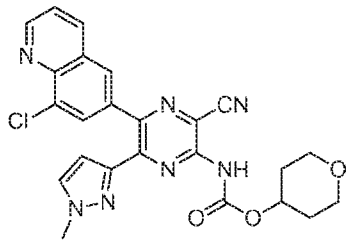
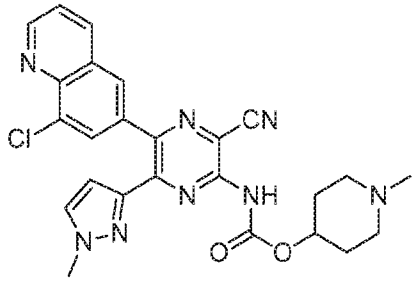
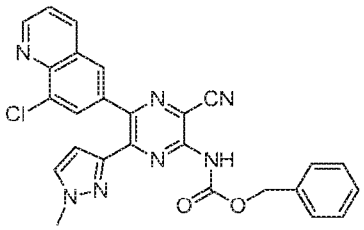
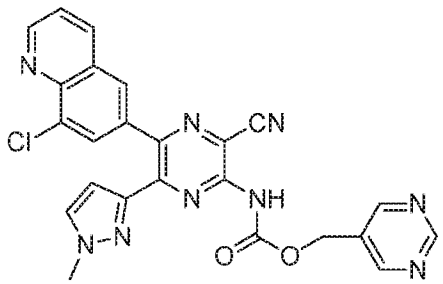
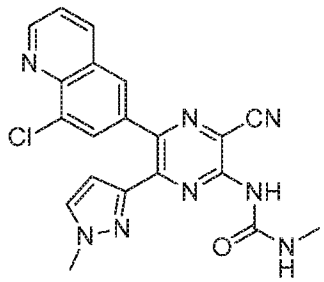
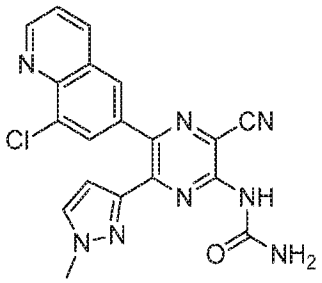
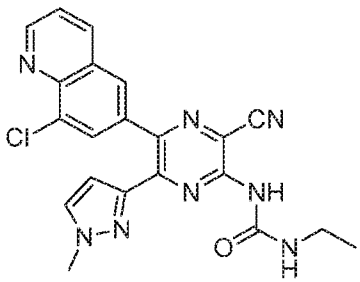
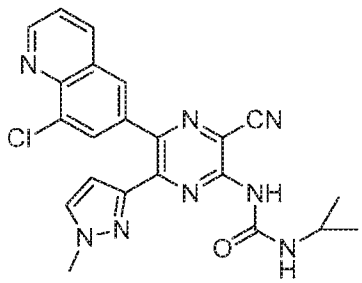
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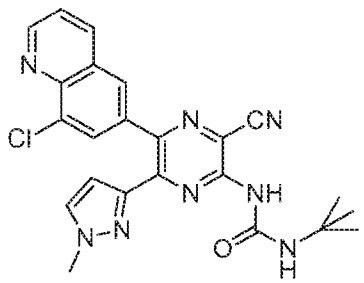
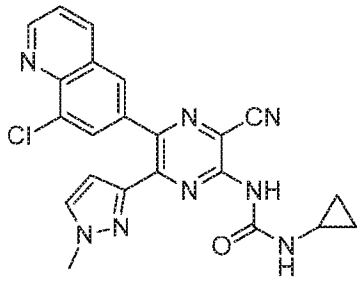
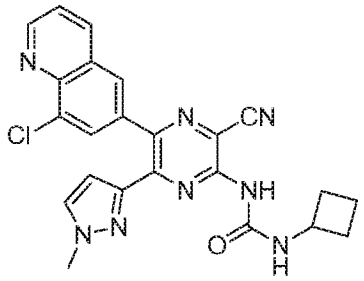
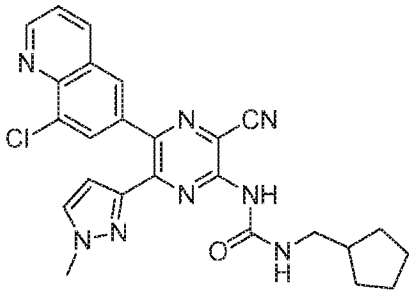
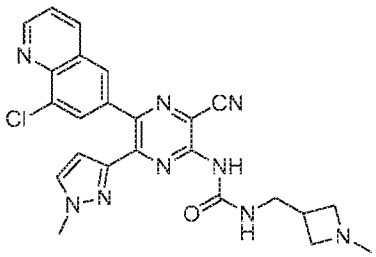
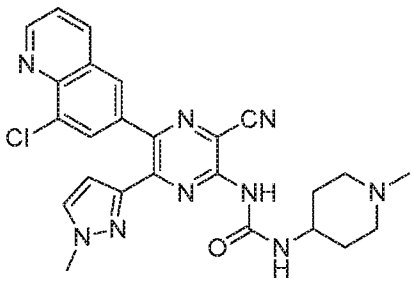
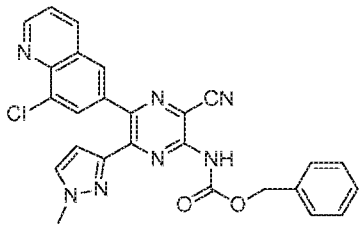
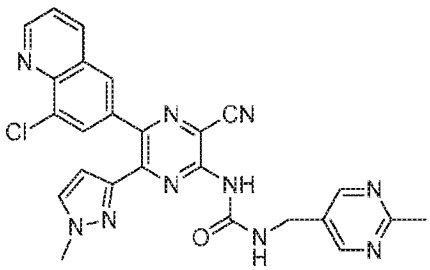
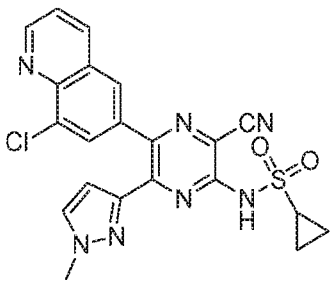
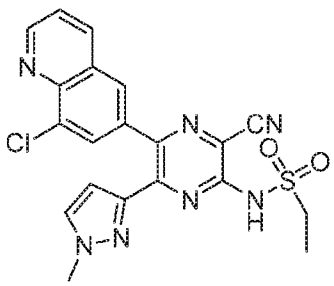
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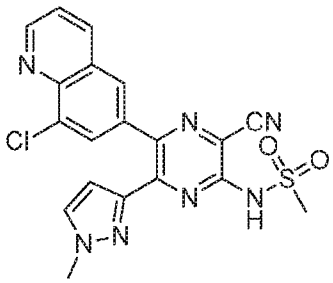
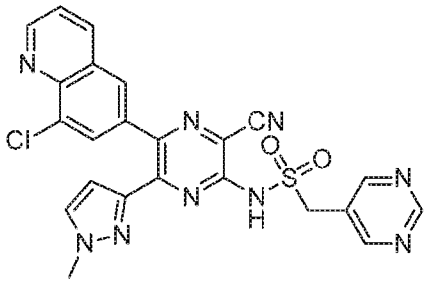
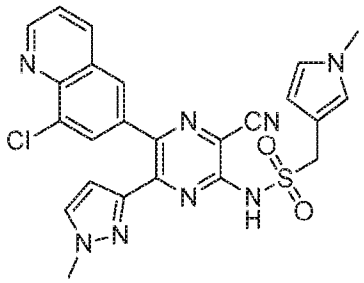
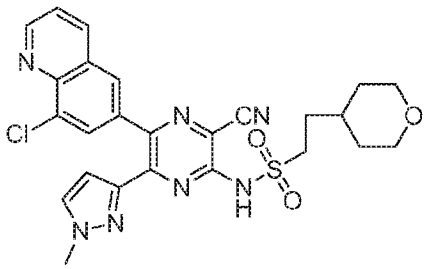
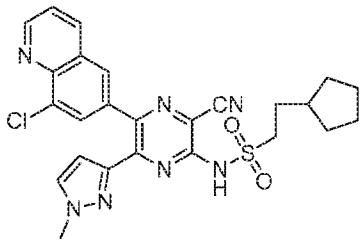
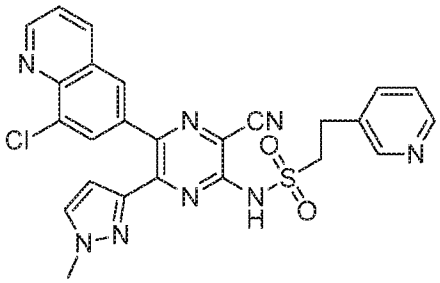
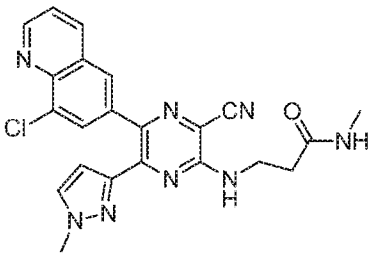
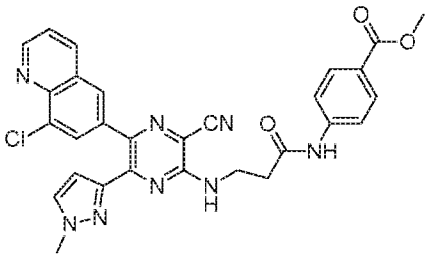
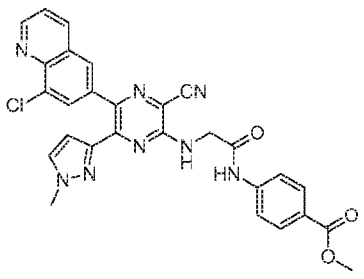
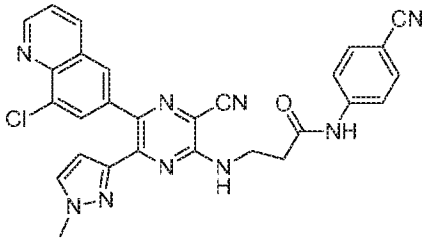
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2.849		2.850	

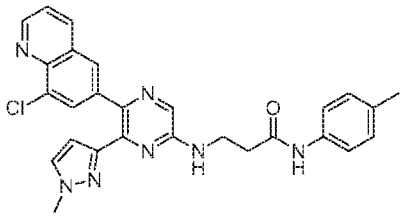
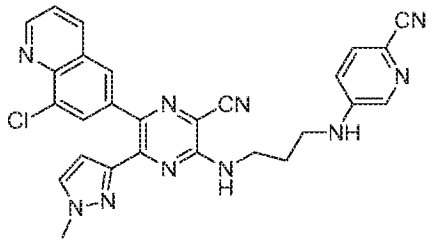
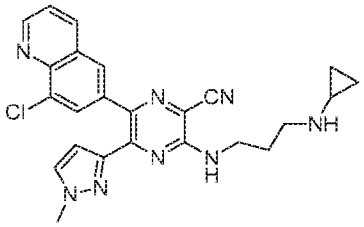
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2.855		2.856	
2.857		2.858	

2.859		2.860	
2.861		2.862	
2.863		2.864	
2.865		2.866	

2.867		2.868	
2.869		2.870	
2.871		2.872	
2.873		2.874	
2.875		2.876	

2.877		2.878	
2.879		2.880	
2.881		2.882	
2.883		2.884	
2.885		2.886	

2.887		2.888	
2.889		2.890	
2.891		2.892	
2.893		2.894	
2.895		2.896	

2.897		2.898	
2.899			

[0133] In some embodiments, provided herein are compounds described in Table 2, including pharmaceutically acceptable salts thereof, and uses thereof. Isomers of compounds of Table 2 are also provided, as are compositions comprising a compound, or any isomer thereof, in any ratio, including racemic mixtures. Isotopic varients of the compounds are also provided.

[0134] The embodiments and variations described herein are suitable for compounds of any formulae detailed herein, where applicable.

[0135] 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.

[0136] 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.

[0137] 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.

[0138] 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, and each unique stereoisomer has a compound number bearing a suffix "a", "b", *etc.* 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.

[0139] 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 study. 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.

[0140] 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.

[0141] The invention 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.

[0142] 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.

[0143] Preferably, the compounds detailed herein are orally bioavailable. However, the compounds may also be formulated for parenteral (*e.g.*, intravenous) administration.

[0144] 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

[0145] 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.

[0146] 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.

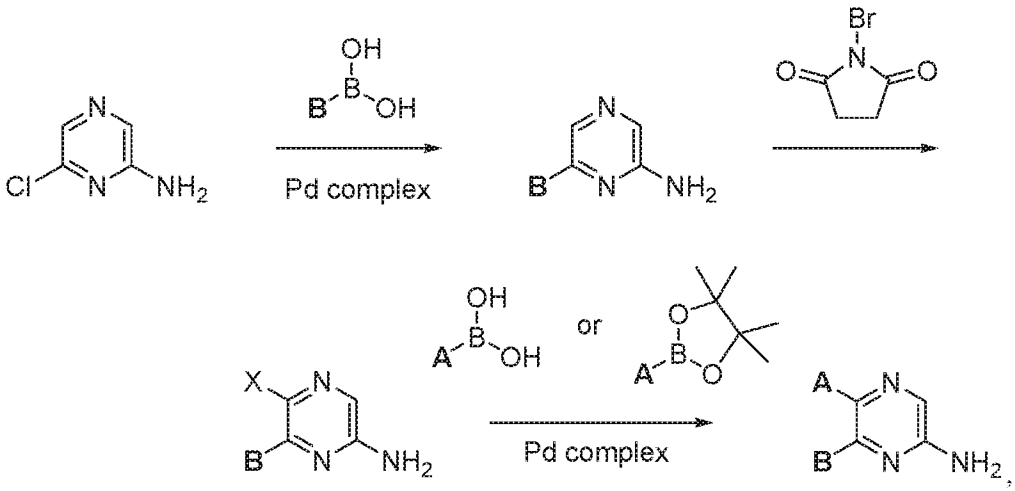
[0147] Chromatography, recrystallization and other conventional separation procedures may also be used with intermediates or final products where it is desired to obtain a particular isomer of a compound or to otherwise purify a product of a reaction.

[0148] Solvates and/or polymorphs of a compound provided herein or a pharmaceutically acceptable salt thereof 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. Polymorphs include the different crystal packing arrangements of the same elemental composition of a compound. Polymorphs usually have different X-ray diffraction patterns, infrared spectra, melting points, density, hardness, crystal shape, optical and electrical properties, stability, and/or solubility. Various factors such as the recrystallization solvent, rate of crystallization, and storage temperature may cause a single crystal form to dominate.

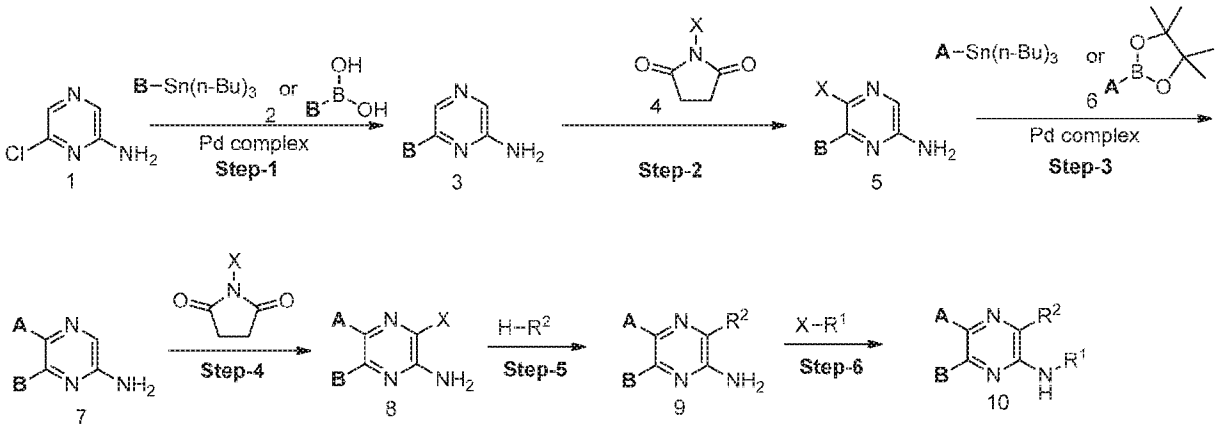
[0149] In some embodiments, compounds of the formula (I) may be synthesized according to Scheme 1. In some embodiments, compounds of the formula (I) may be synthesized according to Scheme 1, 2, 3, 4, 5, or 6.

Scheme 1



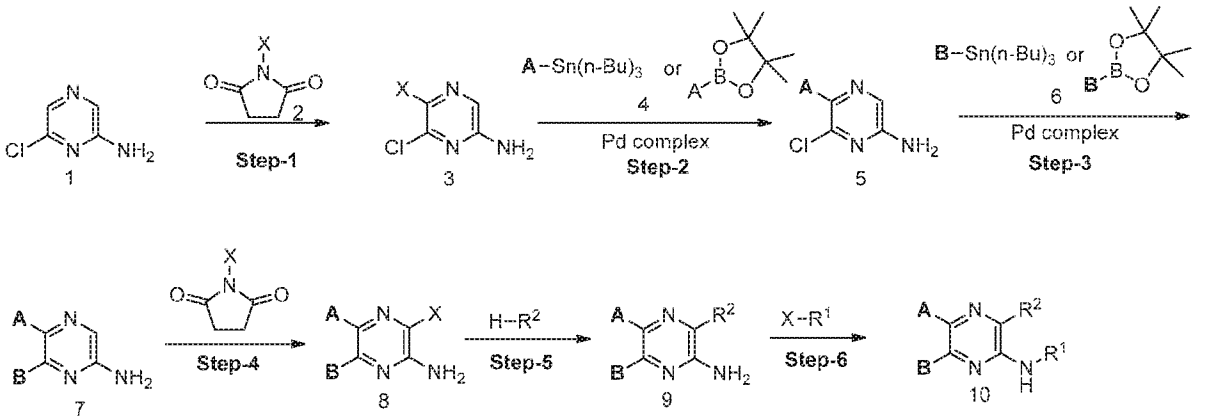
wherein **A** and **B** are as defined for formula (I), or any variation thereof detailed herein; and X is a leaving group (*e.g.*, alkoxy or halogen).

Scheme 2

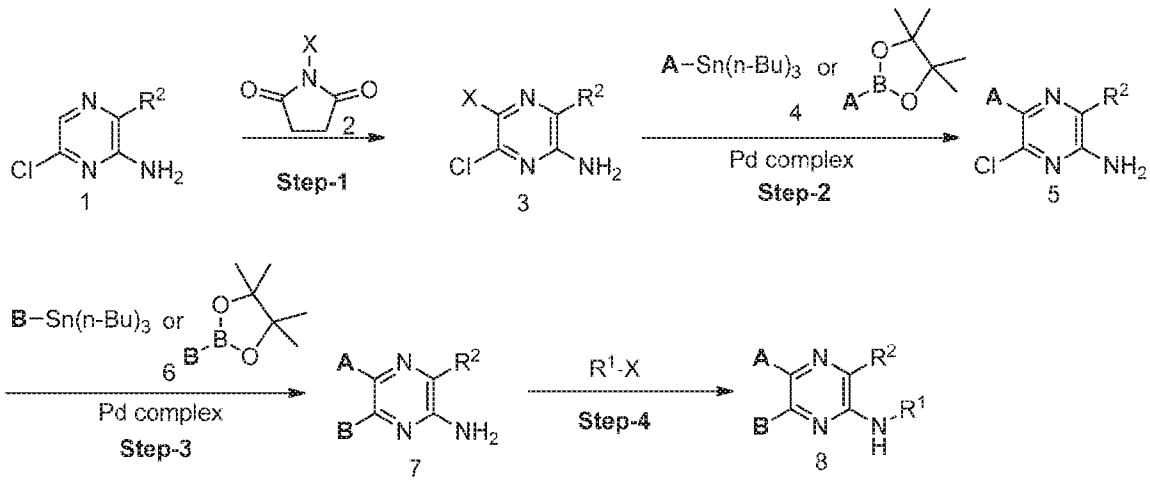


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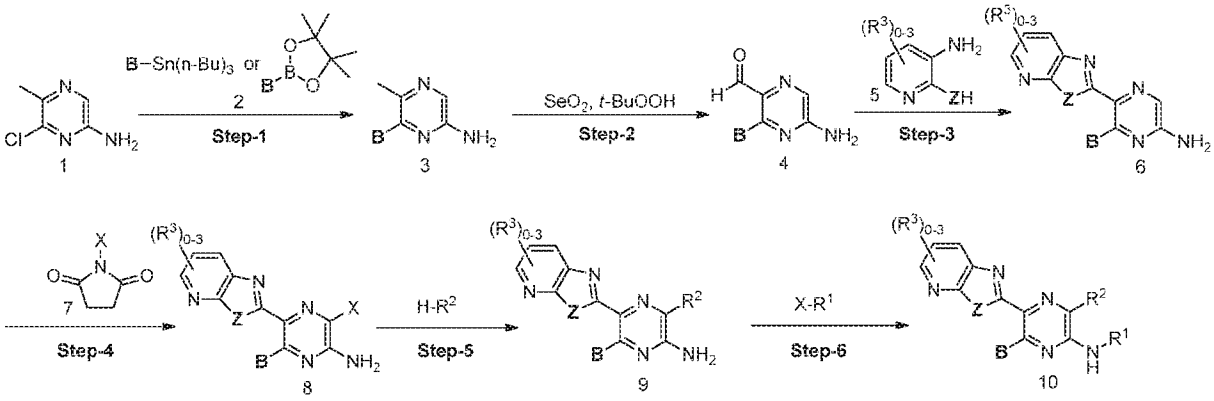
Scheme 3



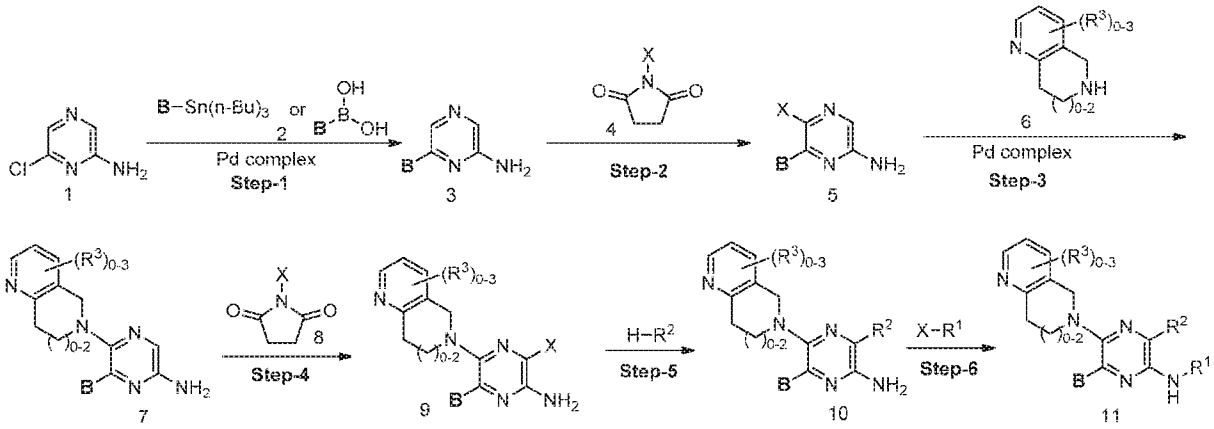
Scheme 4



Scheme 5



Scheme 6



wherein **A**, **B**, R^1, R^2 and R^3 are as defined for formula (I), or any variation thereof detailed herein; X is a leaving group (*e.g.*, alkoxy or halogen) and Z is a heteroatom selected from O, S or NH. R^3 groups may be the same or different, and which may be present on either one ring or both rings.

[0150] It is understood that General Synthetic Schemes 1-6 and present synthetic routes involving steps clearly familiar to those skilled in the art, wherein the substituents described in compounds of formula (I) herein can be varied with a choice of appropriate starting materials and reagents utilized in the steps presented.

Pharmaceutical Compositions and Formulations

[0151] 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 pharmaceutically acceptable salt thereof 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.

[0152] 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 salt thereof are provided, such as compositions of substantially pure compounds. In some embodiments, a composition containing a compound as detailed herein or a salt thereof is in substantially pure form.

[0153] 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.

[0154] 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.

[0155] One or several compounds described herein or a salt thereof can be used in the preparation of a formulation, such as a pharmaceutical formulation, by combining the compound

or compounds, or a salt thereof, 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.

[0156] 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.

[0157] 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 pharmaceutically acceptable salt thereof can be formulated as a 10 mg tablet.

[0158] 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

[0159] Compounds and compositions detailed herein, such as a pharmaceutical composition containing a compound of any formula provided herein or a salt thereof 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.

[0160] Provided herein is a method of treating a disease in an individual comprising administering an effective amount of a compound of formula (I) or any embodiment, variation or aspect thereof (collectively, a compound of formula (I) or the present compounds or the compounds detailed or described herein) or a pharmaceutically acceptable salt thereof, to the individual. In some embodiments, provided herein is a method of treating a disease mediated by a G protein coupled receptor signaling pathway in an individual comprising administering an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, to the individual. In some embodiments, the disease is mediated by a class A G protein coupled receptor. In some embodiments, the disease is mediated by a class B G protein coupled receptor. In some embodiments, the disease is mediated by a class C G protein coupled receptor. In some embodiments, the G protein coupled receptor is a purinergic G protein receptor. In some embodiments, the G protein coupled receptor is an adenosine receptor, such as any of the A_1, A_{2A}, A_{2B}, and A_3 receptors.

[0161] The present compounds or salts thereof are believed to be effective for treating a variety of diseases and disorders. For example, in some embodiments, the present compositions 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 lung cancer, including small cell carcinoma, cutaneous T cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, cancer of the adrenal cortex, ACTH-producing tumors, 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.

[0162] In some embodiments, the present compounds or salts thereof are used in treatment of tumors which produce high levels of ATP and/or adenosine. For example, in some embodiments the extracellular concentration of adenosine is 10-20 times higher in the tumor compared to adjacent tissue. In some embodiments, the present compounds or salts thereof are used in treatment of tumors that express high levels of an ectonucleotidase. In some embodiments, the ectonucleotidase is CD39. In some embodiments, the ectonucleotidase is CD73.

[0163] Also provided herein is a method of enhancing an immune response in an individual in need thereof comprising administering an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, to the individual. Adenosine receptors are known to play an immunosuppressive role in cancer biology. High levels of adenosine present in the tumor microenvironment bind to adenosine receptors on immune cells to provide an immunosuppressive microenvironment. Specifically, binding of adenosine to the A_{2A} receptor provides an immunosuppressive signal that inhibits T cell proliferation, cytokine production and cytotoxicity. The A_{2A} receptor signaling has been implicated in adenosine-mediated inhibition of NK cell cytotoxicity, NKT cell cytokine production and CD40L upregulation. Therefore, use of an A_{2A} receptor antagonist, such as those provided herein, may reverse the immunosuppressive effect of adenosine on immune cells. In some embodiments, the immune response is enhanced by a compound of formula (I) or a salt thereof enhancing activity of natural killer (NK) cells. In some embodiments, the present compounds or salts thereof increase NK cell-meditated

cytotoxicity. In some embodiments, the immune response is enhanced by enhancing the activity of $CD8^+$T cells. In some embodiments, the present compounds or salts thereof cause an inflammatory response in the tumor microenvironment.

[0164] The present disclosure further provides a method of increasing the activity of a natural killer cell in an individual comprising administering an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, to the individual. In some of these embodiments, the present compounds or salts thereof increase NK cell-meditated cytotoxicity. In some embodiments, a compound of formula (I) or a salt thereof increases the number of NK cells.

[0165] A compound of formula (I) or a salt thereof may be useful for modulating the activity of G protein receptor coupled signaling pathway proteins. In some embodiments, a compound of formula (I) or a salt thereof activates a G protein receptor coupled signaling pathway protein (i.e. is an agonist of a G protein receptor). In some embodiments, a compound of formula (I) or a salt thereof inhibits a G protein receptor coupled signaling pathway protein (i.e., is a G protein receptor antagonist). In some embodiments, a compound of formula (I) or a salt thereof is an adenosine receptor antagonist. In some embodiments, a compound of formula (I) or a salt thereof is an antagonist of any of the A_1, A_{2A}, A_{2B}, and A_3 receptors.

[0166] Accordingly, also provided herein is a method of modulating the activity of an A_{2A} receptor in an individual comprising administering an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof to an individual. In some embodiments a compound of formula (I) or a salt thereof is an A_{2A} receptor antagonist. In some embodiments, a compound of formula (I) or a salt thereof reduces A_{2A} receptor signaling by at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%. In some embodiments, a compound of formula (I) or a salt thereof reduces A_{2A} receptor signaling by 40-99%, 50-99%, 60-99%, 70-99%, 80-99%, 90-99%, or 95-99%. In some of these embodiments, a compound of formula (I) or a salt thereof binds to the A_{2A} receptor 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 10 nM, less than 1 nM or less than 100 pM. In some embodiments, [compound x] binds to the A_{2A} receptor with an IC_{50} of 500 nM to 100 pM, 400 nM to 100 pM, 300 nM to 100 pM, 200 nM to 100 pM, or 100 nM to 100 pM.

[0167] Also provided herein is a method of modulating the activity of an A_{2B} receptor in an individual comprising administering an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof to an individual. In some embodiments a compound of formula (I) or a salt thereof is an A_{2B} receptor antagonist. In some embodiments, a compound of formula (I) or a salt thereof reduces A_{2B} receptor signaling by at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%. In some embodiments, a compound of formula (I) or a salt thereof reduces A_{2B} receptor signaling by 40-99%, 50-99%, 60-99%, 70-99%, 80-99%, 90-99%, or 95-99%. In some of these embodiments, a compound of formula (I) or a salt thereof binds to the A_{2B} receptor 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 10 nM, less than 1 nM or less than 100 pM. In some embodiments, a compound of formula (I) or a salt thereof binds to the A_{2B} receptor with an IC_{50} of 500 nM to 100 pM, 400 nM to 100 pM, 300 nM to 100 pM, 200 nM to 100 pM, or 100 nM to 100 pM.

[0168] Also provided herein is a method of modulating the activity of an A_3 receptor in an individual comprising administering an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof to an individual. In some embodiments a compound of formula (I) or a salt thereof is an A_3 receptor antagonist. In some embodiments, a compound of formula (I) or a salt thereof reduces A_3 receptor signaling by at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%. In some embodiments, a compound of formula (I) or a salt thereof reduces A_3 receptor signaling by 40-99%, 50-99%, 60-99%, 70-99%, 80-99%, 90-99%, or 95-99%. In some of these embodiments, a compound of formula (I) or a salt thereof binds to the A_3 receptor 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 10 nM, less than 1 nM or less than 100 pM. In some embodiments, a compound of formula (I) or a salt thereof binds to the A_3 receptor with an IC_{50} of 500 nM to 100 pM, 400 nM to 100 pM, 300 nM to 100 pM, 200 nM to 100 pM, or 100 nM to 100 pM.

[0169] In some embodiments, the present invention comprises a method of inhibiting tumor metastasis in an individual in need thereof comprising administering a compound of formula (I), or a pharmaceutically acceptable salt thereof, to the individual. In some embodiments, the

metastasis is to the lung, liver, lymph node, bone, adrenal gland, brain, peritoneum, muscle, or vagina. In some embodiments, a compound of formula (I) or a salt thereof inhibits metastasis of melanoma cells. In some embodiments, the present disclosure includes a method of delaying tumor metastasis comprising administering a compound of formula (I), or a pharmaceutically acceptable salt thereof, to the individual. In some of these embodiments, the time to metastatic is delayed by 1 month, 2 months 3 months, 4 months, 5 months, 6 months, 12 months, or more, upon treatment with the compounds of the present invention.

[0170] In some embodiments, a compound of formula (I) or a salt thereof 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. In some embodiments, the individual has a cancer that expresses a high level of a nucleotide metabolizing enzyme. In some embodiments, the nucleotide metabolizing enzyme is a nucleotidase, such as CD73 (ecto-5'-nucleotidase, Ecto5'NTase). In some of these embodiments, the individual has a cancer that expresses a high level of a nucleotidase, such as CD73. In any of these embodiments, the nucleotide metabolizing enzyme is an ecto-nucleotidase. In some embodiments, the ecto-nucleotidase degrades adenosine monophosphate. In some embodiments, the nucleotide metabolizing enzyme is CD39 (ecto-nucleoside triphosphate diphosphohydrolase 1, E-NTPDase1). In some of these embodiments, the individual has a cancer that expresses a high level of CD39. In some embodiments, the individual has a cancer that expresses a high level of an adenosine receptor, such as the A_{2A} receptor.

Combination Therapy

[0171] As provided herein, the presently disclosed compounds or a salt thereof may activate the immune system by modulating the activity of a G protein coupled receptor signaling pathway, for example acting as an A_{2A} receptor antagonist, which results in significant anti-tumor effects. Accordingly, the present compounds or a salt thereof may be used in combination with other anti-cancer agents to enhance tumor immunotherapy. In some embodiments, provided herein is a

method of treating a disease mediated by a G protein coupled receptor signaling pathway in an individual comprising administering an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, and an additional therapeutic agent to the individual. In some embodiments, the disease mediated by a G protein coupled receptor signaling pathway is a proliferative disease such as cancer.

[0172] In some embodiments, the additional therapeutic agent is a cancer immunotherapy. In some embodiments, the additional therapeutic agent is an immunostimulatory agent. In some embodiments, the additional therapeutic agent targets a checkpoint protein. In some embodiments, the additional therapeutic agent is effective to stimulate, enhance or improve an immune response against a tumor.

[0173] In another aspect, provided herein is a combination therapy in which a compound of formula (I) 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 of formula (I) or a salt thereof 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 of formula (I) or a salt thereof and an anti-PD-1 antibody. In another embodiment, provided is a method for stimulating an immune response in a subject comprising administering to the subject a compound of formula (I) or a salt thereof and one or more immunostimulatory antibodies or immunotherapy like Chimeric antigen receptor (CAR) T-cell therapy; 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 another embodiment, the subject is administered a compound of formula (I) or a salt thereof and an anti-PD-L1 antibody. In yet another embodiment, the subject is administered a compound of formula (I) or a salt thereof 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). In another

embodiment, the subject is administered a compound of formula (I) or a salt thereof and CAR T-cells (genetically modified T cells).

[0174] In one embodiment, the present disclosure provides a method for treating a proliferative disease (e.g., cancer), comprising administering a compound of formula (I) or a salt thereof and an anti-PD-1 antibody to a subject. In further embodiments, a compound of formula (I) or a salt thereof 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 administering a compound of formula (I) or a salt thereof 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

[0175] In one embodiment, the present invention provides a method for treating a hyperproliferative disease (e.g., cancer), comprising administering a compound of formula (I) or a salt thereof and an anti-PD-L1 antibody to a subject. In further embodiments, a compound of formula (I) or a salt thereof 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 of formula (I) or a salt thereof 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.

[0176] 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 of formula (I) or a salt thereof can be administered sequentially, such as anti-CTLA-4 antibody being administered first and a compound of formula (I) or a salt thereof second, or a compound of formula (I) or a salt thereof being administered first and anti-CTLA-4 antibody second. Additionally or alternatively, an anti-PD-1 antibody and a compound of formula (I) or a salt thereof can be administered sequentially,

such as anti-PD-1 antibody being administered first and a compound of formula (I) or a salt thereof second, or a compound of formula (I) or a salt thereof being administered first and anti-PD-1 antibody second. Additionally or alternatively, an anti-PD-L1 antibody and a compound of formula (I) or a salt thereof can be administered sequentially, such as anti-PD-L1 antibody being administered first and a compound of formula (I) or a salt thereof second, or a compound of formula (I) or a salt thereof being administered first and anti-PD-L1 antibody second.

[0177] 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.

[0178] Optionally, the combination of a compound of formula (I) or a salt thereof 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.

[0179] A compound of formula (I) or a salt thereof can also be further combined with standard cancer treatments. For example, a compound of formula (I) or a salt thereof can be effectively combined with chemotherapeutic regimes. In these instances, it is possible to reduce the dose of other chemotherapeutic reagent administered with the combination of the instant disclosure (Mokyr et al. (1998) *Cancer Research* 58: 5301-5304). Other combination therapies with a compound of formula (I) or a salt thereof include radiation, surgery, or hormone deprivation. Angiogenesis inhibitors can also be combined with a compound of formula (I) or a salt thereof. Inhibition of angiogenesis leads to tumor cell death, which can be a source of tumor antigen fed into host antigen presentation pathways.

[0180] In another example, a compound of formula (I) or a salt thereof 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 of formula (I) or a salt thereof. 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 of formula (I) or a salt thereof 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 of formula (I) or a salt thereof.

[0181] In some embodiments, a compound of formula (I) or a salt thereof can be combined with an anti-CD73 therapy, such as an anti-CD73 antibody.

[0182] In some embodiments, a compound of formula (I) or a salt thereof can be combined with an anti-CD39 therapy, such as an anti-CD39 antibody.

[0183] In yet further embodiments, a compound of formula (I) or a salt thereof is administered in combination another G protein receptor antagonist, such as an adenosine A_1 and/or A_3 antagonist.

Dosing and Method of Administration

[0184] 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.

[0185] 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.

[0186] 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 salt thereof and a pharmaceutically acceptable excipient.

[0187] 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.

[0188] The compounds provided herein or a salt thereof 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.

[0189] 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.

[0190] 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.

[0191] Also provided are articles of manufacture comprising a compound of the disclosure or a salt thereof, 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

[0192] 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 pharmaceutically acceptable salt thereof. 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.

[0193] 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.

[0194] 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 (e.g., hypertension) 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).

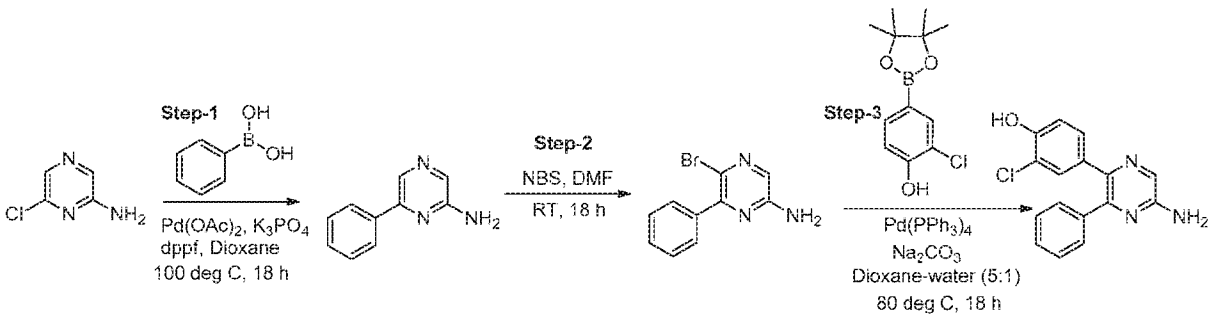
[0195] The kits may optionally include a set of instructions, generally written instructions, although electronic storage media (*e.g.*, magnetic diskette or optical disk) containing instructions are also acceptable, relating to the use of component(s) of the methods of the present invention. The instructions included with the kit generally include information as to the components and their administration to an individual.

[0196] 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.

EXAMPLES

Synthetic Examples

Example S1. Synthesis of 4-(5-amino-3-phenylpyrazin-2-yl)-2-chlorophenol (Compound No. 1.1)



[0197] Step-1 Synthesis of 6-phenylpyrazin-2-amine: To a solution of 6-chloropyrazin-2-amine (1.00 g, 7.75 mmol, 1 eq.) in 1,4-dioxane (30 mL) was added phenylboronic acid (1.42 g, 11.62 mmol, 1.5 eq.), K_3PO_4 (3.286 g, 15.50 mmol, 2 eq.), $Pd(OA_C)_2$ (0.086 g, 0.38 mmol, 0.05 eq.), 1,1'-bis(diphenylphosphino)ferrocene (0.214 g, 0.38 mmol, 0.05 eq.). The reaction mixture was deoxygenated using N_2 atmosphere and the reaction mixture was heated at 100°C overnight. The reaction was monitored by TLC and LCMS and found to be complete after 18 h. The reaction mixture was cooled to RT, filtered through Celite-bed and washed with ethyl acetate (2 × 20 mL). The reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (2 × 50 mL). The separated organic layer was dried over sodium sulfate and concentrated under reduced pressure. The crude product was purified by CombiFlash on silica gel using CH_3OH-CH_2Cl_2 system as eluent to afford 1.10 g (63%) of 6-phenylpyrazin-2-amine. LC/MS: 172 $[M+1]^+$.

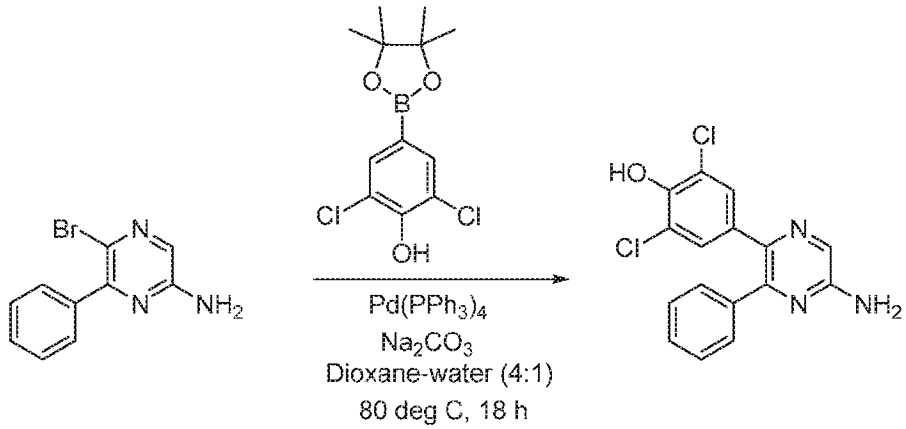
[0198] Step-2: Synthesis of 5-bromo-6-phenylpyrazin-2-amine: To a solution of 6-phenylpyrazin-2-amine (0.150 g, 0.877 mmol, 1 eq.) in DMF (3 mL) was added N-bromosuccinimide (0.156 g, 0.877 mmol, 1 eq.) and the reaction mixture was stirred at RT for 1 h. The reaction was monitored by TLC and NMR. After completion, the reaction mixture was diluted with water (50 mL) and extracted by ethyl acetate (2 × 20 mL). Combined organic layer was washed with water (5 × 20 mL) followed by brine and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to get the crude product which was purified

by CombiFlash on silica gel using EtOAc-Hexane system as eluent to afford 100 mg (46%) of 5-bromo-6-phenylpyrazin-2-amine. LC/MS: 251 $[M+1]^+$.

[0199] Step-3: Synthesis of 4-(5-amino-3-phenylpyrazin-2-yl)-2-chlorophenol: To a solution of 5-bromo-6-phenylpyrazin-2-amine (100 mg, 0.4 mmol, 1 eq.) in 1,4-dioxane-water (6 mL, 5:1) was added 2-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol[1] (121 mg, 0.48 mmol, 1.2 eq.), Na_2CO_3 (84 mg, 0.8 mmol, 2eq.), $Pd(PPh_3)_4$ (23 mg, 0.02 mmol, 0.05 eq.). The reaction mixture was deoxygenated using N_2 atmosphere and the reaction mixture was allowed to stir at 80 °C overnight. The reaction was monitored by NMR and LCMS and found to be complete after 18 h. The reaction mixture was cooled to RT, diluted with water (50 mL) and extracted with EtOAc (3 × 50 mL). Combined organic layer was washed with brine (50 mL) and dried over sodium sulfate. Removal of solvent under reduced pressure gave crude which was purified by SFC to afford 20 mg (17%) of 4-(5-amino-3-phenylpyrazin-2-yl)-2-chlorophenol. LC/MS: 298 $[M+1]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 7.90 (s, 1H), 7.45 (s, 4H), 7.20 (s, 1H), 6.90 (d, 1H), 7.78 (d, 1H), 6.58 (s, 2H).

[0200] Reference: WO2014/209034 A1.

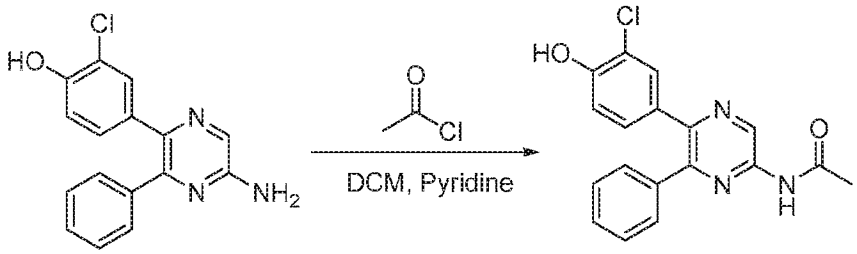
Example S2. Synthesis of 4-(5-amino-3-phenylpyrazin-2-yl)-2,6-dichlorophenol (Compound No. 1.2)



[0201] To a solution of 5-bromo-6-phenylpyrazin-2-amine (100 mg, 0.40 mmol, 1 eq.) in 1,4-dioxane-water (10 mL, 4:1) was added 2,6-dichloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (174 mg, 0.48 mmol, 1.2 eq.), Cs_2CO_3 (391 mg, 1.20 mmol, 3.0 eq.), $PdCl_2(dppf)CH_2Cl_2$ complex (32 mg, 0.04 mmol, 0.05 eq.). The reaction mixture was

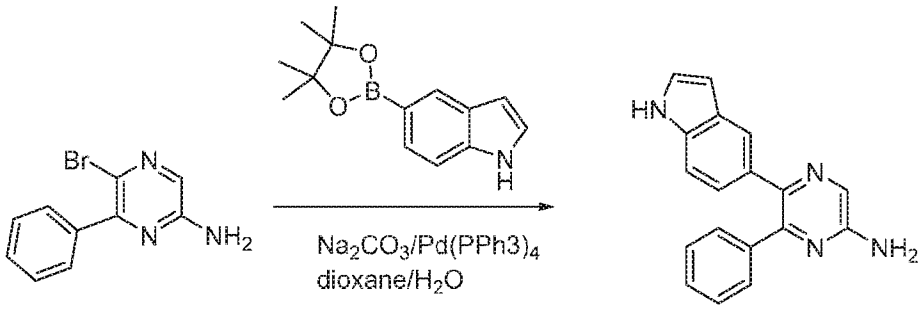
deoxygenated using N_2 atmosphere and the reaction mixture was allowed to stir at 80 °C overnight. The progress of reaction was monitored by TLC and LCMS and found to be complete after 18 h. The reaction mixture was cooled to RT, diluted with water (50 mL) and extracted using ethyl acetate (3 × 50 mL). Combined organic layer was washed with brine (50 mL) and dried over sodium sulfate. Removal of solvent under reduced pressure gave crude which was purified by SFC to afford 15 mg (11%) of 4-(5-amino-3-phenylpyrazin-2-yl)-2,6-dichlorophenol.
LCMS: 332 $[M+1]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.28 (s, 2H), 6.64 (s, 1H), 7.10 (s, 2H), 7.38 (s, 4H), 7.90 (s, 1H).

Example S3. Synthesis of N-(5-(3-chloro-4-hydroxyphenyl)-6-phenylpyrazin-2-yl)acetamide. (Compound No. 1.3)



[0202] To a solution of 4-(5-amino-3-phenylpyrazin-2-yl)-2-chlorophenol (200 mg, 0.67 mmol, 1.0 eq) in CH_2Cl_2 (20 mL) was added pyridine (79 mg, 1.01 mmol, 1.5 eq) and acetyl chloride (78 mg, 1.01 mmol, 1.5 eq). The reaction mixture was allowed to stir at room temperature overnight. Progress of reaction was monitored by TLC and LCMS and found to be complete after for 18 h. The reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layer was washed with brine (30 mL) and dried over sodium sulfate. Removal of solvent under reduced pressure gave crude which was purified by reversed phase column chromatography to afford 10 mg (4%) of N-(5-(3-chloro-4-hydroxyphenyl)-6-phenylpyrazin-2-yl)acetamide.
LCMS: 340 $[M+1]^+$.

Example S4. Synthesis of 5-(1H-indol-5-yl)-6-phenylpyrazin-2-amine (Compound No 1.4)

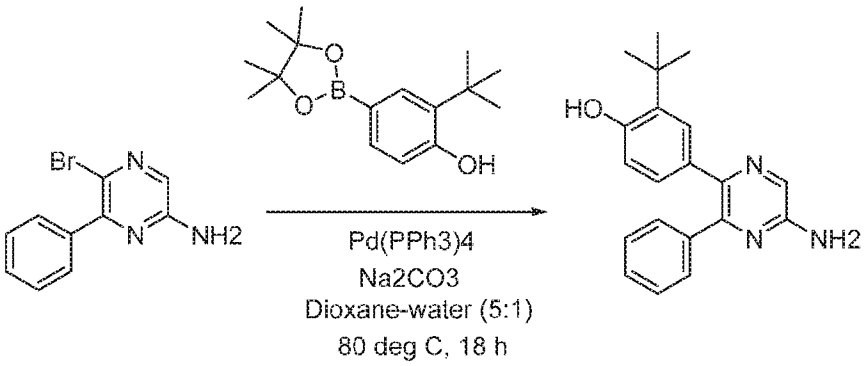


[0203] To a solution of 5-bromo-6-phenylpyrazin-2-amine (100 mg, 0.4 mmol, 1 eq.) in 1,4 dioxane (5 mL): water (1 mL) was added 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole (77 mg, 0.48 mmol, 1.2 eq.), Na_2CO_3 (84 mg, 0.8 mmol, 2eq.), $Pd(PPh3)_4$ (23 mg, 0.02 mmol, 0.05 eq.). The reaction mixture was deoxygenated using N_2 atmosphere and the reaction mixture was heated at 80°C for 18 h. The reaction was monitored by NMR and LCMS. The reaction mixture was diluted with water (50 mL) and extracted using ethyl acetate (2 × 50 mL). The separated organic layer was dried over sodium sulfate and concentrated under reduced pressure. The crude product was purified by Supercritical Fluid Chromatography to afford 5-(6-amino-3-pyridyl)-6-phenyl-pyrazin-2-amine (20mg, 17.8%) as white solid.

LCMS: 287.1 $(M+1)^+$.

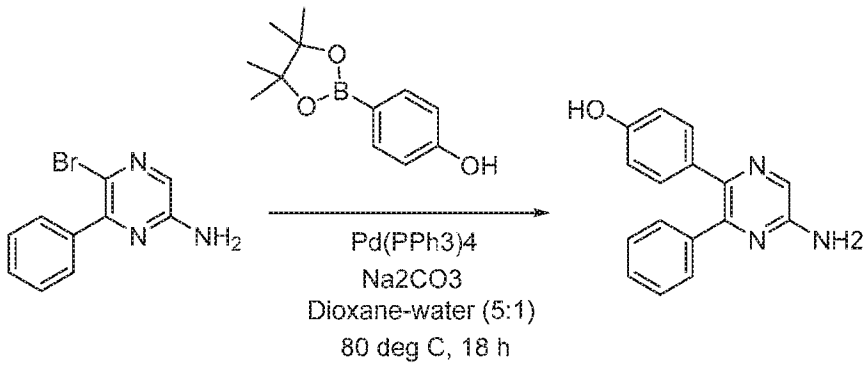
^{1}HNMR (400 MHz, DMSO-d_6) 11.00 s(1H), 7.98 s(1H), 7.62 s(1H), 7.59-7.18 m(7H), 6.95d(1H), 6.40 d(2H), 6.35 s(1H).

Example S5. Synthesis of 4-(5-amino-3-phenylpyrazin-2-yl)-2-tert-butylphenol. (Compound No. 1.6)



[0204] To a solution of 5-bromo-6-phenylpyrazin-2-amine (100 mg, 0.4 mmol, 1 eq.) in 1,4-dioxane-water (6 mL, 5:1) was added 2-tert-butyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (132 mg, 0.48 mmol, 1.2 eq.), Na_2CO_3 (84 mg, 0.8 mmol, 2eq.), $(PdCl_2(PPh_3)_2$ (14 mg, 0.02 mmol, 0.05 eq.). The reaction mixture was deoxygenated with N_2 and the reaction mixture was stirred at 80 °C overnight. The reaction was monitored by NMR and LCMS and found to be complete after 18 h. The reaction mixture was cooled to RT, diluted with water (50 mL) and extracted with ethyl acetate (2 × 50 mL). Combined organic layer was washed with brine (20 mL) and dried over sodium sulfate. Removal of solvent under reduced pressure gave crude which was purified by SFC to afford 4-(5-amino-3-phenyl-pyrazin-2-yl)-2-tert-butyl-phenol (20 mg, 15.7%) as white solid.
LCMS: 320.2 $[M+1]^+$. ^{1}HNMR (400 MHz, DMSO-d_6) 9.36 (s, 1H), 7.95 (s, 1H), 7.40-7.23 (m, 5H), 7.15 (d, 1H), 6.80 (s, 1H), 6.63 (d, 1H), 6.40 (s, 2H), 1.03(s, 9H).

Example S6. Synthesis of 4-(5-amino-3-phenylpyrazin-2-yl)phenol. (Compound No. 1.7)

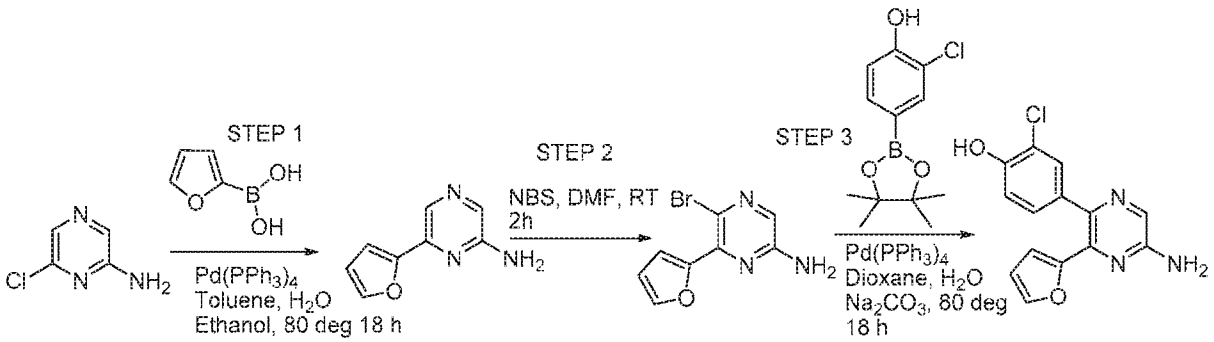


[0205] To a solution of 5-bromo-6-phenylpyrazin-2-amine (100 mg, 0.4 mmol, 1 eq.) in 1,4-dioxane-water (6 mL, 5:1) was added 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (105.6 mg, 0.48 mmol, 1.2 eq.), Na_2CO_3 (84 mg, 0.8 mmol, 2eq.), $PdCl_2(PPh_3)_2$ (15 mg, 0.02 mmol, 0.05 eq.). The reaction mixture was deoxygenated with N_2 and the reaction mixture was stirred at 80 °C overnight. The reaction was monitored by NMR and LCMS and found to be complete after 18 h. The reaction mixture was cooled to RT, diluted with water (50 mL) and extracted with ethyl acetate (2 × 50 mL). Combined organic layer was washed with brine (20 mL) and dried over sodium sulfate. Removal of solvent under reduced pressure gave crude

which was purified by SFC to afford 4-(5-amino-3-phenyl-pyrazin-2-yl) phenol (35 mg, 33.33%) as white solid.

LCMS: 264.1 $[M+1]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 9.40 (brs, 1H), 7.98 (s, 1H), 7.40-7.20 (m, 5H), 7.00 (d, 2H), 6.60 (d, 2H), 6.20 (s, 1H).

Example S7. Synthesis of 4-(5-amino-3-(furan-2-yl)pyrazin-2-yl)-2-chlorophenol. (Compound No. 1.8)



[0206] Step-1 Synthesis of 6-(furan-2-yl)pyrazin-2-amine: To a solution of 6-chloropyrazin-2-amine (1.00 g, 7.75 mmol, 1 eq.) in a solution of toluene and ethanol (20 mL, 1:1) was added furan-2-ylboronic acid (0.955 g, 8.52 mmol, 1.1 eq.), Na_2CO_3 (1.479 g, 13.95 mmol, 1.8 eq.) in H_2O (10 mL), $Pd(PPh_3)_4$ (0.223 g, 0.193 mmol, 0.025 eq.). The reaction mixture was deoxygenated using N_2 atmosphere and the reaction mixture was heated at 100°C for 18 h. The reaction was monitored by NMR. The reaction mixture was filtered through Celite with wash of ethyl acetate (2 × 20 mL). The reaction mixture was diluted with water (50 mL) and extracted using ethyl acetate (2 × 50 mL). The separated organic layer was dried over sodium sulfate and concentrated under reduced pressure. The crude product was purified by CombiFlash on silica gel to afford 1.00 g (80%) of 6-(furan-2-yl)pyrazin-2-amine.

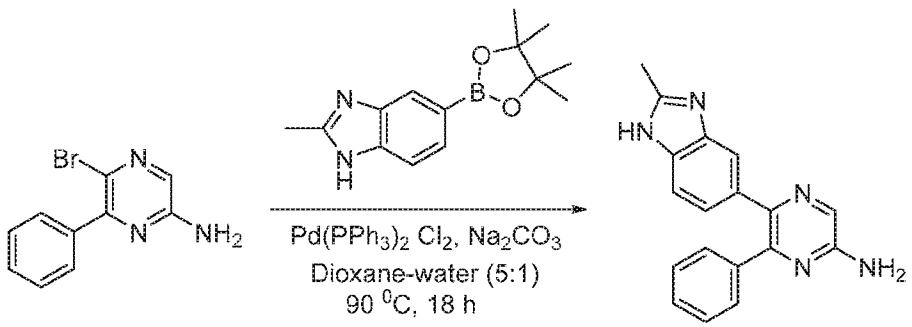
[0207] Step-2 Synthesis of 5-bromo-6-(furan-2-yl)pyrazin-2-amine: To a solution of 6-(furan-2-yl)pyrazin-2-amine (0.200 g, 1.24 mmol, 1 eq.) in DMF (4 mL) was added N-bromosuccinimide (0.222 g, 1.24 mmol, 1 eq.). The reaction mixture was stirred at room temperature for 2 h. The reaction was monitored by TLC and NMR. The reaction mixture was diluted with water (50 mL) and extracted by ethyl acetate (2 × 20 mL). The organic layer was

separated, washed with water (5 × 20 mL) followed by brine and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to get the crude product. The crude product was purified by CombiFlash on silica gel to afford 70 mg (30%) of 5-bromo-6-(furan-2-yl)pyrazin-2-amine.

[0208] Step-3 Synthesis of 4-(5-amino-3-(furan-2-yl)pyrazin-2-yl)-2-chlorophenol: To a solution of 5-bromo-6-(furan-2-yl)pyrazin-2-amine (70 mg, 0.29 mmol, 1 eq.) in a solution of 1,4-dioxane and water (7 mL, 6:1) was added 2-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (89 mg, 0.35 mmol, 1.2 eq.), Na_2CO_3 (62 mg, 0.585 mmol, 2 eq.), $Pd(PPh_3)_4$ (8 mg, 0.007 mmol, 0.025 eq.). The reaction mixture was deoxygenated using N_2 atmosphere and the reaction mixture was heated at 80°C for 18 h. The reaction was monitored by NMR and LCMS. The reaction mixture was diluted with water (50 mL) and extracted using ethyl acetate (2 × 50 mL). The separated organic layer was dried over sodium sulfate and concentrated under reduced pressure. The crude product was purified by SFC to afford 30 mg (36%) of 4-(5-amino-3-(furan-2-yl)pyrazin-2-yl)-2-chlorophenol.

LCMS: 288 $[M+1]^+$ ^{1}H NMR (400 MHz, CD_3OD) δ 6.42 (d, 1H), 6.50 (d, 1H), 6.60-6.64 (m, 2H), 6.90(d, 1H), 7.00-7.02 (d, 1H), 7.20 (d, 1H), 6.60-6.62 (s, 1H), 7.85 (s, 1H), 10.20(bs, 1H).

Example S8. Synthesis of 5-(2-methyl-1H-benzo[d]imidazol-5-yl)-6-phenylpyrazin-2-amine (compound 1.9)



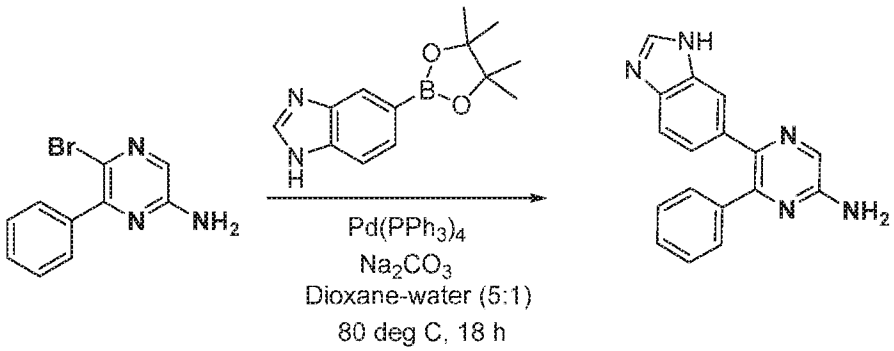
[0209] To a solution of 5-bromo-6-phenylpyrazin-2-amine (100 mg, 0.4 mmol, 1 eq.) in 1,4-dioxane-water (6 mL, 5:1) was added 2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d]imidazole (124mg, 0.48 mmol, 1.2 eq.), Na_2CO_3 (84 mg, 0.8 mmol, 2eq.) and $PdCl_2(PPh_3)_2$ (14 mg, 0.02 mmol, 0.05 eq.). The reaction mixture was deoxygenated with N_2

and the reaction mixture was stirred at 90 °C overnight. The reaction was monitored by NMR and LCMS and found to be complete after 18 h. The reaction mixture was cooled to RT, diluted with water (50 mL) and extracted with ethyl acetate (2 × 50 mL). Combined organic layers were washed with brine (20 mL) and dried over sodium sulfate. Removal of solvent under reduced pressure gave crude which was purified by SFC to afford the desired product as white solid. (20 mg, 16.6%)

LCMS: 302.0 $[M+1]^+$

1H NMR (400 MHz, DMSO-d6) d 12.08 (d, J = 18.42 Hz, 1H), 7.94 (s, 1H), 7.30-7.25(m, 6H), 6.96 - 7.10 (m, 1H), 6.49 (d, J = 9.65 Hz, 2H), 2.43 (s, 3H)

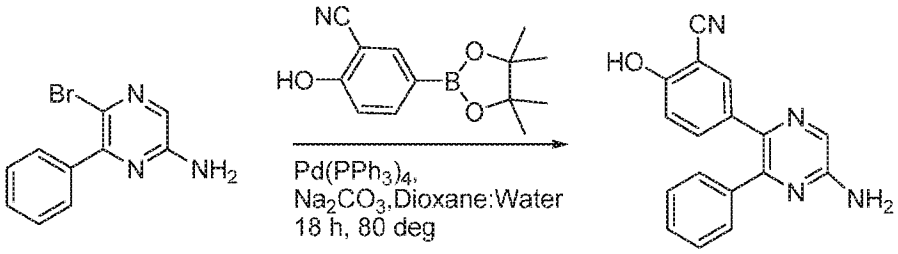
Example S9. Synthesis of 5-(1H-benzo[d]imidazol-6-yl)-6-phenylpyrazin-2-amine. (Compound No. 1.10)



[0210] To a solution of 5-bromo-6-phenylpyrazin-2-amine (100 mg, 0.4 mmol, 1 eq.) in 1,4-dioxane-water (6 mL, 5:1) was added 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzimidazole (124 mg, 0.48 mmol, 1.2 eq.), Na_2CO_3 (84 mg, 0.8 mmol, 2eq.), $(PdCl_2(PPh_3)_2$ (14 mg, 0.02 mmol, 0.05 eq.). The reaction mixture was deoxygenated with N_2 and the reaction mixture was stirred at 80 °C overnight. The reaction was monitored by NMR and LCMS and found to be complete after 18 h. The reaction mixture was cooled to RT, diluted with water (50 mL) and extracted with ethyl acetate (2 × 50 mL). Combined organic layer was washed with brine (20 mL) and dried over sodium sulfate. Removal of solvent under reduced pressure gave crude which was purified by Reverse phase column chromatography to afford 5-(3H-benzimidazol-5-yl)-6-phenyl-pyrazin-2-amine (20 mg, 18.18%) as white solid.

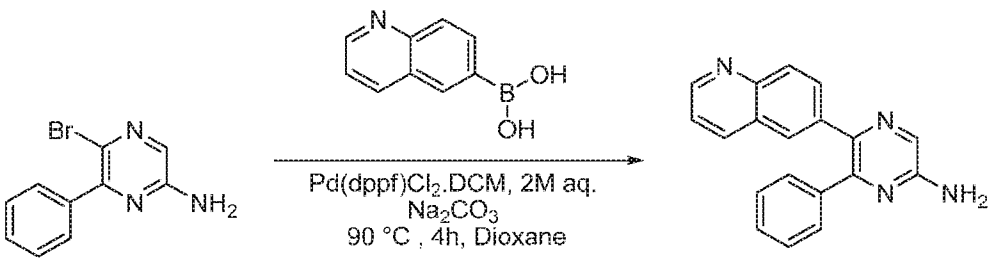
LCMS: 288.1 $[M+1]^+$. ^{1}HNMR (400 MHz, DMSO-d_6) 12.40(s, 1H), 8.18 (s, 1H), 8.00 (s, 1H), 7.65 (s, 1H), 7.40-7.20 (m, 5H), 7.00 (s, 1H), 6.50 (s, 2H).

Example S10. Synthesis of 5-(5-amino-3-phenylpyrazin-2-yl)-2-hydroxybenzonitrile. Compound No. 1.11)



[0211] To a solution of 4-benzyl-5-bromopyrimidin-2-amine (100 mg, 0.40 mmol, 1 eq.) in 1,4-dioxane-water (10 mL, 5:1) was added 2-hydroxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile (107 mg, 0.44 mmol, 1.2 eq.), Na_2CO_3 (84 mg, 0.80 mmol, 2.0 eq.), $Pd(PPh_3)_4$ (11 mg, 0.01 mmol, 0.025 eq.). The reaction mixture was deoxygenated using N_2 atmosphere and the reaction mixture was heated at 90°C for 18 h. The reaction was monitored by NMR and LCMS. The reaction mixture was diluted with water (50 mL) and extracted using ethyl acetate (2 × 50 mL). The separated organic layer was dried over sodium sulfate and concentrated under reduced pressure. The crude product was purified by CombiFlash on silica gel to afford 10 mg (11 %) of 5-(5-amino-3-phenylpyrazin-2-yl)-2-hydroxybenzonitrile.
LCMS: 289 $[M+1]^+$. ^{1}H NMR (400 MHz, CD_3OD) δ 6.80 (d, 1H), 7.32-7.50 (m, 7H), 8.20 (s, 1H).

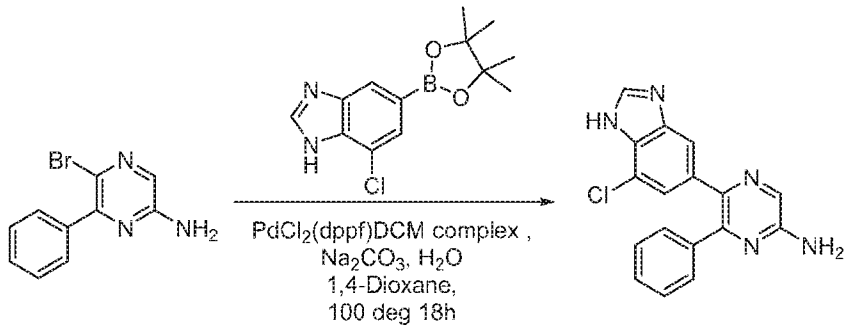
Example S11. Synthesis of 6-phenyl-5-(quinolin-6-yl)pyrazin-2-amine. (Compound No. 1.12)



[0212] To a stirred solution of quinolin-6-ylboronic acid (0.100g, 0.57 mmol, 1.2 equiv) and 5-bromo-6-phenylpyrazin-2-amine (0.120 g, 0.48 mmol, 1.0 equiv) in dioxane (3 mL) was added

2M aqueous Na_2CO_3 (0.101 g, 0.96 mmol, 2.0 equiv, 0.5 mL). The reaction was purged with N_2 for 5 min. To this reaction mixture was added $Pd(dppf)Cl_2$•DCM (0.020 g, 5 mol %) and N_2 was purged again for 5 more mins. The reaction mixture was heated at 90 °C for 4h. The reaction mixture was allowed to cool to RT and extracted using ethyl acetate (2 × 35 mL). The combined organic layers were washed (brine), dried (anhydrous Na_2SO_4) and concentrated under vacuum to get the solid residue which was purified by normal phase silica gel flash column chromatography to get the desired product as off white solid (0.030 g, 21%)
LCMS: 299 $(M+1)^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.84 (d, J = 2.93 Hz, 1H), 8.22 (d, J = 8.31 Hz, 1H), 8.01 (s, 1H), 7.92 (s, 1H), 7.80 (d, J = 8.80 Hz, 1H), 7.42 - 7.60 (m, 2H), 7.20 - 7.41 (m, 4H), 6.73 (s, 2H).

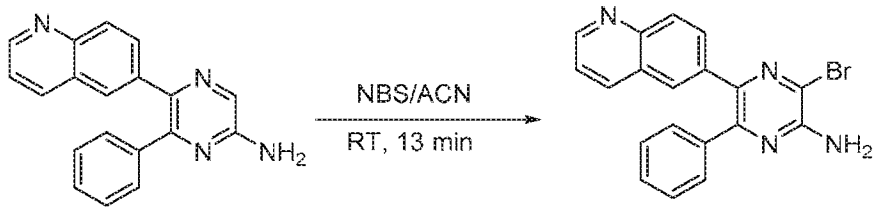
Example S12. Synthesis of 5-(7-chloro-1H-benzo[d]imidazol-5-yl)-6-phenylpyrazin-2-amine. (Compound No. 1.13)



[0213] To a solution of 5-bromo-6-phenylpyrazin-2-amine (120 mg, 0.48 mmol, 1 eq.) in 1,4-dioxane (8 mL): water (2 mL) was added 7-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d]imidazole (146 mg, 0.52 mmol, 1.2 eq.), Na_2CO_3 (101 mg, 0.96 mmol, 2 eq.), $PdCl_2(dppf)$•DCM complex (19 mg, 0.024 mmol, 0.05 eq.). The reaction mixture was deoxygenated using N_2 atmosphere and the reaction mixture was heated at 80 °C for 18 h. The reaction was monitored by NMR and LCMS. The reaction mixture was diluted with water (30 mL) and extracted using ethyl acetate (2 × 50 mL). The separated organic layer was dried over sodium sulfate and concentrated under reduced pressure. The crude product was purified by reverse phase column chromatography to afford 15 mg (8%) of 5-(7-chloro-1H-benzo[d]imidazol-5-yl)-6-phenylpyrazin-2-amine.

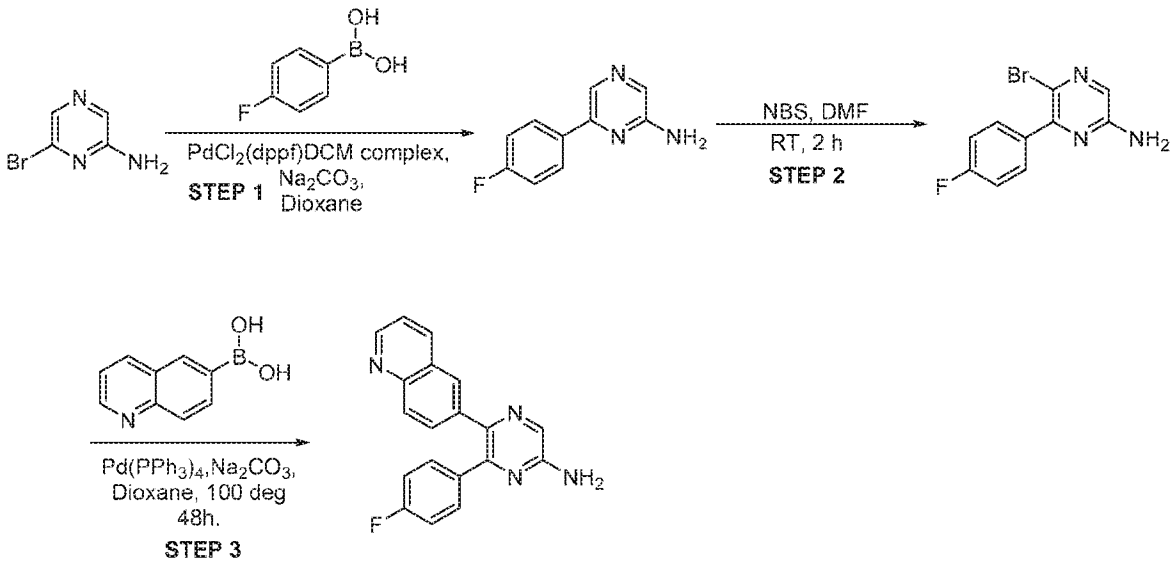
LCMS: 322 $[M+1]^+$. ^1H NMR (400 MHz, DMSO) δ 6.60-6.80 (bs, 2H) 7.22-7.38 (m, 6H), 7.40 (s, 1H), 7.98 (s, 1H), 8.68 (bs, 1H).

Example S13. Synthesis of 3-bromo-6-phenyl-5-(quinolin-6-yl)pyrazin-2-amine. (Compound No. 1.14)



[0214] To a solution of 6-phenyl-5-(quinolin-6-yl)pyrazin-2-amine (20 mg, 0.068 mmol, 1 eq.) in acetonitrile (12 mL) at room temperature was added N-bromosuccinimide (12 mg, 0.068 mmol, 1 eq.) portion wise and the reaction mixture was allowed to stir at room temperature. Progress of reaction was monitored by TLC and was found to be complete after 13 minutes. Reaction mixture was diluted with water and extracted with ethyl acetate (3 × 20 mL). Combined organic layer was washed with water (3 × 20 mL) and dried over anhydrous sodium sulfate. Removal of solvent gave crude which was purified by reversed phase HPLC to give 10 mg (40%) 3-bromo-6-phenyl-5-(quinolin-6-yl)pyrazin-2-amine.
LCMS: 377 $[M+1]^+$. ^1H NMR (400 MHz, DMSO-d6) δ 7.05 (brs, 2H), 7.25-7.40 (m, 5H), 7.45-7.55 (m, 2H), 7.62 (d, 1H), 7.97 (s, 1H), 8.30 (d, 1H), 8.87 (s, 1H).

Example S14. Synthesis of 6-(4-fluorophenyl)-5-(quinolin-6-yl)pyrazin-2-amine. (Compound No. 1.15)



[0215] Step 1: Synthesis of 6-(4-fluorophenyl)pyrazin-2-amine: To a solution of 6-bromopyrazin-2-amine (1.00 g, 5.780 mmol, 1 eq.) in 1,4 dioxane (20 mL) was added 4-fluorophenylboronic acid (1.213 g, 8.67 mmol, 1.5 eq.), Na_2CO_3 (1.225 g, 11.56 mmol, 2 eq.) and $PdCl_2$(dppf)•DCM complex (0.235 g, 0.289 mmol, 0.05 eq.). The reaction mixture was deoxygenated using N_2 atmosphere and the reaction mixture was heated at 100 °C for 48 h. The reaction was monitored by NMR. The reaction mixture was filtered through Celite with wash of ethyl acetate (2 × 50 mL). The reaction mixture was diluted with water (50 mL) and extracted using ethyl acetate (2 × 50 mL). The separated organic layer was dried over sodium sulfate and concentrated under reduced pressure. The crude product was purified by Combi-Flash column chromatography to afford 550 mg (50%) of 6-(4-fluorophenyl)pyrazin-2-amine.

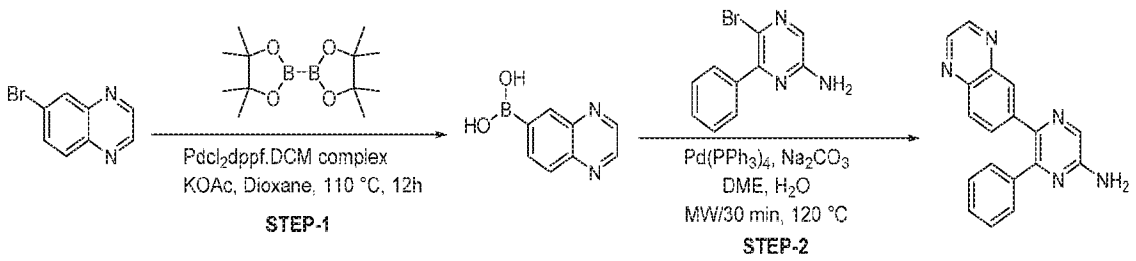
[0216] Step 2: Synthesis of 5-bromo-6-(4-fluorophenyl)pyrazin-2-amine: To a solution of 6-(4-fluorophenyl)pyrazin-2-amine (0.530 g, 2.80 mmol, 1 eq.) in mixture of DMF (5 mL) was added N-bromosuccinimide (0.549 g, 3.08 mmol, 1 eq.). The reaction mixture was stirred at room temperature for 1 h. The reaction was monitored by TLC and NMR. The reaction was diluted with water (50 mL) and extracted by ethyl acetate (2 × 50 mL). The organic layer was separated, washed water (5 × 50 mL) and brine and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to get the crude product. The crude product was

purified by Combi-Flash column chromatography to afford 250 mg (32%) of 5-bromo-6-(4-fluorophenyl)pyrazin-2-amine.

[0217] Step 3: Synthesis of 6-(4-fluorophenyl)-5-(quinolin-6-yl)pyrazin-2-amine: To a solution of 5-bromo-6-(4-fluorophenyl)pyrazin-2-amine (100 mg, 0.37 mmol, 1 eq.) in 1,4 dioxane (8 mL): water (2 mL) was added quinolin-6-ylboronic acid (77 mg, 0.44 mmol, 1.2 eq.), Na_2CO_3 (79 mg, 0.74 mmol, 2eq.), $Pd(PPh_3)_4$ (21 mg, 0.018 mmol, 0.05 eq.). The reaction mixture was deoxygenated using N_2 atmosphere and the reaction mixture was heated at 100 °C for 48 h. The reaction was monitored by TLC and LCMS. The reaction mixture was diluted with water (20 mL) and extracted using ethyl acetate (2 × 50 mL). The separated organic layer was dried over sodium sulfate and concentrated under reduced pressure. The crude product was purified by supercritical fluid chromatography to afford 45 mg (38%) of 6-(4-fluorophenyl)-5-(quinolin-6-yl)pyrazin-2-amine.

LCMS: 317 $[M+1]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 6.58 (bs, 2H), 7.30 (t, 2H), 7.60 (q, 1H), 8.02-8.20 (m, 4H), 8.40-8.50 (m, 2H), 8.60 (s, 1H), 8.98 (bs, 1H) .

Example S15. Synthesis of 6-phenyl-5-quinoxalin-6-yl-pyrazin-2-amine. (Compound No. 1.16)



[0218] Step 1: Synthesis of quinoxalin-6-ylboronic acid: To a solution of 6-bromoquinoxaline (500 mg, 2.39 mmol, 1 eq.) in 1,4-dioxane (10 mL) was added 5-(4,4,5,5-Bis(pinacolato)diboron (729 mg, 2.87 mmol, 1.2 eq.), KOAc (469 mg, 4.78 mmol, 2 eq.), and $PdCl_2$dppf•DCM complex (195 mg, 0.23 mmol, 0.1 eq.). The reaction mixture was deoxygenated with N_2 allowed stir at 80 °C for 18 h. The reaction mixture was cooled to RT, diluted with water (50 mL) and extracted with ethyl acetate (2 × 50 mL). Combined organic layer was washed with brine (20 mL) and dried over sodium sulfate. Removal of solvent under reduced pressure gave crude which was purified by normal phase Combi-Flash column

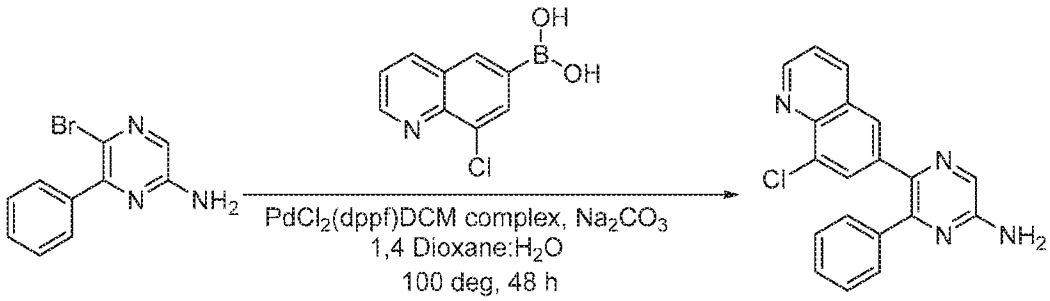
chromatography (0-100% EtOAC-Hexane) to afford quinoxalin-6-ylboronic acid (350 mg, 85%) as brown oil.

LCMS: 175 $[M+1]^+$

[0219] Step 2: Synthesis of 6-phenyl-5-quinoxalin-6-yl-pyrazin-2-amine: To a solution of 5-bromo-6-phenyl-pyrazin-2-amine (100 mg, 0.40 mmol, 1 eq.) in DME-water (2 mL) was added quinoxalin-6-yl boronic acid (69.6 mg, 0.40 mmol, 1 eq.), Na_2CO_3 (106 mg, 1.0 mmol, 2.5 eq.), and $Pd(PPh_3)_4$ (13.86 mg, 0.01 mmol, 0.03 eq.). The reaction mixture was deoxygenated with N_2 and allowed stir at 120 °C for 30 min under Microwave irradiation. The reaction was monitored by LCMS and found to be complete after 30 min. The reaction mixture was cooled to RT, diluted with water (20 mL) and extracted with ethyl acetate (2 × 50 mL). Combined organic layer was washed with brine (20 mL) and dried over sodium sulfate. Removal of solvent under reduced pressure gave crude which was purified by reversed phase column chromatography to afford 6-phenyl-5-quinoxalin-6-yl-pyrazin-2-amine (10 mg, 8 %) as a white solid.

LCMS: 300 $[M+1]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 8.56 (s, 2H), 8.00 (s, 1H), 7.98-7.80 (m, 2H), 7.65 (m, 1H), 7.40-7.20 (m, 5H), 6.80 (s, 2H).

Example S16. Synthesis of 5-(8-chloroquinolin-6-yl)-6-phenylpyrazin-2-amine. (Compound No. 1.17)

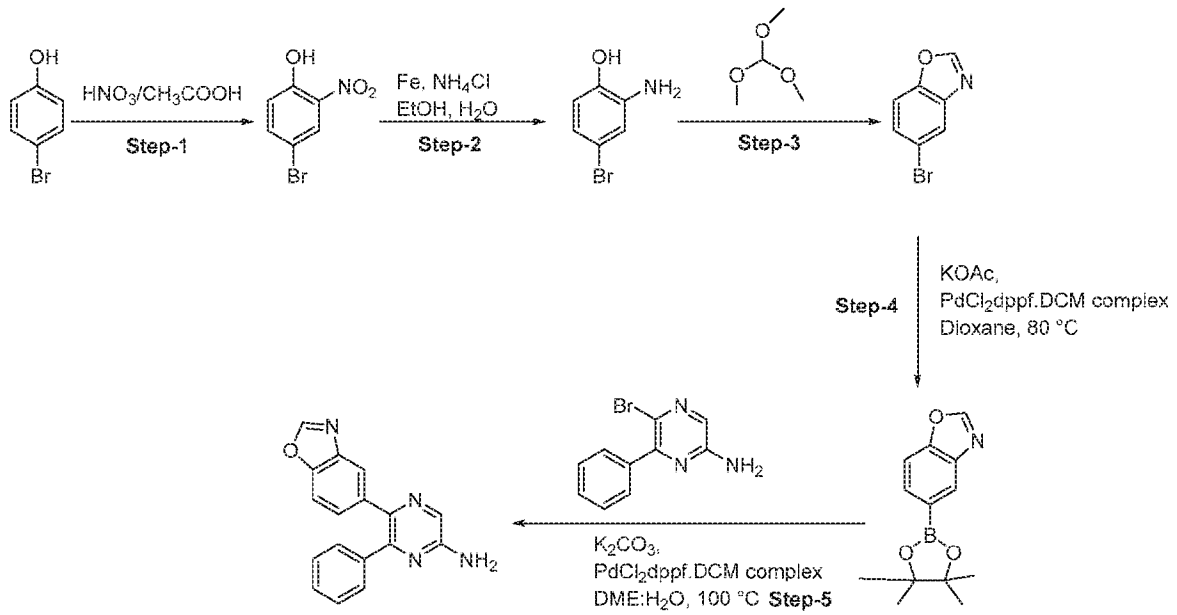


[0220] To a solution of 5-bromo-6-phenylpyrazin-2-amine (100 mg, 0.4 mmol, 1 eq.) in 1,4 dioxane (5 mL): water (1 mL) was added 8-chloroquinolin-6-ylboronic acid (99 mg, 0.48 mmol, 1.2 eq.), Na_2CO_3 (84 mg, 0.8 mmol, 2 eq.), and $PdCl_2(dppf)$•DCM (16 mg, 0.02 mmol, 0.05 eq.). The reaction mixture was deoxygenated using N_2 atmosphere and the reaction mixture was heated at 80 °C for 18 h. The reaction was monitored by NMR and LCMS. The reaction mixture was diluted with water (50 mL) and extracted using ethyl acetate (2 × 50 mL). The separated

organic layer was dried over sodium sulfate and concentrated under reduced pressure. The crude product was purified by Supercritical Fluid Chromatography to afford 10 mg of 5-(8-chloroquinolin-6-yl)-6-phenylpyrazin-2-amine.

LCMS: 333 $[M+1]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 7.30-7.40 (m, 5H), 7.60 (m, 1H), 7.70 (s, 1H), 7.88(s, 1H), 8.00 (s, 1H), 8.30 (d, 1H), 8.98 (d, 1H).

Example S17. Synthesis of 5-(benzo[d]oxazol-5-yl)-6-phenylpyrazin-2-amine. (Compound No. 1.18)



[0221] Step 1: Synthesis of 4-bromo-2-nitrophenol: To a solution of 6-bromophenol (5 g, 28.90 mmol,1 eq.) in acetic acid (10 mL) was added nitric acid (1 mL) drop wise. Reaction mixture was stirred at RT for 5 min. Progress of the reaction was monitored by LCMS and TLC. The reaction mixture was poured over ice, resulting in solid precipitates which were filtered and dried under vacuum to afford 4-bromo-2-nitrophenol (6 g, 95.23%) as yellow solid.

LCMS: 175 $[M+1]^+$

[0222] Step 2: Synthesis of 2-amino-4-bromophenol: To a solution of 4-bromo-2-nitrophenol (3 g, 13.76 mmol, 1 eq.) in ethanol:water (50 mL, 9:1) was added ammonium chloride (2.1 g, 41.28 mmol, 3 eq.) and Iron powder(2.3g, 41.28 mmol). The reaction was stirred at 90 °C for 2 h. Progress of the reaction was monitored by LCMS. The reaction mixture was cooled to RT, evaporated under reduced pressure to remove the solvent, diluted with water (20 mL) and

extracted with ethyl acetate (2 × 50 mL). The combined organic layer was washed with brine (20 mL) and dried over anhydrous sodium sulfate. Removal of solvent under reduced pressure gave crude material which was purified by flash chromatography to obtain the 2-amino-4-bromophenol (2 g, 80%) as brown solid.

LCMS: 188, 190 $[M+1]^+$

[0223] Step 3: Synthesis of 5-bromobenzo[d]oxazole: A solution 2-amino-4-bromophenol (1.5, 7.90 mmol, 1 eq.) in methylorthoformate (10 mL) was stirred at 150 °C for 6 h. Progress of the reaction was monitored by LCMS. The reaction mixture was cooled to RT, evaporated under reduced pressure to remove the solvent; diluted with water (20 mL) and extracted with ethyl acetate (2 × 50 mL). The combined organic layer was washed with brine (20 mL) and dried over anhydrous sodium sulfate. Removal of solvent under reduced pressure gave crude material which was purified by flash chromatography to obtain the 5-bromobenzo[d]oxazole (1.2 g, 80.0%) as yellow solid.

^{1}HNMR (400 MHz, DMSO-d_6) 8.80 (s, 1H), 8.00 (s, 1H), 7.80 (d, 1H), 7.60 (d, 1H).

[0224] Step 4: Synthesis of 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[d]oxazole: To a solution of 5-bromobenzo[d]oxazole (1.2 g, 6.06 mmol, 1 eq.) in DMF (10 mL) was added 5-(4,4,5,5-Bis(pinacolato)diboron (1.68 g, 1.66 mmol, 1.1 eq.), KOAc (1.7 g, 18.09 mmol, 3eq.), and $PdCl_2$(dppf)•DCM complex (247 mg, 0.23 mmol, 0.05 eq.). The reaction mixture was deoxygenated with N_2 and the reaction mixture was stirred at 80 °C for 18 h. The progress of the reaction was monitored by LCMS. The reaction mixture was cooled to RT, diluted with water (50 mL) and extracted with ethyl acetate (2 × 50 mL). Combined organic layer was washed with brine (20 mL) and dried over sodium sulfate. Removal of solvent under reduced pressure gave crude which was purified by flash chromatography(0-100% Hexane-EtOAc) to afford 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[d]oxazole (0.900 g, 60%) as off white solid.

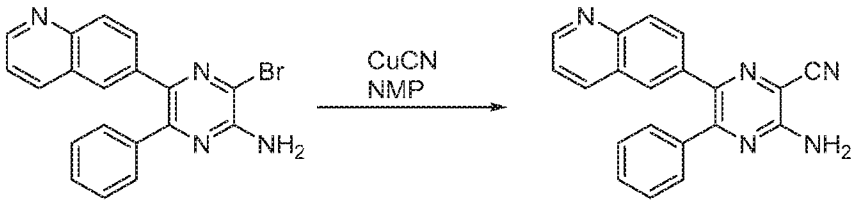
LCMS: 245, 247 $[M+1]^+$

[0225] Step 5: Synthesis of 5-(benzo[d]oxazol-5-yl)-6-phenylpyrazin-2-amine: To a solution of 5-bromo-6-phenylpyrazin-2-amine (100 mg, 0.40 mmol, 1 eq) in dioxane-water (5:1 mL) was added 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[d]oxazole (122 mg, 0.48 mmol, 1.2 eq), Na_2CO_3 (84.8 mg, 0.80 mmol, 2.0 eq), and $PdCl_2$(dppf)•DCM complex (16.32 mg, 0.02 mmol, 0.05 eq.). The reaction mixture was deoxygenated with N_2 and stirred at 100 °C for 12 h. The progress of the reaction was monitored by LCMS. The reaction mixture was cooled to RT,

diluted with water (20 mL) and extracted with ethyl acetate (2 × 50 mL). Combined organic layer was washed with brine (20 mL) and dried over anhydrous sodium sulfate. Removal of solvent under reduced pressure gave crude material which was purified by reversed-phase column chromatography to afford 5-(benzo[d]oxazol-5-yl)-6-phenylpyrazin-2-amine (10 mg, 9.00%) as an off white solid.

LCMS: 289.1 (M+1). ^{1}HNMR (400 MHz, DMSO-d_6) 8.70(s, 1H), 8.50 (s, 1H), 7.72-7.56 (m, 2H), 7.40-7.20 (m, 6H), 6.60 (s, 2H).

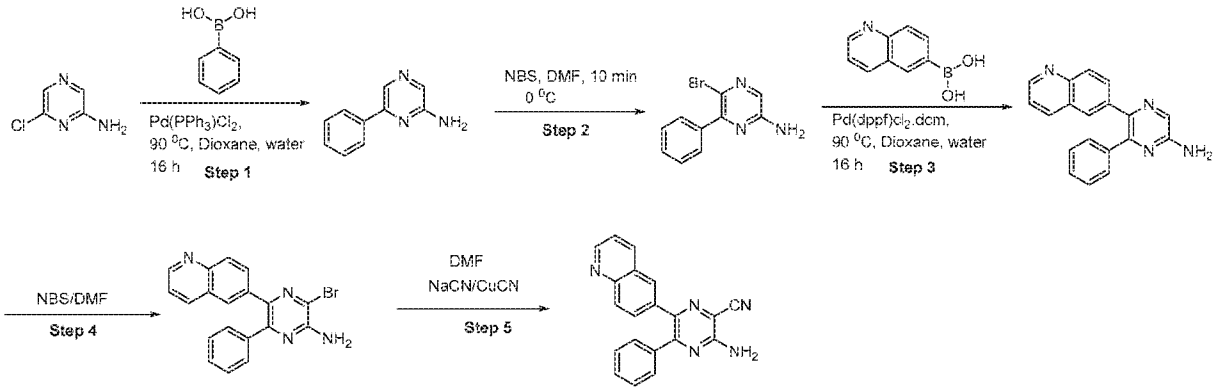
Example S18A. Synthesis of 3-amino-5-phenyl-6-(quinolin-6-yl)pyrazine-2-carbonitrile. (Compound No. 1.19)



[0226] To a stirred solution of 6-phenyl-5-(quinolin-6-yl)pyrazin-2-amine (0.220 g, 0.58 mmol, 1.0 eq) in NMP (1.5 mL) was added cuprous cyanide (0.155 g, 1.74 mmol, 3.0 eq). The reaction mixture was allowed to stir at 170 °C for 1h. The progress of the reaction was monitored by LCMS. The reaction mixture was allowed to cool to RT and extracted using ethyl acetate (3 × 50 mL). The combined organic layers were washed (brine), dried (anhydrous Na_2SO_4) and concentrated under vacuum to get the solid which was purified by normal phase column chromatography to get the desired product as an off white solid (0.020 g, 10 %).

LCMS: 324 $(M+1)^+$. ^{1}H NMR (400 MHz, METHANOL-d_4) δ 8.83 (d, J = 3.07 Hz, 1H), 8.25 (d, J = 7.45 Hz, 1H), 7.95 (d, J = 2.19 Hz, 1H), 7.88 (d, J = 8.77 Hz, 1H), 7.65 (dd, J = 2.19, 8.77 Hz, 1H), 7.52 (dd, J = 4.38, 8.33 Hz, 1H), 7.40 - 7.47 (m, 2H), 7.36 (d, J = 7.45 Hz, 1H), 7.22 - 7.32 (m, 2H).

Example S18B. Alternative synthesis of 3-amino-5-phenyl-6-(quinolin-6-yl)pyrazine-2-carbonitrile. (Compound No. 1.19)



[0227] Step 1: Synthesis of 6-phenylpyrazin-2-amine: To a stirred solution of 6-chloropyrazin-2-amine (50g, 0.3861mol) in dioxane:water (400 mL;100mL) was added benzeneboronic acid (56.4 g,0.46 mol). The reaction mixture was purged with nitrogen for 20 min then charged Na_2CO_3 (70.6g, 0.57 mol) and $Pd(PPh_3)Cl_2$ (13.5g, 0.01930 mol). The reaction mixture was again purged with nitrogen .The reaction mixture was stirred at RT for 10 min followed by heating at 90 ^{0}C for 16 h. The reaction was monitored by TLC & LCMS. The reaction mixture was filter through celite and distilled. The reaction was diluted with water and extracted with ethyl acetate (3x 200 mL). The combined organic layers were washed (brine), dried (anhydrous Na_2SO_4) & concentrated under vacuum to get the solid which was purified by column chromatography over silica gel (100-200 mesh) [Ethyl acetate: Hexane (3:7) as eluent] to get the desired product (55 g, 83%).

LCMS: 172 $[M+1]^+$. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.38 (s, 1H), 7.83 - 7.99 (m, 3H), 7.40 - 7.49 (m, 3H), 4.82 (br. s., 2H)

[0228] Step 2: Synthesis of 5-bromo-6-phenylpyrazin-2-amine: To a stirred solution of 6-phenylpyrazin-2-amine (48g, 0.2803mol) in DMF was added NBS (49.9 g, 0.28 mol) at 0^{0}c under nitrogen atmosphere. The reaction mixture was stirred at RT for 16 h. The reaction was monitored by TLC & LCMS. The reaction was diluted with water and extracted with ethyl acetate (3x 100 mL). The combined organic layers were washed (brine), dried (anhydrous Na_2SO_4) & concentrated under vacuum to get the solid which was purified by column chromatography silica gel (100-200 mesh) [Ethyl acetate: Hexane (1:4) as eluent] to get the desired product (38 g, 55%).

LCMS: 252 $[M+2]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.68 (s, 1H), 7.55 - 7.64 (m, 2H), 7.40 - 7.51 (m, 3H), 6.75 (br. s., 2H)

[0229] Step 3: synthesis of 6-phenyl-5-(quinolin-6-yl)pyrazin-2-amine: To a stirred solution of 5-bromo-6-phenylpyrazin-2-amine (38g, 0.1519mol) in dioxane:water (320 mL; 80mL) was added quinolin-6-ylboronic acid (46.4g, 0.18 mol). The reaction mixture was purged with nitrogen for 20 min then charged with Na_2CO_3 (32.2g, 0.3038mol) and $Pd(dppf)Cl_2$ (6.19 g, 0.007 mol). The reaction mixture was again purged with nitrogen .The reaction mixture was stirred at RT for 10 min followed by heating at 90 ^{0}C for 16 h. The reaction was monitored by TLC & LCMS. The reaction mixture was filtered through celite and distilled. The reaction was diluted with water and extracted with ethyl acetate (3x 200 mL). The combined organic layers were washed (brine), dried (anhydrous Na_2SO_4) & concentrated under vacuum to get the solid which was purified by column chromatography over basic alumina [Ethyl acetate: Hexane (3:7) as eluent] to get the desired product (31 g, 68%).

LCMS: 299 $[M+1]^+$. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.83 (d, J = 3.07 Hz, 1H), 8.21 (d, J = 7.89 Hz, 1H), 8.02 (s, 1H), 7.93 (s, 1H), 7.80 (d, J = 8.33 Hz, 1H), 7.41 - 7.64 (m, 2H), 7.16 - 7.40 (m, 5H), 6.73 (s, 2H)

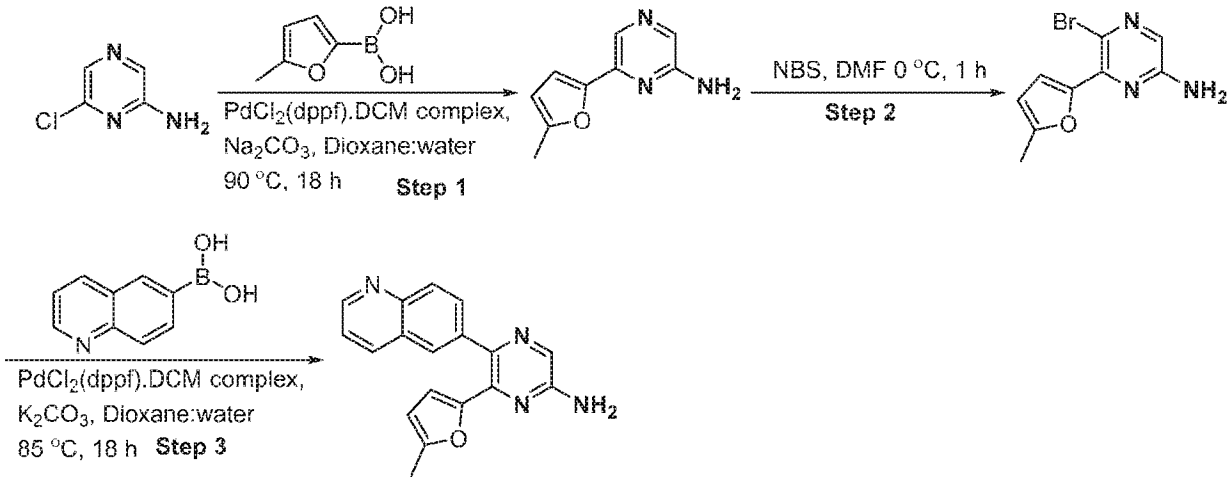
[0230] Step 4: synthesis of 3-bromo-6-phenyl-5-(quinolin-6-yl)pyrazin-2-amine**:** To a stirred solution of 6-phenyl-5-(quinolin-6-yl) pyrazin-2-amine (21g, 0.07 mol) in DMF was added NBS (12.5g, 0.07 mol) at 0^{0}c under nitrogen atmosphere. The reaction mixture was stir at RT for 16h. The reaction was monitored by TLC & LCMS. The reaction was diluted with water and extracted with ethyl acetate (3x 30 mL). The combined organic layers were washed (brine), dried (anhydrous Na_2SO_4) & concentrated under vacuum to get the solid which was purified by column chromatography over basic alumina [Ethyl acetate: Hexane (3:7) as eluent] to get the desired product (18 g, 69%).

LCMS: 377 $[M+1]^+$. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.88 (br. s., 1H), 8.11-7.96 (m, 3H), 7.60-7.26(m, 7H), 5.23 (br. s., 2H).

[0231] Step 5: Synthesis of 3-amino-5-phenyl-6-(quinolin-6-yl)pyrazine-2-carbonitrile: To a stirred solution of NaCN (1.56g, 0.03 mol) and CuCN (5.7g, 0.06 mol) in dry DMF (150 mL) was added 3-bromo-6-phenyl-5-(quinolin-6-yl)pyrazin-2-amine (12.0 g, 0.03 mol) at 120^0 C. The reaction mixture was stirred at 145 ^{0}C for 12h. The reaction was monitored by TLC & LCMS. The reaction was distilled. The crude product was poured in ice-water the solid precipitate out. The reaction mixture pH was adjusted with aqueous ammonia and extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed (brine), dried (anhydrous Na_2SO_4) &

concentrated under vacuum to get the solid which was purified by column chromatography using basic alumina [Ethyl acetate: Hexane (1:1) as eluent] to get the desired product (3.8 g, 34%). LCMS: 354 $[M+1]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.88 (d, J = 2.63 Hz, 1H), 8.29 (d, J = 7.89 Hz, 1H), 7.99 (s, 1H), 7.84 (d, J = 8.77 Hz, 1H), 7.58 (br. s., 2H), 7.47 - 7.54 (m, 2H), 7.35 - 7.42 (m, 3H), 7.27 - 7.34 (m, 2H)

Example S19. Synthesis of 6-(5-methylfuran-2-yl)-5-(quinolin-6-yl)pyrazin-2-amine. (Compound No. 1.20)



[0232] Step 1: Synthesis of 6-(5-methylfuran-2-yl)pyrazin-2-amine: To a solution of 6-chloropyrazin-2-amine (1.00 g, 7.75 mmol, 1 eq.) in 1,4-dioxane (20 mL) was added 5-methylfuran-2-ylboronic acid (1.074 g, 8.52 mmol, 1.1 eq.), Na_2CO_3 (1.23 g, 11.62 mmol, 1.5 eq.), and $PdCl_2(dppf)$•DCM complex (0.316 g, 0.38 mmol, 0.05 eq.). The reaction mixture was deoxygenated using N_2 atmosphere and the reaction mixture was heated at 90°C for 18 h. The progress of the reaction was monitored by LCMS. The reaction mixture was filtered through Celite and washed with ethyl acetate (2 × 20 mL). The filtrate was diluted with water (50 mL) and extracted using ethyl acetate (2 × 50 mL). The separated organic layer was dried over sodium sulfate and concentrated under reduced pressure. The crude product was purified by flash column chromatography to afford 6-(5-methylfuran-2-yl)pyrazin-2-amine (0.600 g, 43%). LCMS: 176 $[M+1]^+$

[0233] Step 2: Synthesis of 5-bromo-6-(5-methylfuran-2-yl)pyrazin-2-amine: To a solution of 6-(5-methylfuran-2-yl)pyrazin-2-amine (300 mg, 1.69 mmol, 1 eq.) in DMF (5 mL) was

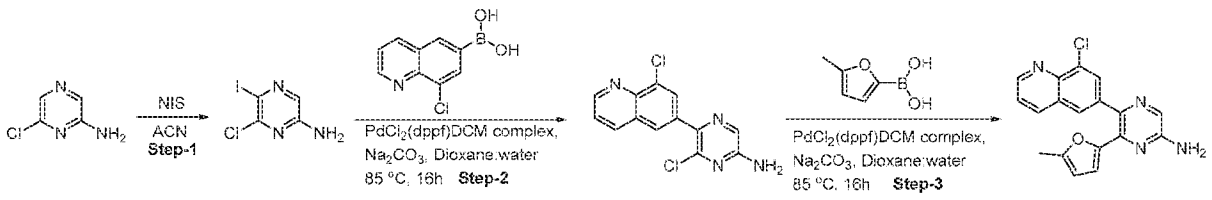
added NBS (301 mg, 1.69 mmol, 1 eq.) portion-wise at 0 °C. The reaction mixture was stirred at 0 °C for 1 h. The reaction was monitored by TLC and NMR. The reaction was diluted with water (50 mL) and extracted by ethyl acetate (2 × 20 mL). The organic layer was separated, washed with water (5 × 20 mL) and brine and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to get the crude product. The crude product was purified by flash column chromatography to afford 5-bromo-6-(5-methylfuran-2-yl)pyrazin-2-amine (0.100 g, 22%).

LCMS: 254 $[M+1]^+$

[0234] Step 3: Synthesis of 6-(5-methylfuran-2-yl)-5-(quinolin-6-yl)pyrazin-2-amine: To a solution of 5-bromo-6-(5-methylfuran-2-yl)pyrazin-2-amine (100 mg, 0.39 mmol, 1 eq.) in 1,4-dioxane (8 mL): water (1 mL) was added quinolin-6-ylboronic acid (74 mg, 0.43 mmol, 1.2 eq.), K_2CO_3 (81 mg, 0.59 mmol, 1.5 eq.), and $PdCl_2$(dppf)•DCM complex (16 mg, 0.019 mmol, 0.05 eq.). The reaction mixture was deoxygenated using N_2 atmosphere and the reaction mixture was heated at 100 °C for 18 h. The reaction was monitored by NMR and LCMS. The reaction mixture was diluted with water (50 mL) and extracted using ethyl acetate (2 × 50 mL). The separated organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by supercritical fluid chromatography to afford 6-(5-methylfuran-2-yl)-5-(quinolin-6-yl)pyrazin-2-amine (0.020 g, 16.80%).

LCMS: 303 $[M+1]^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.03 (s, 3H), 6.12 (s, 1H), 6.20 (s, 1H), 6.70 (bs, 2H), 7.50 (d, 1H), 7.64 (d, 1H), 7.90 (s, 1H), 7.99 (d, 1H), 8.00 (s, 1H), 8.38 (d, 1H), 8.90 (d, 1H).

Example S20. Synthesis of 5-(8-chloroquinolin-6-yl)-6-(5-methylfuran-2-yl)pyrazin-2-amine. (Compound No. 1.21)



[0235] Step-1: Synthesis of 6-chloro-5-iodopyrazin-2-amine: To a stirred solution of 2-amino-6-chloropyrazine (2.0 g, 1.0 eq., 15.50 mmol) in acetonitrile (20 mL) was added NIS (3.46 g, 1.0 eq., 15.50 mmol) at 0 °C. The reaction was allowed to stir at RT. Progress of the reaction was

monitored by TLC and LCMS. After completion of the reaction the solvent was evaporated under vacuum and the solid was extracted using ethyl acetate (3 × 100 mL). The combined organic layers were washed (brine), dried (anhydrous Na_2SO_4) and concentrated under vacuum to get the solid which was purified by normal phase column chromatography to get the desired product (1.7 g, 42%).

LCMS: 256 $[M+1]^+$

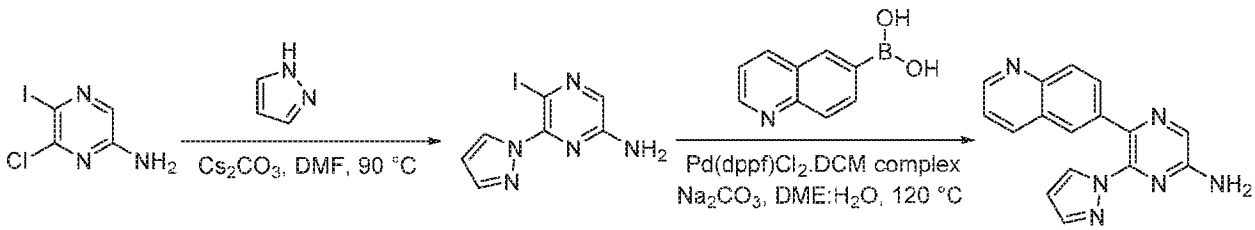
[0236] Step-2: Synthesis of 6-chloro-5-(8-chloroquinolin-6-yl)pyrazin-2-amine: To a stirred solution of 6-chloro-5-iodopyrazin-2-amine (0.500 g, 1.95 mmol, 1.0 eq.) and (8-chloroquinolin-6-yl)boronic acid (0.487 g, 2.3 mmol, 1.2 eq.) in 1,4-dioxane (4.0 mL) was added sodium carbonate (0.307g, 2.9 mmol, 1.5 eq.) and 1 mL of water. The reaction mixture was purged with nitrogen and Pd(dppf)Cl_2•DCM complex (0.084 g, 0.05 eq.) was added. The reaction mixture was again purged with nitrogen and heated at 85 °C for 16 h. Progress of the reaction was monitored by TLC and LCMS. Reaction mixture was allowed to cool to RT and extracted using ethyl acetate (3 x 50 mL). The combined organic layers were washed (brine), dried (anhydrous Na_2SO_4) and concentrated under vacuum to get the solid which was purified by normal phase column chromatography to get the desired product (0.140 g, 25%).

LCMS: 291 $[M+1]^+$

[0237] Step-3: Synthesis of 5-(8-chloroquinolin-6-yl)-6-(5-methylfuran-2-yl)pyrazin-2-amine: To a stirred solution of 6-chloro-5-(8-chloroquinolin-6-yl)pyrazin-2-amine (0.100 g, 0.34 mmol, 1.0 eq.) and (5-methylfuran-2-yl)boronic acid (0.051 g, 0.41 mmol, 1.2 eq.) in1,4-dioxane (3.0 mL) was added sodium carbonate (0.054 g, 0.54 mmol, 1.5 eq.) and 1 mL of water. The reaction mixture was purged with nitrogen and Pd(dppf)Cl_2•DCM complex (0.014 g, 0.05 eq.) was added. The reaction mixture was again purged with nitrogen and heated at 85 °C for 16 h. Progress of the reaction was monitored by TLC and LCMS. Reaction mixture was allowed to cool to RT and extracted using ethyl acetate (3 x 25 mL). The combined organic layers were washed (brine), dried (anhydrous Na_2SO_4) and concentrated under vacuum to get the solid which was purified by normal phase column chromatography to get the desired product (0.025 g, 14%).

LCMS: 337 $[M+1]^+$. ^1H NMR (400 MHz, DMSO-d_6) d 9.00 (br. s., 1H), 8.45 (d, J = 7.89 Hz, 1H), 8.01 (br. s., 1H), 7.90 (s, 1H), 7.83 (br. s., 1H), 7.65 (br. s., 1H), 6.80 (br. s., 2H), 6.38 (br. s., 1H), 6.14 (br. s., 1H), 2.08 (s, 3H).

Example S21. Synthesis of 6-(1H-pyrazol-1-yl)-5-(quinolin-6-yl)pyrazin-2-amine (Compound No. 1.22)



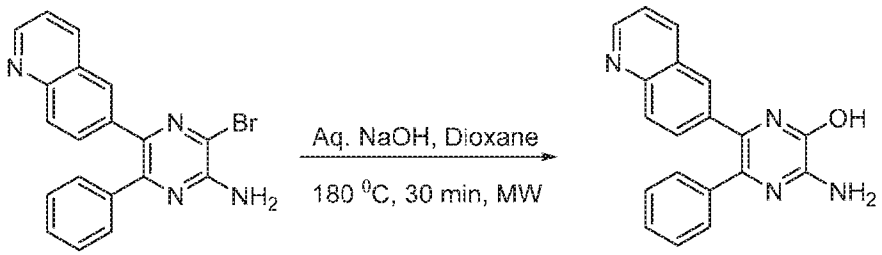
[0238] Step 1: Synthesis of 5-iodo-6-(1H-pyrazol-1-yl)pyrazin-2-amine : To a solution of 6-chloro-5-iodopyrazin-2-amine (300 mg, 1.2 mmol, 1 eq.) in DMF (8 mL) was added pyrazole (159 mg, 2.3 mmol, 2.0 eq.) and Cs_2CO_3 (1.148 g, 3.5 mmol, 3.0 eq.). The reaction mixture was allowed to heat at 90 °C for 18 h. The progress of the reaction was monitored by TLC and LCMS. The reaction mixture was diluted with water (30 mL) and extracted using ethyl acetate (2 × 50 mL). The separated organic layer was dried over sodium sulfate and concentrated under reduced pressure. The crude product was purified by reverse phase column chromatography to afford the desired product (120 mg, 35%).

LCMS: 288 $[M+1]^+$

[0239] Step 2: Synthesis of 6-(1H-pyrazol-1-yl)-5-(quinolin-6-yl)pyrazin-2-amine: To a solution of 5-iodo-6-(1H-pyrazol-1-yl)pyrazin-2-amine (0.100 g, 0.34 mmol, 1 eq.) in DME (4.0 mL) was added boronic acid (0.071 g, 0.41 mmol, 1.2 eq.), Na_2CO_3 (0.047 g, 0.45 mmol, 1.3 eq.) and $PdCl_2(dppf)$•DCM complex (0.014 g, 0.017 mmol, 0.05 eq.). The reaction mixture was deoxygenated using N_2 atmosphere and the reaction mixture was heated at 120 °C for 1.5 h under microwave irradiation. The reaction was monitored by TLC and LCMS. The reaction mixture was filtered through Celite. The filtrate was extracted with ethyl acetate (2 × 25 mL). The separated organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude product was purified by reverse phase column chromatography to afford desired product (13 mg, 13%).

LCMS 289 $[M+1]^+$. ^1H NMR (400 MHz, DMSO-d6) δ 8.84 (d, J = 2.63 Hz, 1H), 8.23 (d, J = 8.33 Hz, 1H), 8.12 (s, 1H), 8.07 (d, J = 2.19 Hz, 1H), 7.74 - 7.84 (m, 2H), 7.56 (s, 1H), 7.49 (dd, J = 4.17, 8.11 Hz, 1H), 7.30 (d, J = 7.02 Hz, 1H), 7.07 (s, 1H), 6.47 (br. s., 1H).

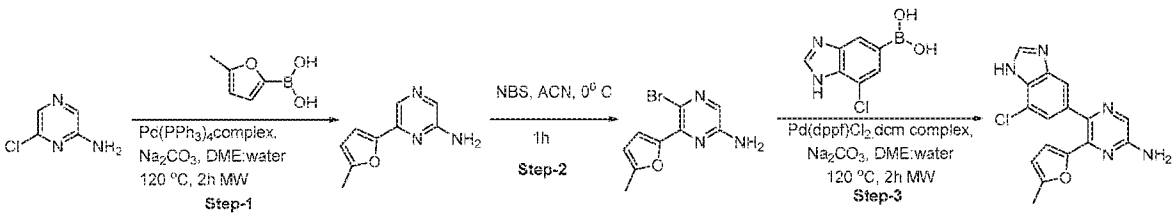
Example S22. Synthesis of 3-amino-5-phenyl-6-(quinolin-6-yl)pyrazin-2-ol (Compound No. 1.241)



[0240] To a stirred solution of 3-bromo-6-phenyl-5-(quinolin-6-yl)pyrazin-2-amine (0.050 g, 0.13 mmol, 1.0 eq) in dioxane (1 mL) was added 10% aqueous NaOH solution (1 mL). The resulting reaction mixture was heated at 180 ^{0}C for 30 min under microwave irradiation. The reaction mixture was allowed to cool to RT. The solvent was evaporated under vacuum to get the solid which was purified by reversed phase column chromatography to get the desired product as yellowish green solid (0.018 g, 45 %).

LCMS: 315 $(M+1)^{+}$. ^{1}H NMR: (400 MHz, DMSO-d_6) δ 11.96 (br. s., 1H), 8.88 (s, 1H), 8.28 (d, *J* = 7.45 Hz, 1H), 7.93 (br. s., 1H), 7.82 (d, *J* = 8.77 Hz, 1H), 7.52 (d, *J* = 3.95 Hz, 1H), 7.40 (d, *J* = 9.21 Hz, 1H), 6.99 - 7.28 (m, 5H), 6.84 (br. s., 2H).

Example S23. Synthesis of 5-(7-chloro-1H-benzimidazol-5-yl)-6-(5-methylfuran-2-yl)pyrazin-2-amine (Compound No. 1.45)



[0241] Step-1: Synthesis of 6-(5-methylfuran-2-yl)pyrazin-2-amine: 6-chloropyrazin-2-amine (1.0 g, 7.7 mmol, 1.0 eq.) and (5-methylfuran-2-yl)boronic acid (1.2 g, 9.3 mmol, 1.2 eq) was dissolved in DME:water (10.0 mL, 8:2). The reaction mixture was deoxygenated using nitrogen followed by addition of $Pd(PPh_3)_4$ complex (0.045 g, 0.04 mmol, 0.05 eq.) and sodium carbonate (1.6 g, 15.4 mmol, 2.5 eq.). The reaction mixture was again purged with nitrogen and heated at 150 °C for 2 h under microwave irradiation. Progress of the reaction was monitored by TLC and

LCMS. Reaction mixture was allowed to cool to RT and quenched by adding water and extracted using ethyl acetate (3 x 100 mL) The combined organic layers were washed (brine), dried (anhydrous Na_2SO_4) and concentrated under vacuum to get the solid which was purified by silica gel column chromatography to get the desired product (0.350 g, 24%)

LCMS: 176 $[M+1]^+$

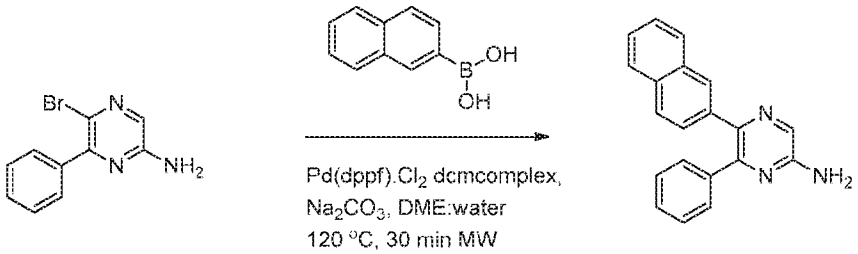
[0242] Step-2: Synthesis of 5-bromo-6-(5-methylfuran-2-yl)pyrazin-2-amine: To a stirred solution of 6-(5-methylfuran-2-yl)pyrazin-2-amine (0.7 g, 3.9 mmol, 1.0 eq.) in ACN (3.0 mL) was added N-bromosuccinimide (0.7 g, 3.9 mmol, 1.0 eq.) portionwise at 0 °C. Progress of the reaction was monitored by TLC and LCMS. The reaction mixture was quenched by adding cold water and extracted using ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4 and concentrated under vacuum to get the solid which was purified by normal phase column chromatography to get the desired product (0.140 g, 14%)

LCMS: 254 $[M+1]^+$

[0243] Step-3: Synthesis of 5-(7-chloro-1*H*-benzimidazol-5-yl)-6-(5-methylfuran-2-yl)pyrazin-2-amine: 5-bromo-6-(5-methylfuran-2-yl)pyrazin-2-amine (0.140 g, 0.27 mmol, 1.0 eq.) and (7-chloro-1H-benzo[d]imidazol-5-yl)boronic acid (0.140 g, 0.35 mmol, 1.3 eq.) was dissolved in DME:water (10.0 mL, 8:2). The reaction mixture was deoxygenated using nitrogen followed by addition of $Pd(dppf)Cl_2.DCM$ complex (0.022 g, 5 mol%) and sodium carbonate (0.088 g, 0.41 mmol, 1.5 eq.).The reaction mixture was again purged with nitrogen and allowed to heat at 120 °C for 2 h using microwave irradiation. Progress of the reaction was monitored by TLC and LCMS. Reaction mixture was allowed to cool to RT and quenched by adding water and extracted using ethyl acetate (3 x 30 mL) The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4 and concentrated under vacuum to get the solid which was purified by reversed phase column chromatography to afford the desired product (4.9 mg, 6%)

LCMS: 326 $[M+1]^+$. ^1H NMR: (400 MHz, DMSO-d_6) δ 12.78 (s,1H), 8.31 (s, 1 H), 7.84 (s, 1 H), 7.45 (br. s., 1 H), 7.19 (br. s., 1 H), 6.64 (br. s., 2 H), 6.07 (br. s., 2 H), 1.91 - 2.20 (m, 3 H).

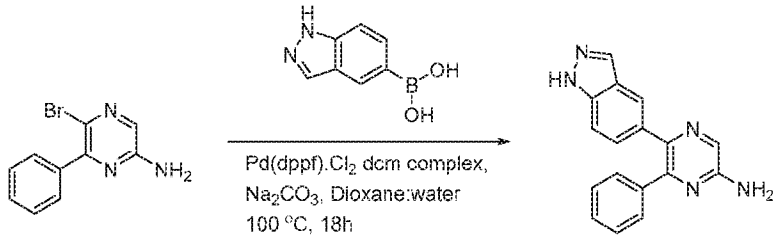
Example S24. Synthesis of 5-(naphthalen-2-yl)-6-phenylpyrazin-2-amine (Compound No. 1.185)



[0244] To a stirred solution of 5-bromo-6-phenylpyrazin-2-amine (0.100 g, 0.39 mmol, 1.0 eq.)) in DME:water (5.0 mL, 4:1) was added naphthalen-2-ylboronic acid (0.089g, 0.51mmol, 1.3 eq.). The reaction mixture was deoxygenated using nitrogen gas, and Pd(dppf)Cl_2 DCM complex (0.016 g, 0.05 eq. 0.019 mmol) was added. The reaction mixture was again purged with nitrogen and heated at 120 °C for 2 h under microwave irradiation. Progress of the reaction was monitored by TLC and LCMS. Reaction mixture was allowed to cool to RT and quenched by adding water and extracted using ethyl acetate (3 x 30mL) The combined organic layers were washed (brine), dried (anhydrous Na_2SO_4) and concentrated under vacuum to get the solid which was purified by normal phase column chromatography to get the desired product (0.05 g, 43.10%)

LCMS: 298 $[M+1]^+$. ^{1}H NMR: (400 MHz, DMSO-d_6) δ 6.66 (s, 2 H) 7.17 - 7.33 (m, 4 H) 7.35 (br. s., 2 H) 7.40 - 7.50 (m, 2 H) 7.64 - 7.79 (m, 2 H) 7.82 (br. s., 1 H) 7.87 (s, 1 H) 8.00 (s, 1 H).

Example S25. Synthesis of 5-(1H-indazol-5-yl)-6-phenylpyrazin-2-amine (Compound No. 1.270)

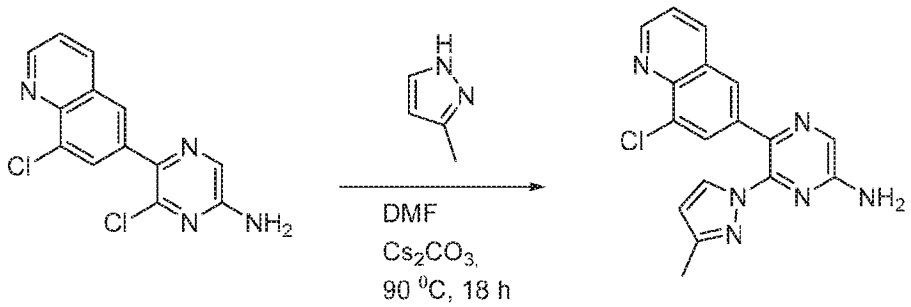


[0245] To a stirred solution of 5-bromo-6-phenylpyrazin-2-amine (0.1 g, 0.4 mmol, 1.0 eq.) and (1H-indazol-5-yl)boronic acid (0.127 g, 0.44 mmol, 1.1 eq.) in dioxane (4 mL) was added Na_2CO_3 (0.085g, 0.8 mmol, 2.0 eq.) and 1 mL water. The reaction was purged with N_2 for 5 min. To this reaction mixture was added with Pd(dppf)Cl_2.DCM complex (0.016 g, 5 mol %) and N_2 was purged again for another 5 min. The reaction mixture was heated at 100 °C for 18 h. The reaction mixture was allowed to cool to RT and extracted using ethyl acetate (3 × 35 mL). The

combined organic layers were washed (brine), dried (anhydrous Na_2SO_4) and concentrated under vacuum to get the solid residue which was purified by reversed phase column chromatography to get the desired product as off white solid (0.02g, 17%)

LCMS: 288 $[M+1]^+$. ^1H NMR: (400 MHz, DMSO-d_6) δ 13.01 (br. s., 1H), 7.96 (d, J = 5.26 Hz, 2H), 7.64 (s, 1H), 7.28 - 7.43 (m, 3H), 7.10 - 7.28 (m, 4H), 6.54 (br. s., 2H).

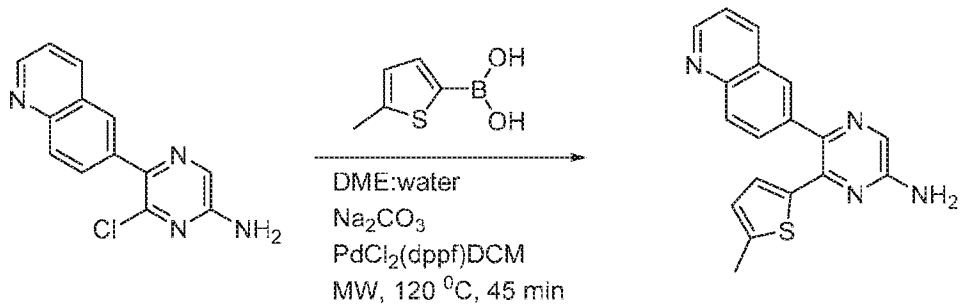
Example S26. Synthesis of 5-(8-chloroquinolin-6-yl)-6-(3-methyl-1H-pyrazol-1-yl)pyrazin-2-amine (Compound No. 1.271)



[0246] To a stirred solution of 5-(8-chloroquinolin-6-yl)-6-(3-methyl-1*H*-pyrazol-1-yl)pyrazin-2-amine (120 mg, 0.41 mmol, 1 eq.) in DMF (2 mL), was added 3-methyl-1*H*-pyrazole (169 mg, 2.06 mmol, 5 eq.) and Cs_2CO_3 (671 mg, 2.06 mmol, 5 eq.). Resulting mixture was heated at 90 °C for 18 h. Progress of the reaction was monitored by TLC and LCMS. On completion of the reaction, reaction mixture was diluted with water (30 mL) and extracted with ethyl acetate (50 mL×2). Combined organic layer was washed with water (100 mL × 2), dried with anhydrous Na_2SO_4 and concentrated under vacuum to get the solid residue which was purified by reversed phase column chromatography to get the desired product 5-(8-chloroquinolin-6-yl)-6-(3-methyl-1*H*-pyrazol-1-yl)pyrazin-2-amine (16 mg, 11%).

LCMS: 337 $[M+1]^+$. ^1H NMR: (400 MHz, DMSO-d_6) δ 2.08 (s, 3 H) 6.31 (d, J=2.19 Hz, 1 H) 7.20 (s, 2 H) 7.61 (s, 1 H) 7.81 (dd, J=8.11, 4.17 Hz, 1 H) 7.93 (s, 1 H) 8.10 (d, J=2.19 Hz, 1 H) 8.18 (s, 1 H) 8.90 (d, J=8.77 Hz, 1 H) 9.01 (d, J=3.07 Hz, 1 H)

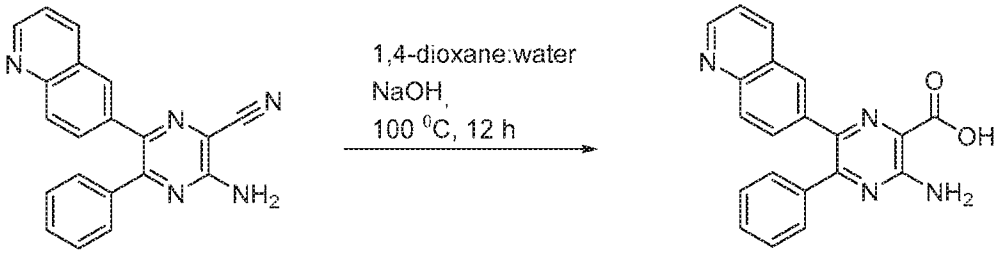
Example S27. Synthesis of 6-(5-methylthiophen-2-yl)-5-(quinolin-6-yl)pyrazin-2-amine (Compound No. 1.210)



[0247] To a stirred solution of 5-(8-chloroquinolin-6-yl)-6-(3-methyl-1*H*-pyrazol-1-yl)pyrazin-2-amine (120 mg, 0.46 mmol, 1.0 eq.) and 5-methyl-2-thiopheneboronic acid (79 mg ,0.56 mmol, 1.2 eq.) in dioxane (6 mL) and water (0.5 mL), was added Na_2CO_3 (173 mg, 0.69 mmol, 1.5 eq.). The reaction was purged with N_2 for 5 min. To this reaction mixture was added $Pd(dppf)Cl_2$·DCM complex (18 mg, 0.02 mmol) and N_2 was purged again for another 5 min. The reaction mixture was irradiated at 120 °C for 45 min using microwave. Progress of the reaction was monitored by TLC and LCMS. On completion of the reaction, reaction mixture was filtered through layer of celite and washed with ethyl acetate. Organic layer was washed with water (50 mL × 2) and dried with anhydrous Na_2SO_4 and concentrated under vacuum to get the solid residue which was purified by reversed phase column chromatography to get the desired product 6-(5-methylthiophen-2-yl)-5-(quinolin-6-yl)pyrazin-2-amine (14 mg, 9%) as an off white solid.

LCMS: 319 $[M+1]^+$. ^1H NMR: (400 MHz, DMSO-d_6) δ 8.91 (br. s., 1 H), 8.37 (br. s., 1 H), 8.07 (br. s., 1 H), 7.99 (d, *J*=8.33 Hz, 1 H), 7.86 (br. s., 1 H), 7.72 (br. s., 1 H), 7.54 (br. s., 1 H), 6.67 (br. s., 2 H), 6.52 (br. s., 1 H), 6.40 (br. s., 1 H), 2.40 (br.s., 3H)

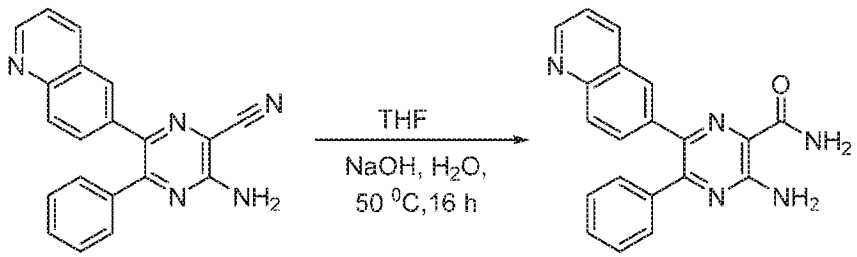
Example S28. Synthesis of 3-amino-5-phenyl-6-(quinolin-6-yl) pyrazine-2-carboxylic acid (Compound No. 1.238)



[0248] A stirred solution of 3-amino-5-phenyl-6-(quinolin-6-yl)pyrazine-2-carbonitrile (100 mg, 0.30 mmol, 1 eq.) in 1,4-dioxane (5 mL) and aqueous NaOH (61 mg dissolved in 5 mL water) was heated at 100 ^{0}C for 12 h. Progress of reaction was monitored by LCMS. On completion of the reaction, the reaction mixture was concentrated under vacuum to get the solid residue which was diluted with water (15 mL) and acidified with 3N HCl solution (10 mL), and extracted with ethyl acetate (50 mL × 2). Organic layer was washed with water (100 mL×2), dried over anhydrous Na_2SO_4 and concentrated under vacuum to get the solid residue which was purified by reversed phase column chromatography to get the desired product (8 mg, 7.5%).

LCMS: 343 $[M+1]^+$. ^{1}H NMR: (400 MHz, DMSO-d_6) δ 7.18 - 7.31 (m, 4 H) 7.31 - 7.39 (m, 2 H) 7.43 - 7.50 (m, 2 H) 7.53 (d, *J*=8.77 Hz, 1 H) 7.78 (d, *J*=8.77 Hz, 1 H) 7.96 (br. s., 1 H) 8.22 (d, *J*=7.45 Hz, 1H) 8.83 (br. s., 1 H).

Example S29. Synthesis of 3-amino-5-phenyl-6-(quinolin-6-yl)pyrazine-2-carboxamide (Compound No. 1.272)

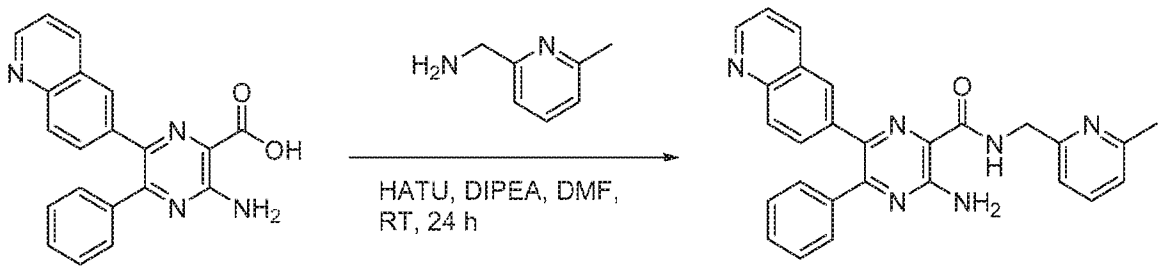


[0249] To a stirred solution of 3-amino-5-phenyl-6-(quinolin-6-yl)pyrazine-2-carbonitrile (100 mg, 0.307 mmol, 1 eq.) in THF (5 mL), was added aq. solution of NaOH (5 mL, 10%). Resulting mixture was heated at 50 °C for 16 h. Progress of reaction was monitored by LCMS. On completion of reaction, reaction mixture was concentrated under vacuum to obtain a solid

residue which was diluted with water (15 mL), was extracted with ethyl acetate (50 mL × 2). Organic layer was washed with water (50 mL × 2), dried over anhydrous Na_2SO_4 and concentrated under vacuum to get the solid residue which was purified by reversed phase column chromatography to get the desired 3-amino-5-phenyl-6-(quinolin-6-yl)pyrazine-2-carboxamide (19 mg, 18%).

LCMS: 342 $[M+1]^+$. ^1H NMR: (400 MHz, DMSO-d_6) δ 7.22 - 7.46 (m, 5 H) 7.50 (dd, *J*=8.11, 4.17 Hz, 1 H) 7.63 (dd, *J*=8.77, 1.75 Hz, 1 H) 7.74 (br. s., 1 H) 7.81 (d, *J*=8.77 Hz, 1 H) 8.13 (s, 1 H) 8.16 - 8.26 (m, 2 H) 8.86 (d, *J*=2.63 Hz, 1 H).

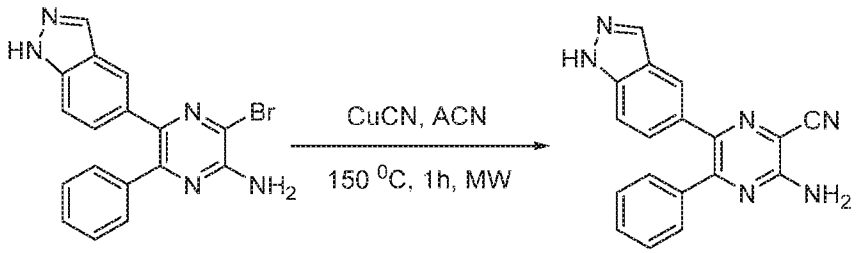
Example S30. Synthesis of 3-amino-N-((6-methylpyridin-2-yl)methyl)-5-phenyl-6-(quinolin-6-yl)pyrazine-2-carboxamide (Compound No. 1.273)



[0250] To a stirred solution of 3-amino-5-phenyl-6-(quinolin-6-yl)pyrazine-2-carboxylic acid (0.110 g, 0.32 mmol, 1 eq.) and (6-methylpyridin-2-yl)methanamine in DMF (2 mL), was added HATU (0.182 g, 0.48 mmol, 1.5 eq.) and DIPEA (0.124g, 0.96 mmol, 3.0 eq.). The reaction mixture was allowed to stir at RT for 24 h. Progress of reaction was monitored by TLC and LCMS. On completion of the reaction, the reaction mixture was diluted with water (15 mL) and extracted with ethyl acetate (50 mL×2). Combined organic layer was washed with water (50mL×2), dried over anhydrous Na_2SO_4 and concentrated under vacuum to get the solid residue which was purified by reversed phase column chromatography to get the desired 3-amino-N-((6-methylpyridin-2-yl)methyl)-5-phenyl-6-(quinolin-6-yl)pyrazine-2-carboxamide (10 mg, 7%).

LCMS: 447 $[M+1]^+$. ^1H NMR: (400 MHz, DMSO-d_6) δ 9.45 (br. s., 1H), 8.86 (br. s., 1H), 8.21 (d, *J* = 8.77 Hz, 1H), 8.06 (br. s., 1H), 7.86 (d, *J* = 9.21 Hz, 2H), 7.59 - 7.79 (m, 4H), 7.51 (br. s., 2H), 7.24 - 7.47 (m, 6H), 7.08 - 7.20 (m, 2H), 4.60 (d, *J* = 5.70 Hz, 3H).

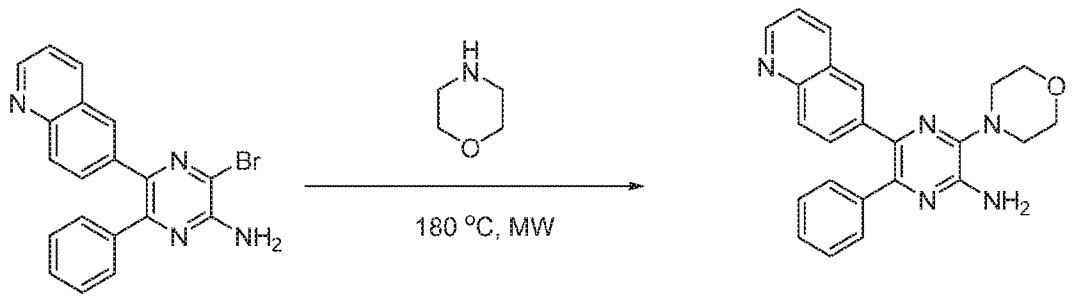
Example S31. Synthesis of 3-amino-6-(1H-indazol-5-yl)-5-phenylpyrazine-2-carbonitrile (Compound No. 1.274)



[0251] To a stirred solution of 3-bromo-5-(1H-indazol-5-yl)-6-phenylpyrazin-2-amine (0.080 g, 0.21 mmol, 1.0 eq.) in ACN (5 mL) was added cuprous cyanide (0.058 g, 0.65 mmol, 3.0 eq.). The reaction mixture was allowed to stir at 150 °C for 1 h under microwave irradiation. The reaction mixture was allowed to cool to RT, diluted with aqueous ammonia (5 mL) and extracted using ethyl acetate (3 × 25 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum to get the solid which was purified by reversed phase column chromatography to get the desired product as an off white solid (0.010 g, 15 %).

LCMS: 313 $[M+1]^+$. ^1H NMR: (400 MHz, DMSO-d_6) δ 13.07 (br. s., 1H), 8.00 (br. s., 1H), 7.67 (s, 1H), 7.24 - 7.45 (m, 8H), 7.17 (d, J = 8.77 Hz, 1H).

Example S32. Synthesis of 3-morpholino-6-phenyl-5-(quinolin-6-yl)pyrazin-2-amine (Compound No. 1.275)

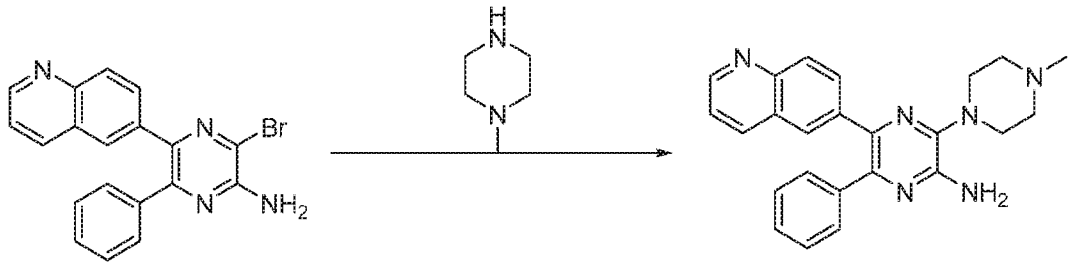


[0252] Mixture of 3-bromo-6-phenyl-5-(quinolin-6-yl)pyrazin-2-amine (0.100 g, 0.26 mmol, 1.0 eq.) and morpholine (0.226 g, 2.6 mmol, 10.0 eq.) was heated at 180 °C for 1 h using microwave irradiation. The reaction mixture was allowed to cool to RT. The solvent was evaporated under

vacuum to get the solid which was purified by normal phase column chromatography to get the desired product as off white solid (0.055 g, 56%).

LCMS: 384 $[M+1]^+$. ^{1}H NMR: (400 MHz, DMSO-d_6) δ 8.83 (d, *J* = 3.07 Hz, 1H), 8.19 (d, *J* = 8.33 Hz, 1H), 7.92 (s, 1H), 7.80 (d, *J* = 8.77 Hz, 1H), 7.59 (d, *J* = 7.45 Hz, 1H), 7.46 (dd, *J* = 4.17, 8.11 Hz, 1H), 7.29 - 7.38 (m, 2H), 7.18 - 7.29 (m, 3H), 6.35 (br. s., 2H), 3.82 (br. s., 4H), 3.12 - 3.25 (m, 4H).

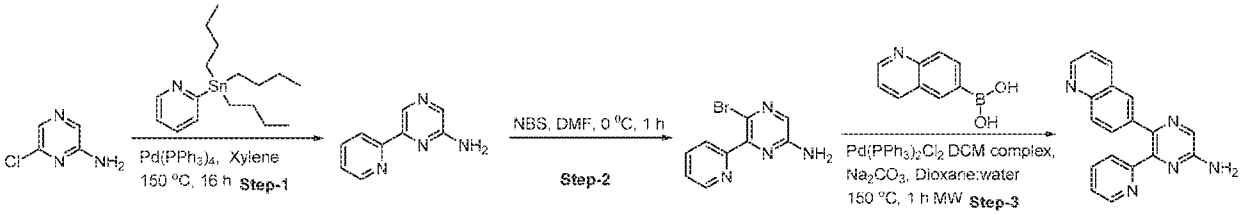
Example S33. Synthesis of 3-morpholino-6-phenyl-5-(quinolin-6-yl)pyrazin-2-amine (Compound No. 1.276)



[0253] Mixture of 3-bromo-6-phenyl-5-(quinolin-6-yl)pyrazin-2-amine (0.150 g, 0.39 mmol, 1.0 eq.) and 1-methylpiperazine (0.390 g, 3.9 mmol, 10.0 eq.) was heated at 180 °C for 30 min using microwave irradiation. The reaction mixture was allowed to cool to RT. The solvent was evaporated under vacuum to get the solid which was purified by normal phase column chromatography to get the desired product as off white solid (0.060 g, 39%).

LCMS: 397 $[M+1]^+$. ^{1}H NMR: (400 MHz, DMSO-d_6) δ 8.83 (d, *J* = 3.07 Hz, 1H), 8.19 (d, *J* = 7.89 Hz, 1H), 8.14 (s, 1H), 7.90 (s, 1H), 7.81 (d, *J* = 8.33 Hz, 1H), 7.59 (d, *J* = 8.33 Hz, 1H), 7.46 (dd, *J* = 3.95, 7.89 Hz, 1H), 7.29 - 7.37 (m, 2H), 7.26 (br. s., 3H), 6.23 (br. s., 2H), 3.24 (br. s., 3H), 2.57 - 2.69 (m, 4H), 2.31 (br. s., 4H).

Example S34. Synthesis of 6-[3-(pyridin-2-yl)pyrazin-2-yl]quinolone (Compound No. 1.25)



[0254] Step-1: Synthesis of 6-(pyridin-2-yl)pyrazin-2-amine: To a stirred solution of 6-chloropyrazin-2-amine (0.500 g, 3.85 mmol, 1.0 eq.) in xylene (20.0 mL) was added 2-(tributylstannyl)pyridine reagent (1.42g, 3.85 mmol, 1.0 eq.). The reaction mixture was deoxygenated using N_2 gas and $Pd(PPh_3)_4$ (0.223 g, 0.05 eq. 0.192 mmol) was added. The reaction mixture was again purged with N_2 and allowed to heat at 150 °C for 16 h in seal tube. Progress of the reaction was monitored by TLC and LCMS. Reaction mixture was allowed to cool to RT and quenched by adding aq. NaOH and extracted using ethyl acetate (3 x 100 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum to get the solid which was purified by normal phase column chromatography to get the desired product (0.400 g, 60%).

LCMS: 173 $[M+1]^+$

[0255] Step-2: Synthesis of 5-bromo-6-(pyridin-2-yl)pyrazin-2-amine: To a stirred solution of 6-(pyridin-2-yl)pyrazin-2-amine (0.400 g, 2.32 mmol, 1.0 eq.) in DMF (5.0 mL) was added N-bromosuccinimide (0.413 g, 2.32 mmol, 1.0 eq.) portionwise at 0 °C. Progress of the reaction was monitored by TLC and LCMS. The reaction was quenched by adding cold water and extracted using ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine, dried (anhydrous Na_2SO_4) and concentrated under vacuum to get the solid which was purified by normal phase column chromatography to afford the desired product (0.100 g, 17%).

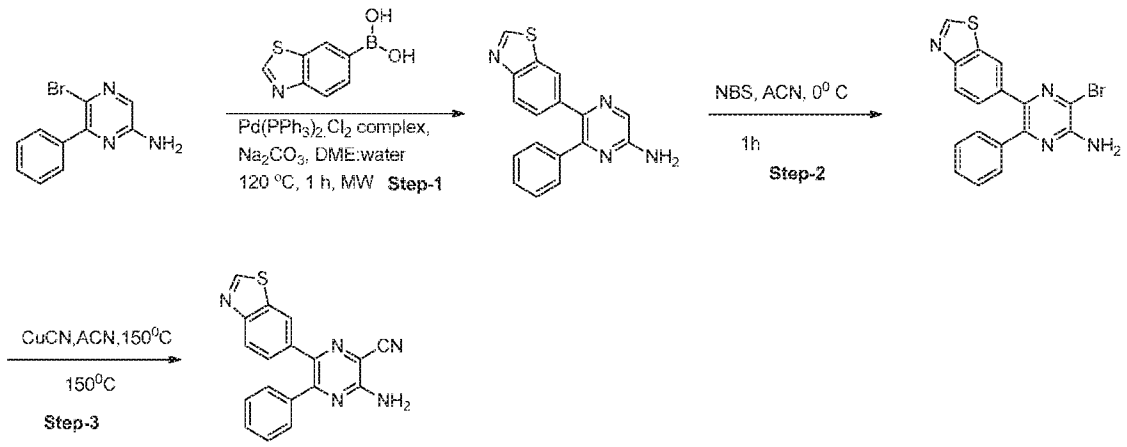
LCMS: 250 $[M+1]^+$

[0256] Step-3: Synthesis of 6-(pyridin-2-yl)-5-(quinolin-6-yl)pyrazin-2-amine: To a stirred solution of 5-bromo-6-(pyridin-2-yl)pyrazin-2-amine (0.100 g, 0.398 mmol, 1.0 eq.) and quinolin-6-ylboronic acid (0.103 g, 0.59 mmol, 1.5 eq.) in 1,4-dioxane (4.0 mL) was added sodium carbonate (0.105 g, 0.95 mmol, 2.5 eq.) and 1 mL of water. The reaction mixture was deoxygenated using nitrogen gas, and $Pd(dppf)Cl_2$·DCM complex (0.016 g, 0.019 mmol,0.05 eq.) was added. The reaction mixture was again purged with nitrogen and allowed to heat at 120 °C

for 1 h under microwave irradiation. Progress of the reaction was monitored by TLC and LCMS. Reaction mixture was allowed to cool to RT and quenched by adding water and extracted using ethyl acetate (3 x 100 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum to get the solid which was purified by normal phase column chromatography to get the desired product (0.010 g, 9%).

LCMS: 300 $[M+1]^+$. ^1H NMR: (400 MHz, DMSO-d_6) δ 8.82 (d, J = 2.63 Hz, 1 H), 8.34 (d, J = 4.38 Hz, 1 H), 8.08 (s, 1 H) 8.20 (d, J = 7.89 Hz, 1 H), 7.81 - 7.88 (m, 2 H), 7.76 (d, J = 8.77 Hz, 1 H), 7.65 (d, J = 7.45 Hz, 1 H), 7.36 - 7.50 (m, 2 H), 7.22 - 7.36 (m, 1 H), 6.77 (br. s., 2 H).

Example S35. Synthesis of 3-amino-6-(benzo[d]thiazol-6-yl)-5-phenylpyrazine-2-carbonitrile (Compound No. 1.192)



[0257] Step-1: Synthesis of 5-(benzo[d]thiazol-6-yl)-6-phenylpyrazin-2-amine: To a stirred solution of 5-bromo-6-phenylpyrazin-2-amine (0.500 g, 2.0 mmol, 1.0 eq.) and benzo[d]thiazol-6-ylboronic acid (0.467g, 2.6 mmol, 1.3 eq.) in DME (8.0 mL) was added sodium carbonate (0.532 g, 4.99 mmol, 2.5 eq.) and 2 mL of water. The reaction mixture was deoxygenated using nitrogen gas Then $Pd(PPh_3)_2.Cl_2$ complex (0.081 g, 0.05 eq. 0.1 mmol) was added. The reaction mixture was again purged with nitrogen and allowed to heat at 120 °C for 1 h under microwave irradiation. Progress of the reaction was monitored by TLC and LCMS. Reaction mixture was allowed to cool to RT and quenched by adding water and extracted using ethyl acetate (3 x 100 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and

concentrated under vacuum to get the solid which was purified by normal phase column chromatography to get the desired product (0.140 g, 23.02%).

LCMS: 305 $[M+1]^+$

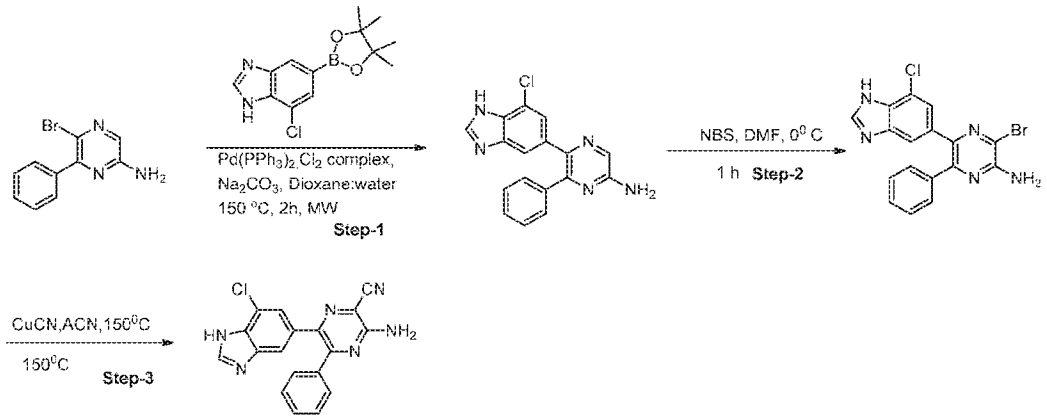
[0258] Step-2: Synthesis of 5-(1,3-benzothiazol-6-yl)-3-bromo-6-phenylpyrazin-2-amine: To a stirred solution of 5-(benzo[d]thiazol-6-yl)-6-phenylpyrazin-2-amine (0.140 g, 0.36 mmol, 1.0 eq.) in ACN (2.0 mL) was added N-bromosuccinimide (0.065g, 0.36 mmol, 1.0 eq.) portionwise at 0 °C. Progress of the reaction was monitored by TLC and LCMS. The reaction was quenched by adding cold water and extracted using ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4 and concentrated under vacuum to get the solid which was purified by normal phase column chromatography to get the desired product (0.140 g, 79.54%).

LCMS: 383 $[M+1]^+$

[0259] Step-3: Synthesis of 3-amino-6-(benzo[d]thiazol-6-yl)-5-phenylpyrazine-2-carbonitrile: To a stirred solution of 5-(1,3-benzothiazol-6-yl)-3-bromo-6-phenylpyrazin-2-amine (0.140 g, 0.36 mmol, 1.0 eq.) in ACN (2 mL) was added CuCN (0.100 g, 1.09 mmol, 3.0 eq.). Reaction was stirred at 150 °C for 1 h under microwave irradiation. Progress of the reaction was monitored by TLC and LCMS. The reaction mixture was then filtered and the filtrate was concentrated under reduced pressure to obtain the crude, which was then purified by reversed phase preparative chromatography to get the desired product (0.015 g, 12%)

LCMS: 330$[M+1]^+$. ^{1}H NMR: (400 MHz, DMSO-d_6) δ 9.39 (s, 1 H), 8.09 - 8.19 (m, 1 H), 7.92 (d, *J*=8.33 Hz, 1 H), 7.54 (s, 2 H), 7.35 - 7.43 (m, 3 H), 7.11 - 7.35 (m, 3 H).

Example S36. Synthesis of 3-amino-6-(7-chloro-1H-benzimidazol-5-yl)-5-phenylpyrazine-2-carbonitrile (Compound No. 1.277)



[0260] Step-1: Synthesis of 5-(7-chloro-1*H*-benzimidazol-5-yl)-6-phenylpyrazin-2-amine: To a stirred solution of 5-bromo-6-phenylpyrazin-2-amine (0.500 g, 1.99 mmol, 1.0 eq.) and 7-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d]imidazole (0.72 g, 2.59 mmol, 1.3 eq.) in 1,4-dioxane (6.0 mL) was added sodium carbonate (0.529 g, 4.99 mmol, 2.5 eq.) and 1.5 mL of water. The reaction mixture was deoxygenated using N_2 and $Pd(PPh_3)_2Cl_2$.DCM complex (0.081 g, 0.099 mmol, 0.05 eq.) was added. The reaction mixture was again purged with N_2 and allowed to heat at 150 °C for 2 h using microwave irradiation. Progress of the reaction was monitored by TLC and LCMS. Reaction mixture was allowed to cool to RT and quenched by adding water and extracted using ethyl acetate (3 x 100 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum to get the solid which was purified by normal phase column chromatography to get the desired product (0.160 g, 24.88%)

LCMS: 322 $[M+1]^+$

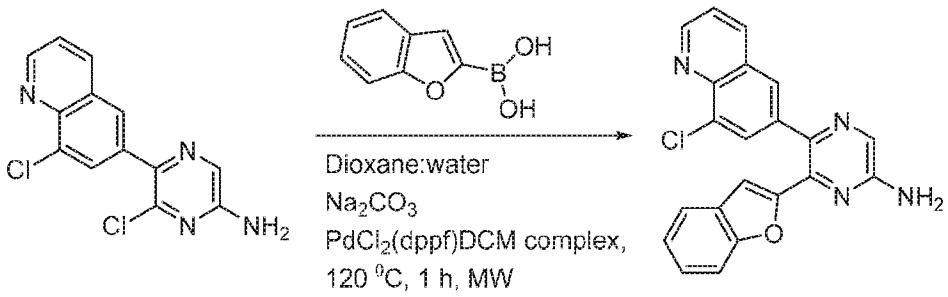
[0261] Step-2: Synthesis of 3-bromo-5-(7-chloro-1*H*-benzimidazol-5-yl)-6-phenylpyrazin-2-amine: To a stirred solution of 5-(7-chloro-1*H*-benzimidazol-5-yl)-6-phenylpyrazin-2-amine (0.160 g, 0.497 mmol, 1.0 eq.) in DMF (3.0 mL) was added N-bromosuccinimide (0.088g, 0.49 mmol, 1.0 eq.) portionwise at 0 °C. Progress of the reaction was monitored by TLC and LCMS. The reaction was stirred for 1 h at same temperature and quenched with cold water. The mixture was extracted using ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum to get the solid product (0.150 g, 75%).

LCMS: 400 $[M+1]^+$

[0262] Step-3: Synthesis of 3-amino-6-(7-chloro-1*H*-benzimidazol-5-yl)-5-phenylpyrazine-2-carbonitrile: To a stirred solution of 3-bromo-5-(7-chloro-1*H*-benzimidazol-5-yl)-6-phenylpyrazin-2-amine (0.150 g, 0.374 mmol, 1.0 eq.) in ACN (3.0 mL) was added CuCN (0.100g, 1.12 mmol, 3.0 eq.). Reaction was stirred at 150 °C for 1 h under microwave irradiation. Progress of the reaction was monitored by TLC and LCMS. Reaction was filtered and concentrated under reduced pressure to get the crude product which was purified by reversed phase column chromatography to get the desired product (0.003 g, 2%).

LCMS: 347 $[M+1]^+$. ^{1}H NMR: (400 MHz, DMSO-d_6) δ 8.28 (s, 1 H), 7.49 (br. s., 2 H), 7.29 - 7.43 (m, 5 H), 7.16-7.20 (s, 1H), 6.66 (br. s., 2 H).

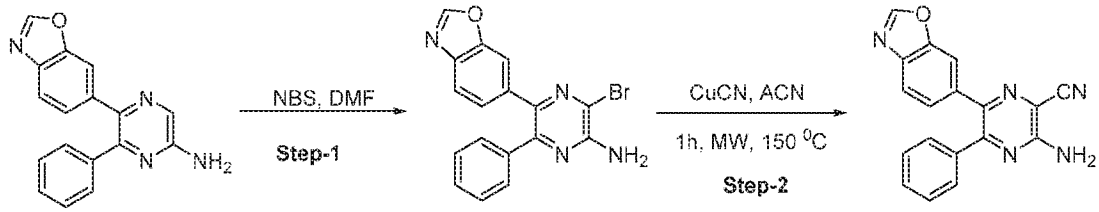
Example S37. Synthesis of 6-(1-methyl-1H-pyrazol-3-yl)-5-(quinolin-6-yl)pyrazin-2-amine (Compound No. 1.278)



[0263] To a stirred solution of 6-chloro-5-(quinolin-6-yl)pyrazin-2-amine (150 mg, 0.52 mmol, 1.0 eq.) and benzofuran-3-ylboronic acid (125 mg, 0.64 mmol, 1.1 eq.) in dioxane (4 mL) and water (1 mL), was added Na_2CO_3 (109 mg, 1.03 mmol, 2.0 eq.). The reaction was purged with N_2 for 5 min. To this reaction mixture was added Pd(dppf)Cl_2·DCM complex (21 mg, 5 mol%) and N_2 was purged again for another 5 min. The reaction mixture was heated at 120 °C for 1 h under microwave irradiation. Progress of the reaction was monitored by TLC and LCMS. On completion of the reaction, the reaction mixture was extracted with ethyl acetate (35 mL x 3). Combined organic layer was washed with water (50 mL × 2), dried over anhydrous Na_2SO_4 and concentrated under vacuum to get the solid residue which was purified by normal phase column chromatography to get the desired product (25 mg, 13%) as an off white solid.

LCMS: 373 $[M+1]^+$. ^{1}H NMR: (400 MHz, DMSO-d_6) δ 8.93 (dd, J = 1.53, 4.17 Hz, 1H), 8.26 (d, J = 7.02 Hz, 1H), 7.96 - 8.05 (m, 1H), 7.87 (d, J = 1.75 Hz, 1H), 7.72 (dd, J = 1.53, 4.60 Hz, 2H), 7.46 - 7.60 (m, 2H), 7.26 (dd, J = 1.53, 8.55 Hz, 1H), 6.93 (d, J = 1.32 Hz, 1H), 6.80 (s, 2H)

Example S38. Synthesis of 3-amino-6-(benzo[d]oxazol-6-yl)-5-phenylpyrazine-2-carbonitrile (Compound No. 1.193)

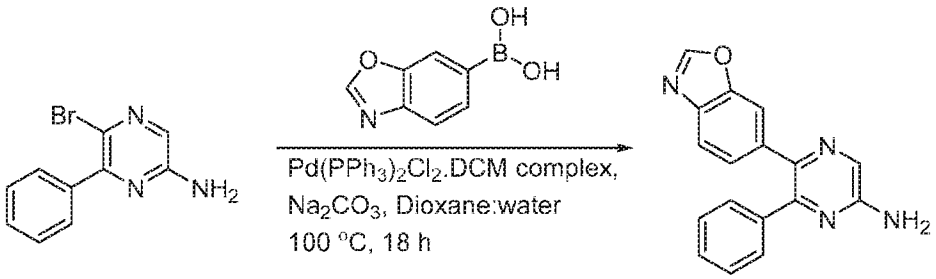


[0264] Step 1. Synthesis of 5-(benzo[d]oxazol-6-yl)-3-bromo-6-phenylpyrazin-2-amine: To a solution of 6-(3-methyl-1H-pyrazol-1-yl)-5-(quinolin-6-yl)pyrazin-2-amine (200 mg, 0.69 mmol, 1 eq.) in ACN (2 mL) at 0 °C was added N-bromosuccinimide (123 mg, 0.69 mmol, 1 eq.) portion wise and the reaction mixture was allowed to stir at the same temperature for 1h. Following this, the reaction mixture was poured over ice-water to afford the solid precipitate which was filtered under vacuum and washed with excess water. The solid was vacuum dried to yield the desired product as off white solid (0.200g, 79%)

[0265] Step 2. Synthesis of 3-amino-6-(8-chloroquinolin-6-yl)-5-(3-methyl-1H-pyrazol-1-yl)pyrazine-2-carbonitrile: To a stirred solution of 5-(benzo[d]oxazol-6-yl)-3-bromo-6-phenylpyrazin-2-amine (0.100 g, 0.27 mmol, 1.0 eq.) in ACN (3 mL) was added cuprous cyanide (0.073 g, 0.88 mmol, 3.0 eq.). The reaction mixture was allowed to stir at 150 °C for 1 h under microwave irradiation. The progress of the reaction was monitored by TLC and LCMS. The reaction mixture was allowed to cool to RT and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum to get the solid which was purified by reversed phase column chromatography to afford the desired product as an off white solid (0.010 g, 12%).

LCMS: 314 $[M+1]^+$. ^{1}H NMR: (400 MHz, DMSO-d_6) δ 8.74 (s, 1H), 7.61 - 7.70 (m, 2H), 7.54 (s, 2H), 7.22 - 7.41 (m, 6H).

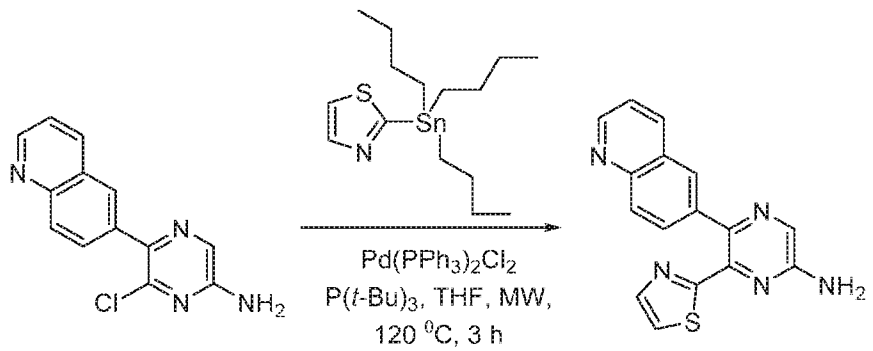
Example S39. Synthesis of 5-(benzo[d]oxazol-6-yl)-6-phenylpyrazin-2-amine (Compound No. 1.35)



[0266] To a stirred solution of 5-bromo-6-phenylpyrazin-2-amine (0.500 g, 2.0 mmol, 1.0 eq.) and benzo[d]oxazol-6-ylboronic acid (0.429 g, 2.5 mmol, 1.3 eq.) in dioxane (8 mL) was added Na_2CO_3 (0.317 g, 3 mmol, 1.5 eq.) and 2 mL water. The reaction was purged with N_2 for 5 min. To this reaction mixture was added $Pd(dppf)Cl_2$·DCM complex (0.08 g, 5 mol %) and N_2 was purged again for another 5 min. The reaction mixture was heated at 100 °C for 18 h. The reaction mixture was allowed to cool to RT and extracted using ethyl acetate (2 × 100 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum to get the solid residue which was purified by normal phase flash column chromatography to afford the desired product as off white solid (0.250 g, 43%)

LCMS: 289 $[M+1]^+$. ^1H NMR: (400 MHz, DMSO-d_6) δ 9.34 (s, 1H), 8.08 (s, 1H), 7.98 (s, 1H), 7.88 (d, J = 8.77 Hz, 1H), 7.23 - 7.38 (m, 6H), 6.68 (s, 2H).

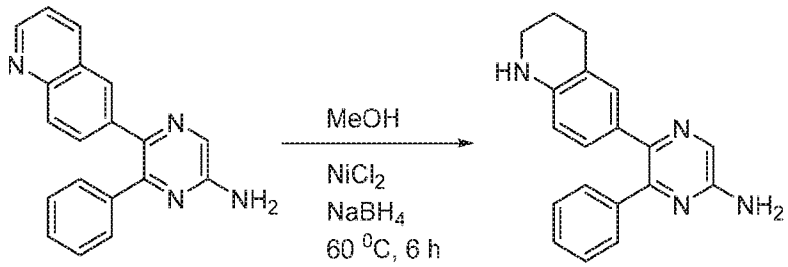
Example S40. Synthesis of 5-(quinolin-6-yl)-6-(1,3-thiazol-2-yl)pyrazin-2-amine (Compound No. 1.279)



[0267] To a stirred solution of 6-chloro-5-(quinolin-6-yl)pyrazin-2-amine (150 mg, 0.58 mmol, 1 eq.) in THF (5 mL) was added 2-(tributylstannyl)thiazole (436 mg, 1.16 mmol). The reaction was purged with N_2 for 5 min. To this reaction mixture was added $Pd(dppf)Cl_2$ (3.5 mg, 5 mol %) and $p(t\text{-}Bu)_3$ (23 mg, 0.2 eq.). The reaction was purged with N_2 for another 5 min. Resulting mixture was heated at 120 °C for 3 h. Progress of the reaction was monitored by LCMS. On completion of the reaction, the reaction mixture was quenched with NaOH solution (10 mL) and diluted with water (15 mL) followed by extraction with ethyl acetate (50 mL × 2). Combined organic layers were washed with water (50 mL × 2), dried over anhydrous Na_2SO_4 and concentrated under vacuum to get the solid residue which was purified by reversed phase column chromatography to get the desired product (8 mg, 4%).

LCMS: 305 $[M+1]^+$. ^1H NMR: (400 MHz, DMSO-d_6) δ 8.88 (d, J = 3.07 Hz, 1 H), 8.50 (br. s., 1 H), 8.33 (d, J = 7.02 Hz, 1 H), 8.08 (s, 1 H), 8.03 (s, 1 H), 7.89 (d, J = 8.33 Hz, 1 H), 7.62 - 7.70 (m,1 H), 7.51 (dd, J = 8.33, 4.38 Hz, 1 H), 6.95 (s, 2 H).

Example S41. Synthesis of 6-phenyl-5-(1,2,3,4-tetrahydroquinolin-6-yl)pyrazin-2-amine (Compound No. 1.186)

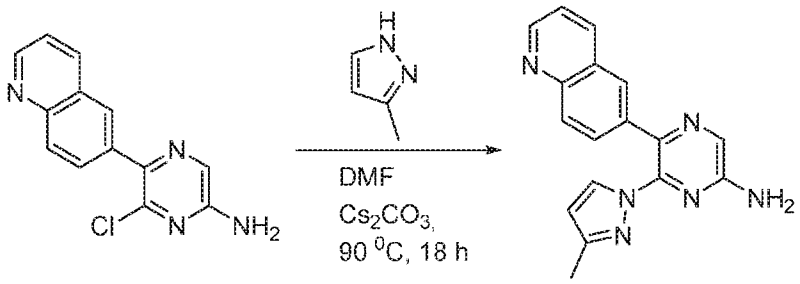


[0268] To a stirred solution of 6-phenyl-5-(quinolin-6-yl)pyrazin-2-amine (100 mg, 0.33 mmol, 1 eq.) in methanol (10 mL), was added $NiCl_2$ (22 mg, 0.16 mmol, 0.5 eq.). Reaction mixture was stirred for 10 min at RT followed by portion wise addition of $NaBH_4$ (90 mg, 2.64 mmol). Resulting reaction mixture was heated at 60 °C for 6 h. Progress of reaction was monitored by TLC and LCMS. On completion of the reaction, the reaction mixture was filtered through layer of celite and concentrated under reduce pressure. The obtained residue was diluted with water (50 mL) and extracted with ethyl acetate (50 mL × 3). Combined organic layers were washed

with water (50 mL), dried over anhydrous Na_2SO_4 and concentrated under reduce pressure to obtain solid residue which was purified by flash chromatography to get the desired product (18 mg, 18%).

LCMS: 302 $[M+1]^+$. ^1H NMR: (400 MHz, DMSO-d_6) δ 7.86 (s, 1 H), 7.20 - 7.40 (m, 4 H), 6.86 (s, 1 H), 6.60 (d, J = 8.33 Hz, 1 H), 6.32 (s, 2 H), 6.18 (d, J = 8.33 Hz, 1 H), 5.66 (br. s., 1 H), 3.14 (br. m., 2 H), 2.58 (br. m., 2 H), 1.74 (br. m., 2 H)

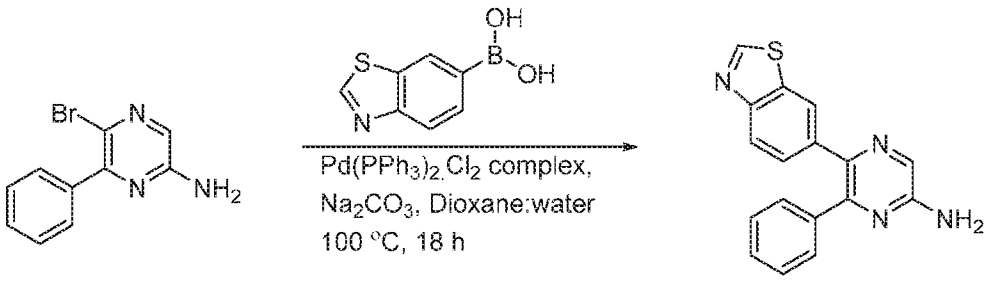
Example S42. Synthesis of 5-(8-chloroquinolin-6-yl)-6-(3-methyl-1H-pyrazol-1-yl)pyrazin-2-amine (Compound No. 1.280)



[0269] To a stirred solution of 6-chloro-5-(quinolin-6-yl)pyrazin-2-amine (300 mg, 1.16 mmol, 1 eq.) in DMF (2 mL), was added 3-methyl-1*H*-pyrazole (478 mg, 5.83 mmol, 5 eq.) and Cs_2CO_3 (1.9 g, 5.83 mmol, 5 eq.). Resulting mixture was heated at 90 °C for 18 h. Progress of the reaction was monitored by TLC and LCMS. On completion of the reaction, the reaction mixture was diluted with water (30 mL) and extracted with ethyl acetate (50 mL × 3). Organic layer was washed with water (100 mL × 3), dried over anhydrous Na_2SO_4 and concentrated under vacuum to get the solid residue which was purified by reversed phase column chromatography to get the desired product (100 mg, 33%).

LCMS: 303 $[M+1]^+$. ^1H NMR: (400 MHz, DMSO-d_6) δ 8.92 (d, J = 3.95 Hz, 1H), 8.41 (d, J = 8.33 Hz, 1H), 8.09 (s, 1H), 7.82 - 7.93 (m, 3H), 7.60 (dd, J = 4.38, 8.33 Hz, 1H), 7.36 (d, J = 9.21 Hz, 1H), 7.06 (br. s., 2H), 6.26 (d, J = 2.19 Hz, 1H), 2.06 (s, 3H).

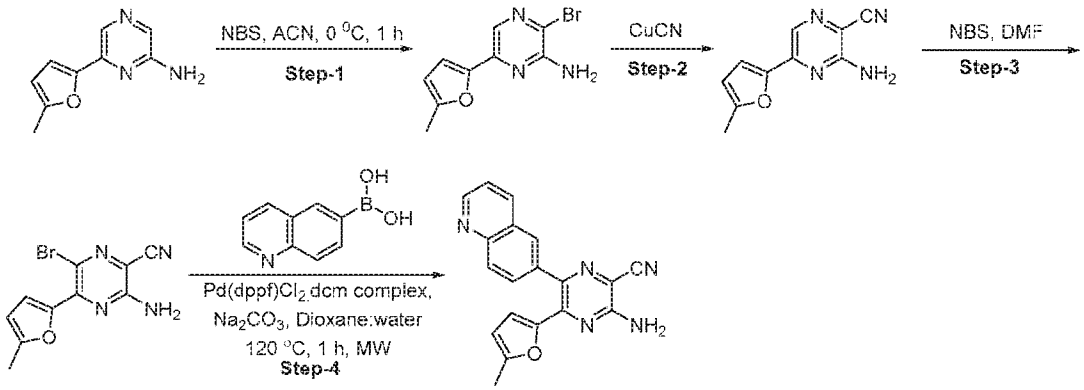
Example S43. Synthesis of 5-(benzo[d]thiazol-6-yl)-6-phenylpyrazin-2-amine (Compound No. 1.36)



[0270] To a stirred solution of 5-bromo-6-phenylpyrazin-2-amine (0.125 g, 0.5 mmol, 1.0 eq.) and 8-chloro-6 benzo[d]thiazol-6-ylboronic acid (0.116 g, 0.65 mmol, 1.3 eq.) in dioxane (4 mL) was added Na_2CO_3 (0.106 g, 1 mmol, 2.0 eq.) and 1 mL of water. The reaction was purged with N_2 for 5 min. To this reaction mixture was added $Pd(dppf)Cl_2$·DCM complex (0.02 g, 5 mol %) and N_2 was purged again for another 5 min. The reaction mixture was heated at 100 °C for 18 h. The reaction mixture was allowed to cool to RT and extracted using ethyl acetate (2 × 35 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum to get the solid residue which was purified by normal phase flash column chromatography to get the desired product as off white solid (0.02 g, 13%)

LCMS: 305 $[M+1]^+$. ^1H NMR: (400 MHz, DMSO-d_6) δ 9.34 (s, 1H), 8.08 (s, 1H), 7.98 (s, 1H), 7.88 (d, J = 8.77 Hz, 1H), 7.23 - 7.38 (m, 6H), 6.68 (s, 2H).

Example S44. Synthesis of 3-amino-5-(5-methylfuran-2-yl)-6-(quinolin-6-yl)pyrazine-2-carbonitrile (Compound No. 1.281)



[0271] Step-1: Synthesis of 3-bromo-6-(5-methylfuran-2-yl)pyrazin-2-amine: To a stirred solution of 6-(5-methylfuran-2-yl)pyrazin-2-amine (0.7 g, 3.9 mmol, 1.0 eq.) in ACN (3.0 mL)

was added N-bromosuccinimide (0.7 g, 3.9 mmol, 1.0 eq.) portionwise at 0 °C. Progress of the reaction was monitored by TLC and LCMS. The reaction was quenched by adding cold water and extracted using ethyl acetate (3 x 50 mL) The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum to get the solid which was purified by normal phase column chromatography to afford the desired product (0.140 g, 14%)

LCMS: 254 $[M+1]^+$

[0272] Step-2: Synthesis of 3-amino-5-(5-methylfuran-2-yl)pyrazine-2-carbonitrile: To a stirred solution of 3-bromo-6-(5-methylfuran-2-yl)pyrazin-2-amine (0.508 g, 2.0 mmol, 1.0 eq.) in ACN (10.0 mL) was added CuCN (0.528 g, 5.9 mmol, 3.0 eq.). Reaction was stirred at 150 °C for 1.5 h under microwave irradiation. Progress of the reaction was monitored by TLC and LCMS. The reaction was filtered and concentrated under reduced pressure to afford the desired product (0.400 g, 99%).

LCMS: 201 $[M+1]^+$

[0273] Step-3: Synthesis of 3-amino-6-bromo-5-(5-methylfuran-2-yl)pyrazine-2-carbonitrile: To a stirred solution of 3-amino-5-(5-methylfuran-2-yl)pyrazine-2-carbonitrile (0.40 g, 2.00 mmol, 1.0 eq.) in DMF (5.0 mL) was added N-bromosuccinimide (0.373 g, 2.09 mmol, 1.0 eq.) slowly at 0 °C. Progress of the reaction was monitored by TLC and LCMS. The reaction was quenched by adding cold water and the precipitate obtained was filtered and vacuum dried to afford the desired product (0.38 g, 68%).

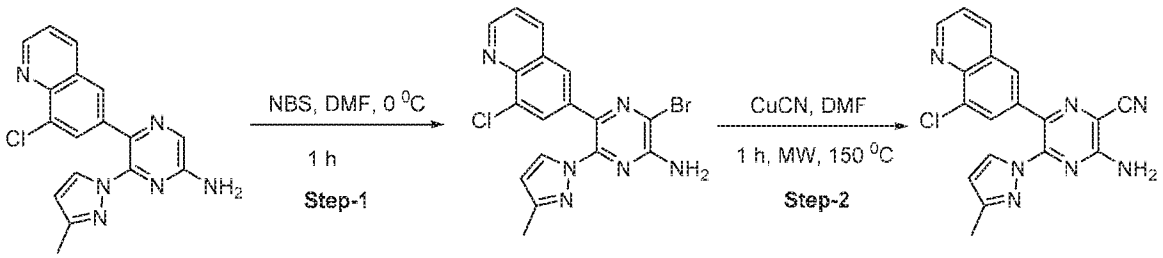
LCMS: 279 $[M+1]^+$

[0274] Step 4: Synthesis of 3-amino-5-(5-methylfuran-2-yl)-6-(quinolin-6-yl)pyrazine-2-carbonitrile: To a stirred solution of 3-amino-6-bromo-5-(5-methylfuran-2-yl)pyrazine-2-carbonitrile (0.100 g, 0.35 mmol, 1.0 eq.) and quinolin-6-ylboronic acid (0.080g, 0.46 mmol, 1.3 eq.) in dioxane (4 mL) was added Na_2CO_3 (0.056 g, 0.53 mmol, 1.5 eq.) and 1 mL water. The reaction was purged with N_2 for 5 min. To this reaction mixture was added $Pd(dppf)Cl_2$·DCM complex (0.02g, 5 mol %) and N_2 was purged again for another 5 min. The reaction mixture was heated at 100 °C for 18 h. The reaction mixture was allowed to cool to RT and extracted using ethyl acetate (2 × 35 mL). The combined organic layers were washed with brine, dried over

anhydrous Na_2SO_4 and concentrated under vacuum to get the solid residue which was purified by normal phase flash column chromatography to afford the desired product as off white solid (0.042g, 37%)

LCMS: 328[M+1]$^+$. ^{1}H NMR: (400 MHz, DMSO-d_6) δ 8.95 (d, *J* = 3.81 Hz, 1H), 8.42 (d, *J* = 7.63 Hz, 1H), 8.00 - 8.13 (m, 2H), 7.72 (d, *J* = 8.90 Hz, 1H), 7.55 - 7.60 (m, 1H), 7.50 (s, 2H), 6.21 (d, *J* = 2.54 Hz, 1H), 6.14 (br. s., 1H), 2.15 (s, 3H).

Example S45. Synthesis of 3-amino-6-(8-chloroquinolin-6-yl)-5-(3-methyl-1H-pyrazol-1-yl)pyrazine-2-carbonitrile (Compound No. 1.292)



[0275] Step1. Synthesis of 3-bromo-5-(8-chloroquinolin-6-yl)-6-(3-methyl-1H-pyrazol-1-yl)pyrazin-2-amine: To a solution of 6-(3-methyl-1H-pyrazol-1-yl)-5-(quinolin-6-yl)pyrazin-2-amine (220 mg, 0.72 mmol, 1 eq.) in DMF (5 mL) at room temperature was added N-bromosuccinimide (123 mg, 0.72 mmol, 1 eq.) portion wise and the reaction mixture was allowed to stir at room temperature for 1h. The reaction was poured over ice-water to obtain the solid precipitate which was filtered under vacuum and washed with excess water. The solid was vacuum dried to afford the desired product as off white solid (0.200g, 67%)

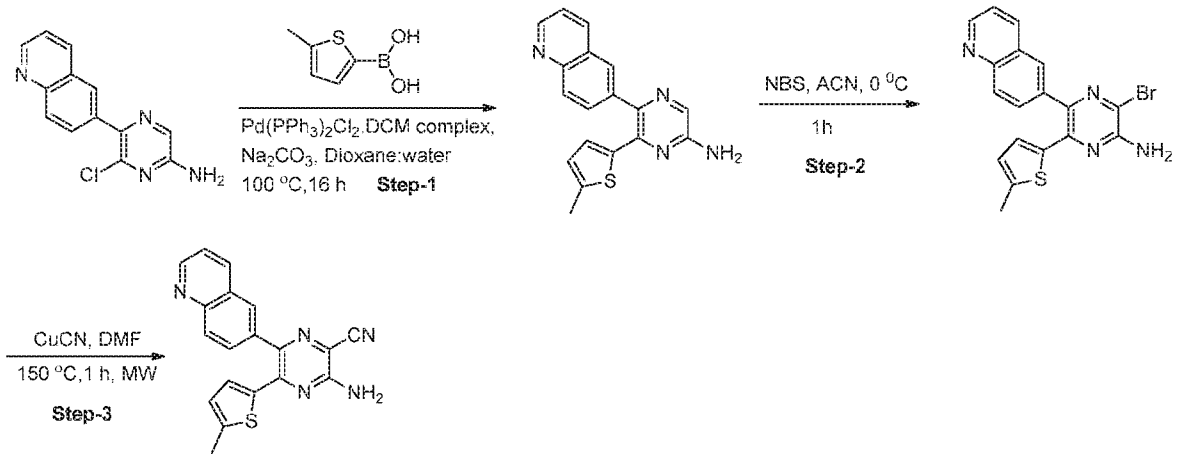
LCMS: 415 [M+1]$^+$.

[0276] Step 2. Synthesis of 3-amino-6-(8-chloroquinolin-6-yl)-5-(3-methyl-1H-pyrazol-1-yl)pyrazine-2-carbonitrile: To a stirred solution of 6-phenyl-5-(quinolin-6-yl)pyrazin-2-amine (0.220 g, 0.26 mmol, 1.0 eq.) in DMF (3 mL) was added cuprous cyanide (0.155 g, 0.78 mmol, 3.0 eq.). The reaction mixture was allowed to stir at 150 °C for 1 h under microwave irradiation. The progress of the reaction was monitored by LCMS. The reaction mixture was allowed to cool to RT and extracted using ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum to get the solid which

was purified by reversed phase column chromatography to get the desired product as an off white solid (0.020 g, 23%).

LCMS: 362 $[M+1]^+$. ^1H NMR: (400 MHz, DMSO-d_6) δ 9.00 (br. s., 1H), 8.47 (d, J = 7.45 Hz, 1H), 8.11 (d, J = 2.63 Hz, 1H), 7.97 (s, 1H), 7.84 (br. s., 2H), 7.65 (dd, J = 3.95, 7.89 Hz, 1H), 7.53 (s, 1H), 6.39 (s, 1H), 1.99 (s, 3H).

Example S46. Synthesis of 3-amino-5-(5-methylthiophen-2-yl)-6-(quinolin-6-yl)pyrazine-2-carbonitrile (Compound No. 1.282)



[0277] Step-1 Synthesis of 6-(5-methylthiophen-2-yl)-5-(quinolin-6-yl)pyrazin-2-amine: 6-chloro-5-(quinolin-6-yl)pyrazin-2-amine (1.0 g, 3.8 mmol, 1.0 eq.) and (5-methylthiophen-2-yl)boronic acid (0.842 g, 5.7 mmol, 1.5 eq.) was dissolved in dioxane:water (8.0 mL, 3:1). The reaction mixture was deoxygenated using nitrogen followed by addition of $Pd(dppf)Cl_2$·DCM complex (0.02g, 5 mol %) and sodium carbonate (0.816 g, 7.7 mmol, 2.0 eq.). The reaction mixture was again purged with nitrogen and allowed to heat at 100 °C for 16 h. Progress of the reaction was monitored by TLC and LCMS. Reaction mixture was allowed to cool to RT and quenched by adding water and extracted using ethyl acetate (3 x 100 mL) The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum to get the solid which was purified by silica gel column chromatography to afford the desired product (0.480 g, 40%).

LCMS: 319 $[M+1]^+$.

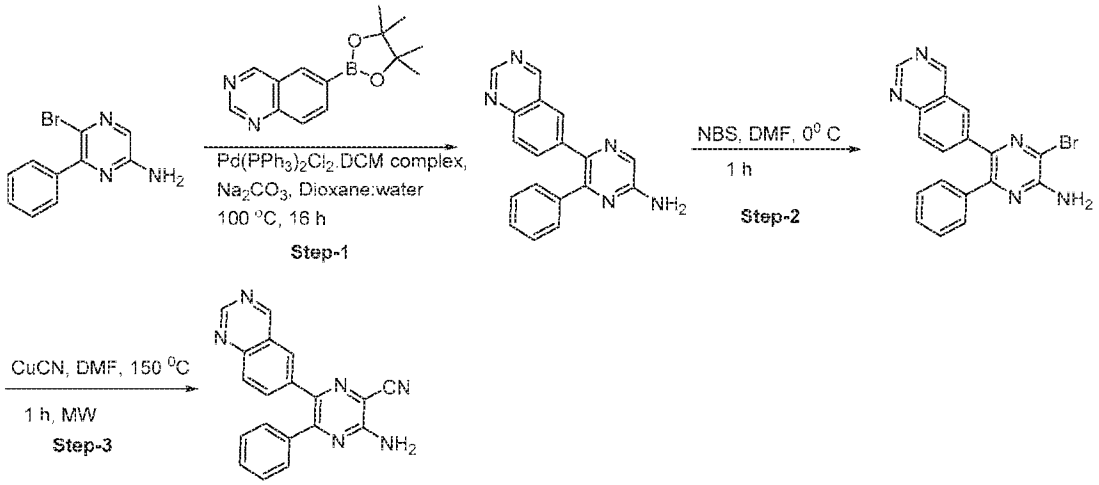
[0278] Step-2: Synthesis of 3-bromo-6-(5-methylthiophen-2-yl)-5-(quinolin-6-yl)pyrazin-2-amine: To a stirred solution of 6-(5-methylthiophen-2-yl)-5-(quinolin-6-yl)pyrazin-2-amine (0.180 g, 0.56 mmol, 1.0 eq.) in DMF (3.0 mL) was added N-bromosuccinimide (0.100 g, 0.56 mmol, 1.0 eq.) portionwise at 0 °C. Progress of the reaction was monitored by TLC and LCMS. Then quenched by adding cold water and extracted using ethyl acetate (3 x 50 mL) The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum to get the solid which was purified by normal phase column chromatography to afford the desired product (0.140 g, 63%).

LCMS: 397 $[M+1]^+$.

[0279] Step-3: Synthesis of 3-amino-5-(5-methylthiophen-2-yl)-6-(quinolin-6-yl)pyrazine-2-carbonitrile: To a stirred solution of 3-bromo-6-(5-methylthiophen-2-yl)-5-(quinolin-6-yl)pyrazin-2-amine (0.140 g, 0.35 mmol, 1.0 eq.) in DMF (3.0 mL) was added CuCN (0.095g, 1.1 mmol, 3.0 eq.). Reaction was stirred at 150 °C for 1 h under microwave irradiation. Progress of the reaction was monitored by TLC and LCMS. Reaction was allowed to cool to RT and aqueous ammonia was added to adjust the pH to 7-8. The mixture was extracted using ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum to obtain the solid which was purified by normal phase column chromatography to afford the desired product (0.012 g, 10%).

LCMS: 344 $[M+1]^+$. ^{1}H NMR: (400 MHz, DMSO-d_6) δ 8.96 (d, J = 2.54 Hz, 1H), 8.43 (d, J = 7.63 Hz, 1H), 8.14 (s, 1H), 8.05 (d, J = 8.90 Hz, 1H), 7.75 (d, J = 8.90 Hz, 1H), 7.59 (dd, J = 4.45, 8.27 Hz, 1H), 7.44 (s, 2H), 6.60 (d, J = 3.81 Hz, 1H), 6.50 (d, J = 3.81 Hz, 1H), 2.40 (s, 3H).

Example S47. Synthesis of 3-amino-5-phenyl-6-(quinazolin-6-yl)pyrazine-2-carbonitrile (Compound No. 1.283)



[0280] Step-1: Synthesis of 6-phenyl-5-(quinazolin-6-yl)pyrazin-2-amine: To a stirred solution of 5-bromo-6-phenylpyrazin-2-amine (0.400 g, 1.59 mmol, 1.0 eq.) and 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinazoline (0.491 g, 1.91 mmol, 1.2 eq.) in 1,4-dioxane (4.0 mL) was added sodium carbonate (0.423 g, 3.9 mmol, 2.5 eq.) and 1 mL water. The reaction mixture was deoxygenated using nitrogen gas and $Pd(PPh_3)_2Cl_2$.DCM complex (0.065 g, 5 mol%) was added. The reaction mixture was again purged with nitrogen and allowed to heat at 100 °C for 16 h. Progress of the reaction was monitored by TLC and LCMS. Reaction mixture was allowed to cool to RT and quenched by adding water and extracted using ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum to obtain the solid which was purified by normal phase column chromatography to afford the desired product (0.205 g, 41%)

LCMS: 300 $[M+1]^+$.

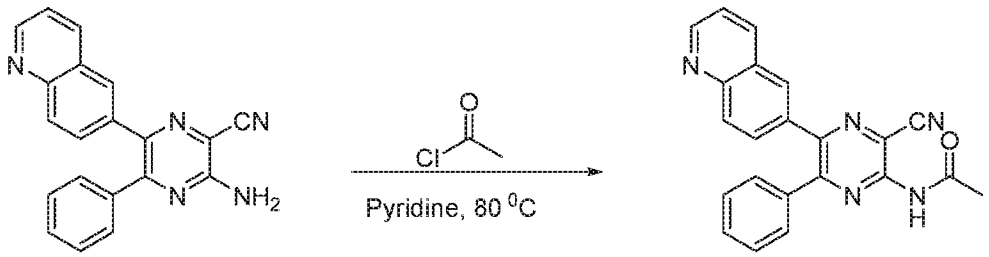
[0281] Step-2: Synthesis of 3-bromo-6-phenyl-5-(quinazolin-6-yl)pyrazin-2-amine: To a stirred solution of 6-phenyl-5-(quinazolin-6-yl)pyrazin-2-amine (0.200 g, 0.67 mmol, 1.0 eq.) in DMF (3.0 mL) was added N-bromosuccinimide (0.118 g, 0.67 mmol, 1.0 eq.) portionwise at 0 °C. Progress of the reaction was monitored by TLC and LCMS. Reaction mixture was diluted with cold water and the obtained precipitate was filtered under vacuum, washed with excess water and vacuum dried to afford the desired product (0.200 g, 79%).

LCMS: 378 $[M+1]^+$.

[0282] Step-3: Synthesis of 3-amino-5-phenyl-6-(quinazolin-6-yl)pyrazine-2-carbonitrile: To a stirred solution of 3-bromo-6-phenyl-5-(quinazolin-6-yl)pyrazin-2-amine (0.200 g, 0.52 mmol, 1.0 eq.) in DMF (3.0 mL) was added CuCN (0.142g, 1.58 mmol, 3.0 eq.). Reaction was stirred at 150 °C for 1 h under microwave irradiation. Progress of the reaction was monitored by TLC and LCMS. Reaction was allowed to cool to RT and aqueous ammonia was added to adjust the pH to 7-8. The mixture was extracted using ethyl acetate (3 x 35 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum to get the solid which was purified by normal phase column chromatography to afford the desired product (0.014 g, 9%).

LCMS: 325 $[M+1]^+$. ^{1}H NMR: (400 MHz, DMSO-d_6) δ 9.56 (s, 1H), 9.28 (s, 1H), 8.20 (s, 1H), 7.84 (d, J = 8.77 Hz, 1H), 7.70 - 7.78 (m, 1H), 7.65 (s, 2H), 7.27 - 7.44 (m, 5H).

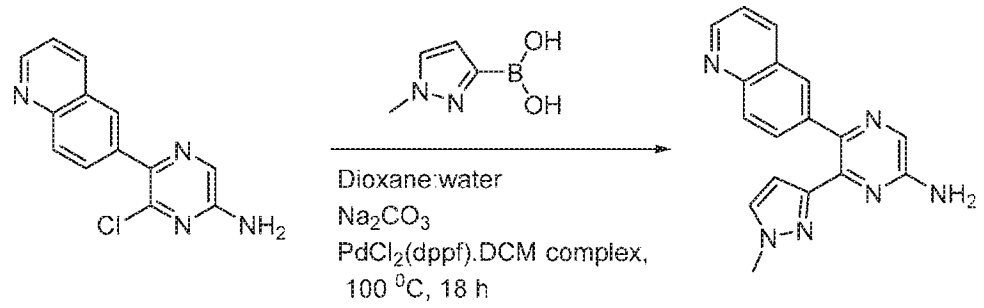
Example S48. Synthesis of N-(3-cyano-6-phenyl-5-(quinolin-6-yl)pyrazin-2-yl)acetamide (Compound No. 1.284)



[0283] To a stirred solution of 3-amino-5-phenyl-6-(quinolin-6-yl)pyrazine-2-carbonitrile (100 mg, 0.31 mmol) in pyridine (4 mL) was added acetyl chloride (0.06 mL,0.93 mmol) at 0 °C under N_2. The reaction mixture was stirred at RT for 30 min followed by heating at 80 °C for 12 h. The reaction was monitored by TLC and LCMS. The reaction was diluted with water and extracted with ethyl acetate (3x 30 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum to obtain the solid which was purified by preparative thin layer chromatography to afford the desired product (18 mg, 16%).

LCMS: 366 $[M+1]^+$. ^{1}H NMR: (400 MHz, DMSO-d_6) δ 11.36 (s, 1H), 8.94 (d, J = 3.81 Hz, 1H), 8.38 (d, J = 7.63 Hz, 1H), 8.22 (s, 1H), 7.92 (d, J = 8.90 Hz, 1H), 7.65 (d, J = 7.63 Hz, 1H), 7.56 (dd, J = 4.45, 8.27 Hz, 1H), 7.50 (d, J = 6.36 Hz, 2H), 7.31 - 7.47 (m, 3H), 2.23 (s, 3H).

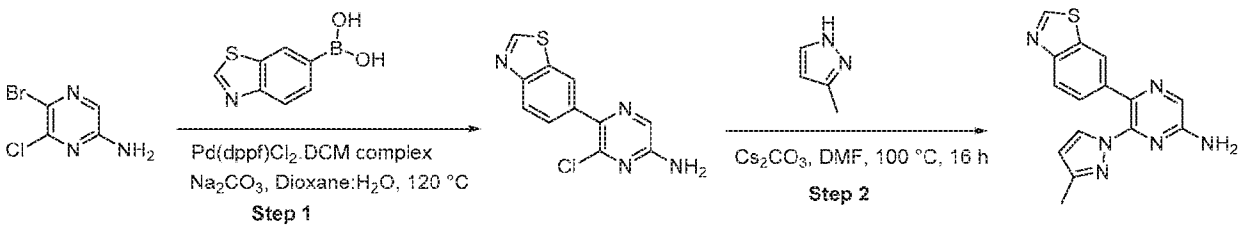
Example S49. Synthesis of 6-(1-methyl-1H-pyrazol-3-yl)-5-(quinolin-6-yl)pyrazin-2-amine (Compound No. 1.285)



[0284] To a stirred solution of 6-chloro-5-(quinolin-6-yl)pyrazin-2-amine (150 mg, 0.58 mmol, 1.0 eq.) and **(1-methyl-1H-pyrazol-3-yl)boronic acid** (81mg ,0.64 mmol, 1.1 eq.) in dioxane (5 mL) and water (1 mL), was added Na_2CO_3 (122 mg, 1.16 mmol, 2.0 eq.). The reaction was purged with N_2 for 5 min. To this reaction mixture was added $Pd(dppf)Cl_2$·DCM complex (24 mg, 5 mol%) and N_2 was purged again for another 5 min. The reaction mixture was heated at 100 °C for 18 h. progress of reaction was monitored by TLC and LCMS. On completion of the reaction, the reaction mixture was extracted with ethyl acetate (35 mL x 3). Combined organic layer was washed with water (50 mL × 2), dried over anhydrous Na_2SO_4 and concentrated under vacuum to get the solid residue which was purified by reversed phase column chromatography to afford the desired product 6-(1-methyl-1H-pyrazol-3-yl)-5-(quinolin-6-yl)pyrazin-2-amine (14 mg, 9%) as an off white solid.

LCMS: 303 $[M+1]^+$. ^1H NMR: (400 MHz, DMSO-d_6) δ 8.85 (d, J = 2.63 Hz, 1H), 8.30 (d, J = 7.89 Hz, 1H), 7.92 - 8.03 (m, 2H), 7.84 (d, J = 8.77 Hz, 1H), 7.55 - 7.64 (m, 2H), 7.49 (dd, J = 4.39, 8.33 Hz, 1H), 6.65 (s, 2H), 6.12 (d, J = 2.19 Hz, 1H), 3.71 (s, 3H).

Example S50. Synthesis of 5-(benzo[d]thiazol-6-yl)-6-(3-methyl-1H-pyrazol-1-yl)pyrazin-2-amine (Compound No. 1.286)



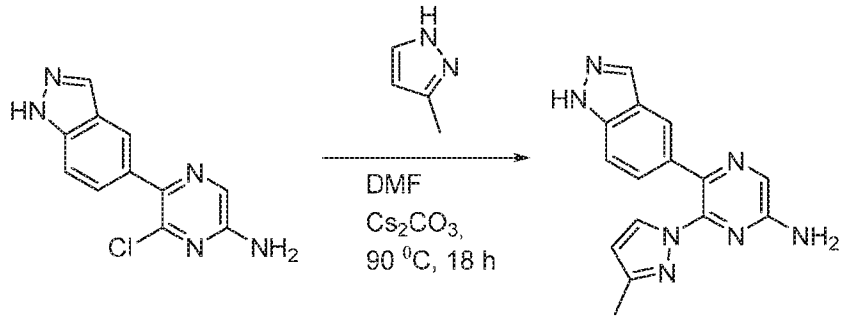
[0285] Step 1: Synthesis of 5-iodo-6-(1H-pyrazol-1-yl)pyrazin-2-amine: To a solution of 5-bromo-6-chloropyrazin-2-amine (0.600 g, 2.8 mmol, 1 eq.) and benzo[d]thiazol-6-ylboronic acid (0.412 g, 2.3 mmol, 0.8 eq.) in dioxane (8 mL) and water (2 mL) was added Na_2CO_3 (0.549 g, 5.18 mmol, 2 eq.). The reaction was purged with N_2 and $PdCl_2(dppf)$•DCM complex (0.117 g, 5 mol%). The reaction mixture was deoxygenated using N_2 atmosphere and the reaction mixture was heated at 100 °C for 16 h under microwave irradiation. The reaction was monitored by TLC and LCMS. The reaction mixture was diluted with water and extracted with ethyl acetate (3 × 100 mL). The separated organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude product was purified by normal phase column chromatography to afford desired product (0.210 g, 28%).

LCMS: 263 $[M+1]^+$.

[0286] Step 2: synthesis of 5-(benzo[d]thiazol-6-yl)-6-(3-methyl-1H-pyrazol-1-yl)pyrazin-2-amine: To a solution of 5-bromo-6-chloropyrazin-2-amine (200 mg, 0.98 mmol, 1 eq.) in DMF (3 mL) was added 3-methyl pyrazole (312 mg, 3.8 mmol, 5.0 eq.) and Cs_2CO_3 (1.24 g, 3.8 mmol, 5.0 eq.). The reaction mixture was allowed to heat at 100 °C for 16 h. The progress of the reaction was monitored by TLC and LCMS. The reaction mixture was diluted with water (30 mL) and extracted using ethyl acetate (2 × 50 mL). The separated organic layer was dried over sodium sulfate and concentrated under reduced pressure. The crude product was purified by normal phase column chromatography to afford the desired product (16 mg, 54%).

LCMS: 309 $[M+1]^+$.^{1}H NMR: (400 MHz, DMSO-d_6) δ 9.35 (s, 1H), 8.06 (s, 1H), 7.96 (d, J = 1.32 Hz, 1H), 7.90 (d, J = 8.77 Hz, 1H), 7.81 (d, J = 2.19 Hz, 1H), 7.13 (dd, J = 1.75, 8.77 Hz, 1H), 6.98 (s, 2H), 6.23 (d, J = 2.19 Hz, 1H), 2.08 (s, 3H).

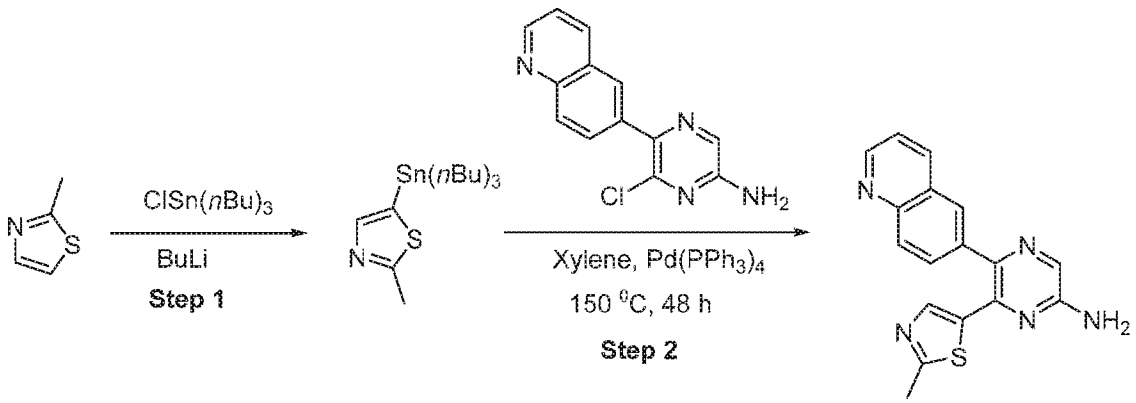
Example S51. Synthesis of 5-(1H-indazol-5-yl)-6-(3-methyl-1H-pyrazol-1-yl)pyrazin-2-amine (Compound No. 1.287)



[0287] To a stirred solution of 6-chloro-5-(1H-indazol-5-yl)pyrazin-2-amine (85 mg, 0.35 mmol, 1 eq.) in DMF (2 mL), was added 3-methyl-1*H*-pyrazole (143 mg, 1.75 mmol, 5 eq.) and Cs_2CO_3 (570 mg, 1.75 mmol, 5 eq.). The resulting reaction mixture was heated at 90 °C for 18 h. Progress of the reaction was monitored by TLC and LCMS. On completion of reaction, reaction mixture was diluted with water (30 mL) and extracted with ethyl acetate (35 mL × 3). Combined organic layer was washed with water (50 mL × 3), dried over anhydrous Na_2SO_4 and concentrated under vacuum to obtain the solid residue which was purified by reversed phase column chromatography to afford the desired product (5 mg, 35%).

LCMS: 292 $[M+1]^+$. ^1H NMR: (400 MHz, DMSO-d_6) δ 13.01 (br. s., 1H), 8.04 (s, 1H), 8.00 (s, 1H), 7.69 (d, J = 2.19 Hz, 1H), 7.55 (s, 1H), 7.36 (d, J = 8.77 Hz, 1H), 7.05 (d, J = 9.21 Hz, 1H), 6.83 (s, 2H), 6.18 (d, J = 2.19 Hz, 1H), 2.11 (s, 3H).

Example S52. Synthesis of 6-(2-methylthiazol-5-yl)-5-(quinolin-6-yl)pyrazin-2-amine (Compound No. 1.288)



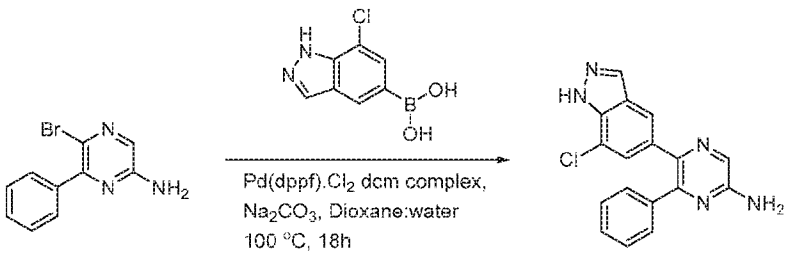
[0288] Step 1: Synthesis of 2-methyl-5-(tributylstannyl)thiazole: To a stirred solution of 2-methylthiazole (1g, 0.01 mol, 1 eq.) in THF (25 mL) was added n-butyl lithium(1.6 M, 6.9 ml, 0.011 mol, 1.1 eq.) at -78 °C under N_2. The reaction mixture was stirred at the same for 30 min then charged tri butyl tin chloride (3.2 mL,0.012 mol, 1.2 eq.) then the reaction mixture was stirred at -78 ^{0}c for 1 h and 16 h at room temperature. The reaction was monitored by TLC and LCMS. The reaction was diluted aq. $NaHCO_3$ and extracted with diethyl ether (3 x 25 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum to obtain the solid which was purified by normal phase column chromatography to afford the desired product as an off white solid (2.1 g, 54%).

LCMS: 390 $[M+1]^+$.

[0289] Step 2: Synthesis of 6-(2-methylthiazol-5-yl)-5-(quinolin-6-yl)pyrazin-2-amine: To a stirred solution of 6-chloro-5-(quinolin-6-yl)pyrazin-2-amine (0.200 g, 0.78 mol, 1.0 eq.) and 2-methyl-5-(tributylstannyl)thiazole (0.911 g, 2.34 mol, 3 eq.) in xylene (5 mL) and DMF (1 mL) was added $Pd(PPh_3)_4$ (0.090g, 10 mol %) under N_2. The reaction mixture was heated at 150 °C for 48 h. The reaction mixture was allowed to cool to RT and charged with water extracted using ethyl acetate (2 × 35 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum to get the solid residue which was purified by reversed phase column chromatography to get the desired product (20 mg, 8%).

LCMS: 320 $[M+1]^+$. ^{1}H NMR: (400 MHz, DMSO-d6) δ 8.93 (d, J = 3.51 Hz, 1H), 8.39 (d, J = 7.89 Hz, 1H), 8.08 (s, 1H), 8.02 (d, J = 8.77 Hz, 1H), 7.93 (s, 1H), 7.73 (d, J = 7.45 Hz, 1H), 7.56 (dd, J = 4.17, 8.55 Hz, 1H), 7.11 (s, 1H), 6.79 (s, 2H), 2.56 (s, 3H).

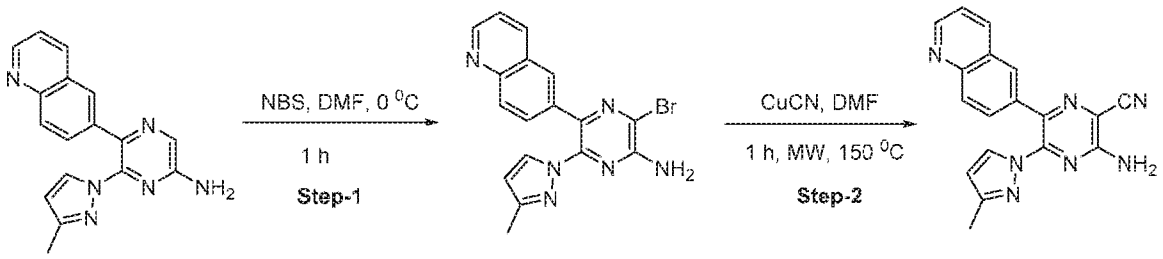
Example S53. Synthesis of 5-(1H-indazol-5-yl)-6-phenylpyrazin-2-amine (Compound No. 1.289)



[0290] To a stirred solution of 5-bromo-6-phenylpyrazin-2-amine (0.120 g, 0.48 mmol, 1.0 eq.) and (7-chloro-1H-indazol-5-yl)boronic acid (0.104 g, 0.53 mmol, 1.1 eq.) in dioxane (4 mL) was added Na_2CO_3 (0.102 g, 0.96 mmol, 2.0 eq.) and 1 mL water. The reaction was purged with N_2 for 5 min. To this reaction mixture was added with $Pd(dppf)Cl_2$.DCM complex (0.020 g, 5 mol %) and N_2 was purged again for another 5 min. The reaction mixture was heated at 100 °C for 18 h. The reaction mixture was allowed to cool to RT and extracted using ethyl acetate (3 × 35 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum to obtain the solid residue which was purified by reversed phase column chromatography to get the desired product as off white solid (0.008 g, 5%).

LCMS: 322 $[M+1]^+$. ^1H NMR: (400 MHz, DMSO-d_6) δ 13.54 (br. s., 1H), 8.07 (br. s., 1H), 7.95 (s, 1H), 7.54 (br. s., 1H), 7.30 (d, J = 9.65 Hz, 6H), 6.63 (br. s., 2H).

Example S54. Synthesis of 3-amino-5-(3-methyl-1H-pyrazol-1-yl)-6-(quinolin-6-yl)pyrazine-2-carbonitrile (Compound No. 1.290)



[0291] Step1. Synthesis of 3-bromo-6-(3-methyl-1H-pyrazol-1-yl)-5-(quinolin-6-yl)pyrazin-2-amine: To a solution of 6-(3-methyl-1H-pyrazol-1-yl)-5-(quinolin-6-yl)pyrazin-2-amine (220 mg, 0.72 mmol, 1 eq.) in DMF (5 mL) at room temperature was added N-bromosuccinimide (123 mg, 0.72 mmol, 1 eq.) portion wise and the reaction mixture was allowed to stir at room temperature for 1h. The reaction was poured over ice-water to get the solid precipitate which was filtered under vacuum and washed with excess water. The solid was vacuum dried to afford the desired product as off white solid (0.200g, 73%).

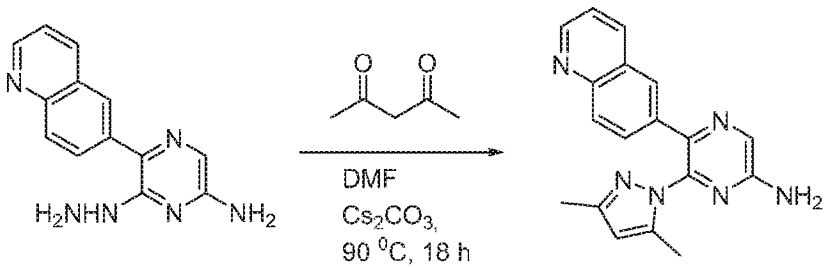
LCMS: 381 $[M+1]^+$.

[0292] Step 2. Synthesis of 3-amino-5-(3-methyl-1H-pyrazol-1-yl)-6-(quinolin-6-yl)pyrazine-2-carbonitrile: To a stirred solution of 6-phenyl-5-(quinolin-6-yl)pyrazin-2-amine (0.220 g, 0.26

mmol, 1.0 eq.) in DMF (3 mL) was added cuprous cyanide (0.155 g, 0.78 mmol, 3.0 eq.). The reaction mixture was allowed to stir at 150 °C for 1h under microwave irradiation. The progress of the reaction was monitored by LCMS. The reaction mixture was allowed to cool to RT and extracted using ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum to obtain the solid which was purified by normal phase column chromatography to afford the desired product as an off white solid (0.020 g, 23%).

LCMS: 328 $[M+1]^+$.1H NMR: (400 MHz, DMSO-d6) δ 8.89 (d, J = 3.07 Hz, 1H), 8.36 (d, J = 7.45 Hz, 1H), 8.01 (d, J = 2.63 Hz, 1H), 7.96 (s, 1H), 7.86 (d, J = 8.77 Hz, 1H), 7.79 (br. s., 2H), 7.53 (dd, J = 3.95, 8.33 Hz, 1H), 7.38 (d, J = 7.45 Hz, 1H), 6.33 (d, J = 2.19 Hz, 1H), 1.99 (s, 3H).

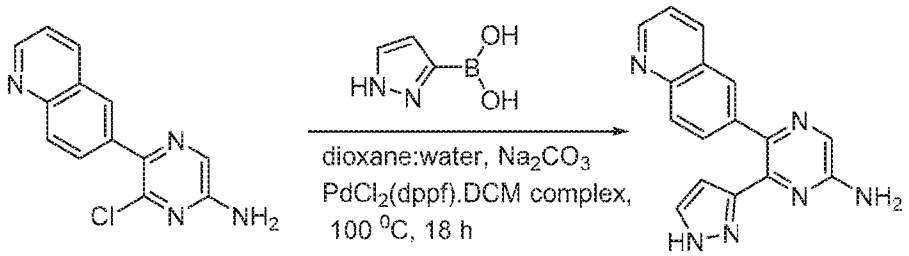
Example S55. Synthesis of 6-(3,5-dimethyl-1H-pyrazol-1-yl)-5-(quinolin-6-yl)pyrazin-2-amine (Compound No. 1.291)



[0293] A mixture of 6-hydrazinyl-5-(quinolin-6-yl)pyrazin-2-amine (0.120 g, 0.48 mmol, 1.0 eq.), acetylacetone (0.071 g, 0.71 mmol, 1.5 eq.), ethanol (4 mL) and concentrated sulfuric acid (0.02 mL) was heated at reflux for 18 h. After cooling the mixture to ambient temperature, the reaction was quenched by adding saturated aqueous sodium hydrogen carbonate. The organic layer was extracted with ethyl acetate (3 × 30 mL), washed with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuum. The residue was purified by reversed column chromatography to afford the desired product (35 mg, 23%).

LCMS: 317 $[M+1]^+$. ^1H NMR: (400 MHz, DMSO-d_6) δ 8.84 (dd, J = 1.53, 4.17 Hz, 1H), 8.12 - 8.26 (m, 2H), 7.84 (d, J = 8.77 Hz, 1H), 7.66 (d, J = 1.32 Hz, 1H), 7.49 (dd, J = 4.38, 8.33 Hz, 1H), 7.36 (dd, J = 1.97, 8.99 Hz, 1H), 7.05 (s, 2H), 5.98 (s, 1H), 2.12 (s, 3H), 1.89 (s, 3H).

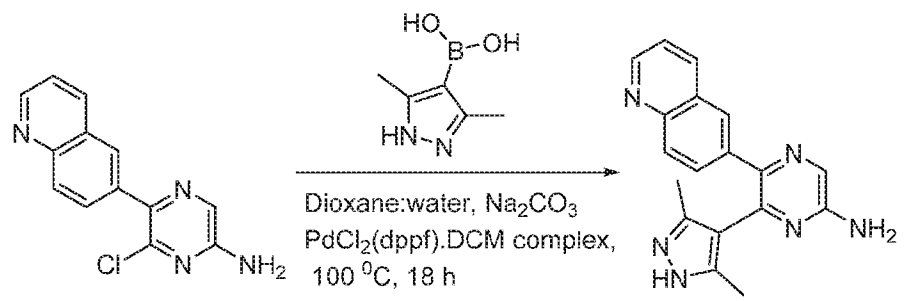
Example S56. Synthesis of 6-(1H-pyrazol-3-yl)-5-(quinolin-6-yl)pyrazin-2-amine (Compound No. 1.293)



[0294] To a stirred solution of 6-chloro-5-(quinolin-6-yl)pyrazin-2-amine (100 mg, 0.39 mmol, 1.0 eq.) and (1*H*-pyrazol-3-yl)boronic acid (81mg ,0.47 mmol, 1.2 eq.) in dioxane (3 mL) and water (0.5 mL), was added Na_2CO_3 (83 mg, 0.78 mmol, 2.0 eq.). The reaction was purged with N_2 for 5 min. To this reaction mixture was added $Pd(dppf)Cl_2$·DCM complex (16 mg, 5 mol%) and N_2 was purged again for another 5 min. The reaction mixture was heated at 100 °C for 18 h. Progress of reaction was monitored by TLC and LCMS. On completion of the reaction, the reaction mixture was extracted with ethyl acetate (35 mL x 3). Combined organic layers were washed with water (20 mL×2), dried over anhydrous Na_2SO_4 and concentrated under vacuum to obtain the solid residue which was purified by reversed phase column chromatography to afford the desired product (10 mg, 9%) as an off white solid.

LCMS: 289 $[M+1]^+$, ^{1}H NMR: (400 MHz, DMSO-d_6) δ12.59 (s, 1H), 8.86 (br. s., 1H), 8.29 (d, *J* = 7.45 Hz, 1H), 7.95 (s, 2H), 7.86 (d, *J* = 8.33 Hz, 2H), 7.58 (d, *J* = 8.33 Hz, 2H), 7.50 (br. s., 1H), 6.64 (br. s., 2H).

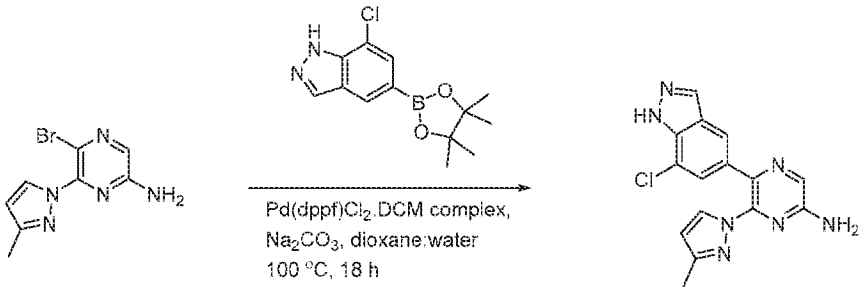
Example S57. Synthesis of 6-(3,5-dimethyl-1H-pyrazol-4-yl)-5-(quinolin-6-yl)pyrazin-2-amine (Compound No. 1.294)



[0295] To a stirred solution of 6-chloro-5-(quinolin-6-yl)pyrazin-2-amine (100 mg, 0.39 mmol, 1.0 eq.) and (3,5-dimethyl-1H-pyrazol-4-yl)boronic acid (104mg ,0.47 mmol, 1.2 eq.) in dioxane (3 mL) and water (0.5 mL), was added Na_2CO_3 (83 mg, 0.78 mmol, 2.0 eq.). The reaction was purged with N_2 for 5 min. To this reaction mixture was added $Pd(dppf)Cl_2$·DCM complex (16 mg, 5 mol%) and N_2 was purged again for another 5 min. The reaction mixture was heated at 100 °C for 16 h. progress of reaction was monitored by TLC and LCMS. On completion of the reaction, the reaction mixture was extracted with ethyl acetate (35 mL x 3). Combined organic layer was washed with water (20 mL×2), dried over anhydrous Na_2SO_4 and concentrated under vacuum to obtain the solid residue which was purified by reversed phase column chromatography to afford the desired product (20 mg, 16%) as an off white solid.

LCMS: 317 $[M+1]^+$. ^1H NMR: (400 MHz, DMSO-d_6) δ8.89 (d, J = 3.95 Hz, 1H), 8.38 (d, J = 8.33 Hz, 1H), 8.02 (s, 1H), 7.96 (s, 1H), 7.85 (d, J = 8.77 Hz, 1H), 7.63 (d, J = 9.21 Hz, 1H), 7.55 (dd, J = 4.38, 7.89 Hz, 1H), 6.63 (br. s., 2H), 1.80 (s, 6H).

Example S58. Synthesis of 5-(7-chloro-1H-indazol-5-yl)-6-(3-methyl-1H-pyrazol-1-yl)pyrazin-2-amine (Compound No. 1.295)

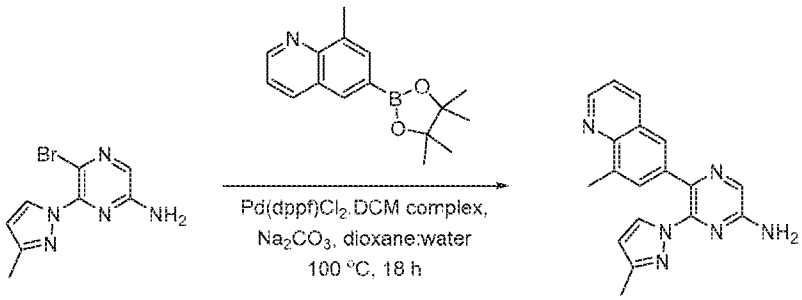


[0296] To a stirred solution of 5-bromo-6-(3-methyl-1H-pyrazol-1-yl)pyrazin-2-amine (0.150 g, 0.60 mmol, 1.0 eq.) and 7-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole (0.198g, 0.71 mmol, 1.2 eq.) in dioxane (4 mL) was added Na_2CO_3 (0.127g, 1.2 mmol, 2.0 eq.) and 1 mL water. The reaction was purged with N_2 for 5 min. To this reaction mixture was added with $Pd(dppf)Cl_2$.DCM complex (0.024 g, 5 mol %) and N_2 was purged again for another 5 min. The reaction mixture was heated at 100 °C for 18 h. The reaction mixture was allowed to cool to RT and extracted using ethyl acetate (3 × 35 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum to obtain the solid

residue which was purified by normal phase column chromatography to afford the desired product as off white solid (0.035g, 8%).

LCMS: 326 $[M+1]^+$. ^{1}H NMR: (400 MHz, DMSO-d_6) δ 13.54 (br. s., 1H), 8.13 (s, 1H), 8.04 (s, 1H), 7.81 (br. s., 1H), 7.50 (s, 1H), 7.04 (s, 1H), 6.93 (br. s., 2H), 6.24 (br. s., 1H), 2.10 (s, 3H).

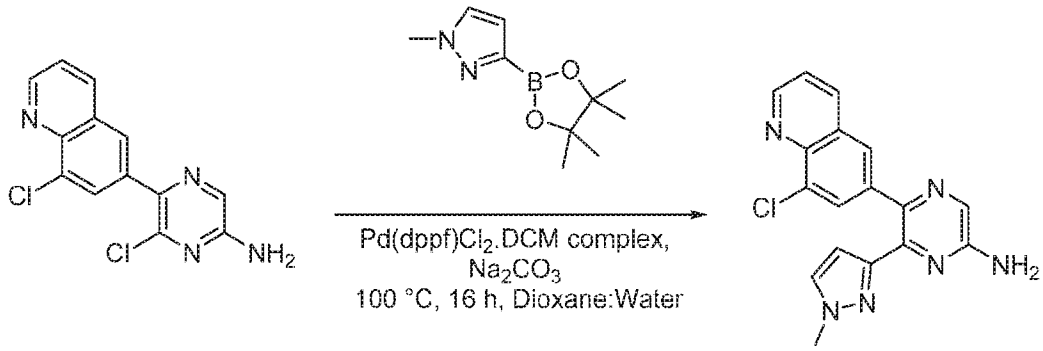
Example S59. Synthesis of 6-(3-methyl-1H-pyrazol-1-yl)-5-(8-methylquinolin-6-yl)pyrazin-2-amine (Compound No. 1.296)



[0297] To a stirred solution of 5-bromo-6-(3-methyl-1H-pyrazol-1-yl)pyrazin-2-amine (0.150 g, 0.60 mmol, 1.0 eq.) and 8-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline (0.175g, 0.65 mmol, 1.1 eq.) in dioxane (4 mL) was added Na_2CO_3 (0.127g, 1.2 mmol, 2.0 eq.) and 1 mL water. The reaction was purged with N_2 for 5 min. To this reaction mixture was added with Pd(dppf)Cl_2.DCM complex (0.024 g, 5 mol %) and N_2 was purged again for another 5 min. The reaction mixture was heated at 100 °C for 18 h. The reaction mixture was allowed to cool to RT and extracted using ethyl acetate (3 × 35 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum to obtain the solid residue which was purified by normal phase column chromatography to afford the desired product as off white solid (0.035g, 19%).

LCMS: 361 $[M+1]^+$. ^{1}H NMR: (400 MHz, DMSO-d_6) δ 8.86 (d, J = 2.63 Hz, 1H), 8.18 (d, J = 7.89 Hz, 1H), 8.09 (s, 1H), 7.81 (s, 1H), 7.56 (s, 1H), 7.48 (dd, J = 4.17, 8.11 Hz, 1H), 7.21 (s, 1H), 7.01 (br. s., 2H), 6.25 (s, 1H), 2.59 (s, 3H), 2.10 (s, 3H).

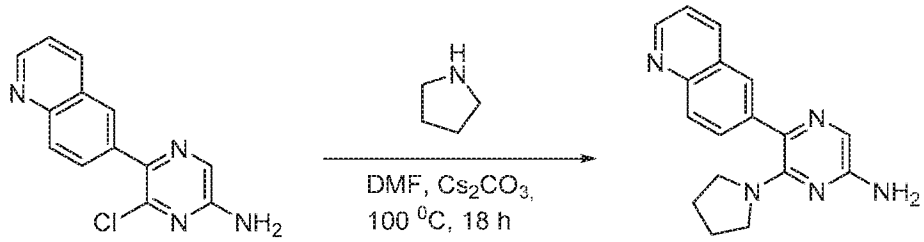
Example S60. Synthesis of 5-(8-chloroquinolin-6-yl)-6-(1-methyl-1H-pyrazol-3-yl)pyrazin-2-amine (Compound No. 1.297)



[0298] To a stirred solution of 6-chloro-5-(8-chloroquinolin-6-yl)pyrazin-2-amine (0.460 g, 1.57 mmol, 1.0 eq.) and 1-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (0.394 g, 1.89 mmol, 1.2 eq.) in dioxane (10 mL) was added Na_2CO_3 (0.334 g, 3.15 mmol, 2.0 eq.) and 2 mL water. Then reaction was purged with N_2 for about 5 min. To this reaction mixture was added Pd(dppf)Cl_2.DCM complex (0.129 g, 10 mol %) and N_2 was purged again for another 5 min. Then reaction mixture was heated at 100 °C for 16 h, allowed to cool to RT and extracted using ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum to obtain the solid residue which was purified by reversed phase column chromatography to afford the desired product as yellow solid (0.005 g, 1%).

LCMS: 337[M+1]$^+$. ^{1}H NMR: (400 MHz, DMSO-d_6) δ 8.97 (d, J = 2.63 Hz, 1H), 8.39 (d, J = 7.89 Hz, 1H), 7.97 (s, 2H), 7.76 (s, 1H), 7.66 (br. s., 1H), 7.61 (dd, J = 4.17, 8.11 Hz, 1H), 6.72 (s, 2H), 6.26 (br. s., 1H), 3.71 (s, 3H).

Example S61. Synthesis of 6-(pyrrolidin-1-yl)-5-(quinolin-6-yl)pyrazin-2-amine (Compound No. 1.298)

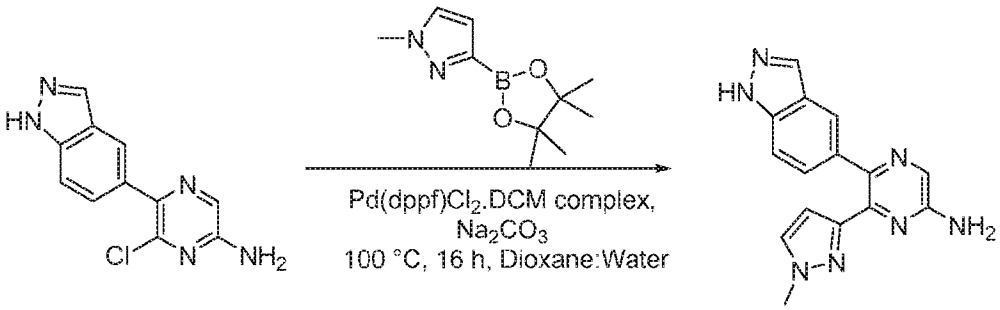


[0299] To a stirred solution of 6-chloro-5-(quinolin-6-yl)pyrazin-2-amine (128 mg, 0.5 mmol, 1 eq.) in DMF (2 mL), was added pyrrolidine (177 mg, 2.5 mmol, 5 eq.) and Cs_2CO_3 (0.815 g, 2.5

mmol, 5 eq.). Resulting mixture was heated at 100 ^{0}C for 18 h. Progress of the reaction was monitored by TLC and LCMS. On completion of the reaction, the reaction mixture was diluted with water (30 mL) and extracted with ethyl acetate (50 mL × 3). Organic layer was washed with water (100 mL × 3), dried (anhydrous Na_2SO_4) and concentrated under vacuum to get the solid residue which was purified by normal phase column chromatography to afford the desired product as off white solid (100 mg, 33%).

LCMS: 292 $[M+1]^+$. ^{1}H NMR: (400 MHz, DMSO-d_6) δ 8.86 (br. s., 1H), 8.42 (d, J = 7.89 Hz, 1H), 7.83 - 8.04 (m, 3H), 7.48 - 7.59 (m, 1H), 7.40 (s, 1H), 6.18 (br. s., 2H), 3.09 (br. s., 4H), 1.72 (br. s., 4H).

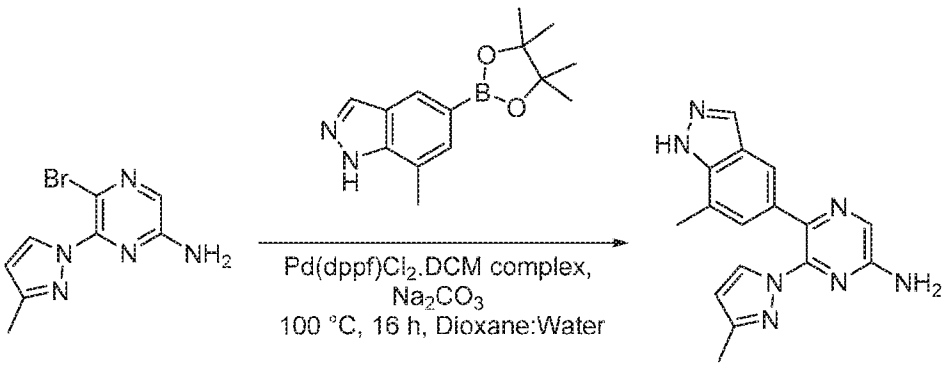
Example S62. Synthesis of 5-(1H-indazol-5-yl)-6-(1-methyl-1H-pyrazol-3-yl)pyrazin-2-amine (Compound No. 1.299)



[0300] To a stirred solution of 6-chloro-5-(1H-indazol-5-yl)pyrazin-2-amine (0.150 g, 0.61 mmol, 1.0 eq.) and 1-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (0.152 g, 0.73 mmol, 1.2 eq.) in dioxane (10 mL) was added Na_2CO_3 (0.129 g, 1.22 mmol, 2.0 eq.) and 2 mL water. Then reaction was purged with N_2 for about 5 min. To this reaction mixture was added Pd(dppf)Cl_2·DCM complex (0.025 g, 5 mol %) and N_2 was purged again for another 5 min. The reaction mixture was heated at 100 °C for 16 h. After that reaction mixture was allowed to cool to RT and extracted using ethyl acetate (3 × 50 mL). The combined organic layers were washed (brine), dried (anhydrous Na_2SO_4) and concentrated under vacuum to get the solid residue which was purified by reversed phase column chromatography to afford the desired product as off white solid (0.010 g, 6 %).

LCMS: 292.2 $[M+1]^+$. ^1H NMR: (400 MHz, DMSO-d_6) δ 13.01 (br. s., 1H), 8.01 (s, 1H), 7.90 (s, 1H), 7.69 (s, 1H), 7.53 (d, J = 1.75 Hz, 1H), 7.40 (d, J = 8.77 Hz, 1H), 7.25 (d, J = 8.77 Hz, 1H), 6.48 (s, 2H), 5.89 (d, J = 2.19 Hz, 1H), 3.74 (s, 3H).

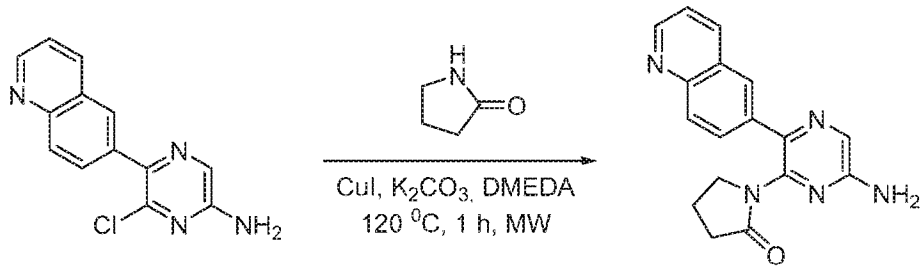
Example S63. Synthesis of 5-(7-methyl-1H-indazol-5-yl)-6-(3-methyl-1H-pyrazol-1-yl)pyrazin-2-amine (Compound No. 1.300)



[0301] To a stirred solution of 5-bromo-6-(3-methyl-1H-pyrazol-1-yl)pyrazin-2-amine (0.100 g, 0.39 mmol, 1.0 eq.) and 7-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole (0.121 g, 0.47 mmol, 1.2 eq.) in dioxane (10 mL) was added Na_2CO_3 (0.083 g, 0.78 mmol, 2.0 eq.) and 2 mL water. The reaction was purged with N_2 for about 5 min and Pd(dppf)Cl_2·DCM complex (0.016 g, 5 mol %) was added. Reaction was purged with N_2 for another 5 min and was heated at 100 °C for 16 h. Following this, reaction mixture was allowed to cool to RT and extracted using ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine, dried anhydrous Na_2SO_4 and concentrated under vacuum to obtain the solid residue which was purified by reversed phase column chromatography to afford the desired product as off white solid (0.012 g, 10%).

LCMS: 306.2 $[M+1]^+$. ^1H NMR: (400 MHz, DMSO-d_6) δ 13.04 (br. s., 1H), 8.04 (s, 1H), 7.96 (s, 1H), 7.66 (br. s., 1H), 7.28 (s, 1H), 6.87 (br. s., 1H), 6.83 (br. s., 2H), 6.17 (br. s., 1H), 2.41 (s, 3H), 2.12 (s, 3H).

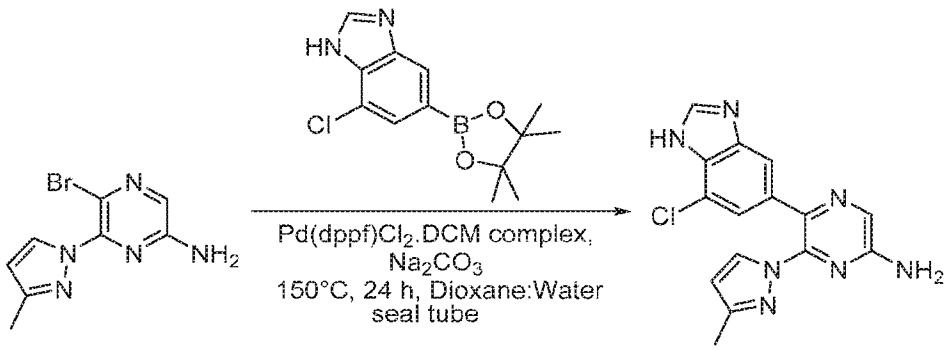
Example S64. Synthesis of 1-(6-amino-3-(quinolin-6-yl)pyrazin-2-yl)pyrrolidin-2-one (Compound No. 1.301)



[0302] To a stirred solution of 6-chloro-5-(quinolin-6-yl)pyrazin-2-amine (128 mg, 0.5 mmol, 1 eq.) in DMF (2 mL), was added pyrrolidin-2-one (64 mg, 0.75 mmol, 1.5 eq.), CuI (19 mg, 0.1 mmol, 0.2 eq.) and DMEDA (17 mg, 0.2 mmol, 0.4 eq.). The reaction mixture was deoxygenated using N_2 and was allowed to heat at 120 ^{0}C for 1 h under microwave irradiation. Reaction was allowed to cool to RT and extracted with ethyl acetate (50 mL×3). Combined organic layers were washed with brine (20 mL×3), dried over anhydrous Na_2SO_4 and concentrated under vacuum to obtain the solid residue which was purified by reversed phase column chromatography to afford the desired product as off white solid (15 mg, 10%).

LCMS: 306 $[M+1]^+$. ^{1}H NMR: (400 MHz, DMSO-d_6) δ 8.86 (s, 1H), 8.39 (d, J = 7.89 Hz, 1H), 8.09 (br. s., 1H), 7.93 - 8.01 (m, 2H), 7.90 (d, J = 7.02 Hz, 1H), 7.52 (dd, J = 4.17, 8.11 Hz, 1H), 6.79 (br. s., 2H), 3.92 (d, J = 6.58 Hz, 2H), 2.18 (d, J = 6.58 Hz, 2H), 2.04 - 2.14 (m, 2H).

Example S65. Synthesis of 5-(7-chloro-1H-benzo[d]imidazol-5-yl)-6-(3-methyl-1H-pyrazol-1-yl)pyrazin-2-amine (Compound No. 1.302)

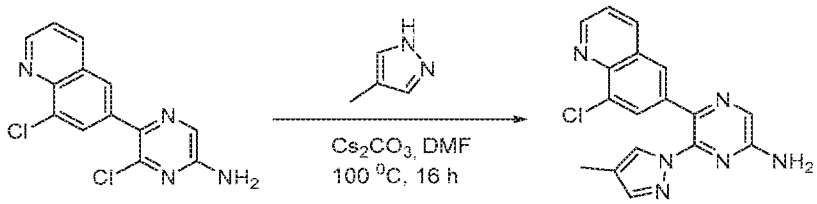


[0303] To a stirred solution of 5-bromo-6-(3-methyl-1H-pyrazol-1-yl)pyrazin-2-amine (0.5 g, 1.96 mmol, 1.0 eq.) and 7-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d]imidazole (0.657 g, 2.36 mmol, 1.2 eq.) in dioxane (20 mL) was added Na_2CO_3 (0.415

g, 3.92 mmol, 2.0 eq.) and 4 mL water. The reaction was purged with N_2 for about 5 min and $Pd(dppf)Cl_2$ DCM complex (0.080 g, 5 mol %) was added. Reaction was purged with N_2 for another 5 min and was heated at 150 °C for 24 h in a sealed tube. Following this, reaction mixture was allowed to cool to RT and extracted using ethyl acetate (3 × 50 mL). The combined organic layer was washed brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum to obtain the solid residue which was purified by reversed phase column chromatography to afford the desired product as off white solid (0.026 g, 4.05 %).

LCMS: 326.2 $[M+1]^+$. ^1H NMR: (400 MHz, DMSO-d_6) δ 12.72 (br. s., 1H), 8.26 (s, 1H), 8.05 (s, 1H), 7.76 (d, J = 1.75 Hz, 1H), 7.22 (br. s., 1H), 6.93 (br. s., 3H), 6.23 (s, 1H), 2.12 (s, 3H).

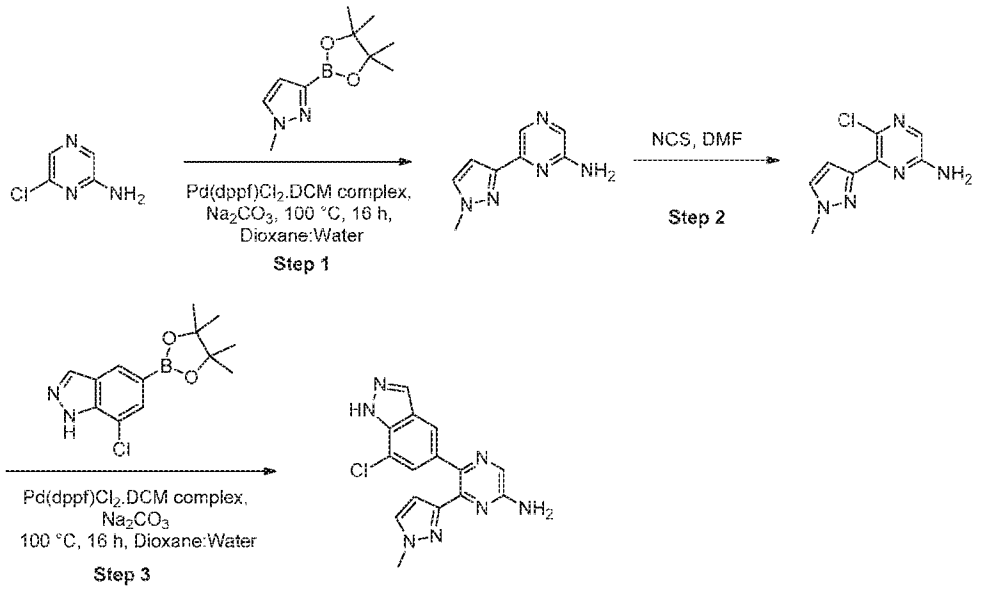
Example S66. Synthesis of 5-(8-chloroquinolin-6-yl)-6-(4-methyl-1H-pyrazol-1-yl)pyrazin-2-amine (Compound No. 1.303)



[0304] To a stirred solution of 6-chloro-5-(8-chloroquinolin-6-yl)pyrazin-2-amine (120 mg, 0.41 mmol, 1 eq.) in DMF (5 mL), was added 4-methyl-1H-pyrazole (84 mg, 1.03 mmol, 2.5 eq.) and Cs_2CO_3 (335 mg, 1.03 mmol, 2.5 eq.). Resulting mixture was heated at 100 ^{0}C for 16 h. Progress of reaction was monitored by TLC and LCMS. On completion of the reaction, the reaction mixture was diluted with water (30 mL) and extracted with ethyl acetate (50 mL × 2). Combined organic layers were washed with water (100 mL × 2), dried over anhydrous Na_2SO_4 and concentrated under vacuum to obtain the solid residue which was purified by normal phase column chromatography to afford the desired product as pale yellow solid (60 mg, 43%).

LCMS: 337.2 $[M+1]^+$. ^1H NMR: (400 MHz, DMSO-d_6) δ 8.96 (d, J = 3.51 Hz, 1H), 8.36 (d, J = 7.45 Hz, 1H), 8.07 (s, 1H), 7.94 (s, 1H), 7.80 (s, 1H), 7.61 (dd, J = 4.17, 8.11 Hz, 1H), 7.41 (d, J = 9.65 Hz, 2H), 7.09 (s, 2H), 2.08 (s, 3H).

Example S67. Synthesis of 5-(7-chloro-1H-indazol-5-yl)-6-(1-methyl-1H-pyrazol-3-yl)pyrazin-2-amine (Compound No. 1.304)



[0305] Step 1: Synthesis of 6-(1-methyl-1H-pyrazol-3-yl)pyrazin-2-amine: To a stirred solution of 6-chloropyrazin-2-amine (1 g, 7.72 mmol, 1.0 eq.) and 1-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (1.76 g, 8.49 mmol, 1.1 eq.) in dioxane (40 mL) was added Na_2CO_3 (1.63 g, 15.4 mmol, 2.0 eq.) and 8 mL of water. The reaction mixture was purged with N_2 for about 5 min and $Pd(dppf)Cl_2$·DCM complex (0.315 g, 5 mol %) was added. Reaction mixture was re-purged with N_2 and heated at 100 °C for 16 h. Following this, reaction was allowed to cool to RT and extracted using ethyl acetate (3 × 150 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum to obtain the solid residue which was purified by normal phase column chromatography to afford the desired product as brown solid (0.380 g, 28%).

LCMS: 176 $[M+1]^+$.

[0306] Step 2: Synthesis of 5-chloro-6-(1-methyl-1H-pyrazol-3-yl)pyrazin-2-amine: To a solution of 6-(1-methyl-1H-pyrazol-3-yl)pyrazin-2-amine (0.380 g, 2.16 mmol, 1 eq.) in DMF (10 mL) was added N-chlorosuccinimide (0.289 g, 2.16 mmol, 1 eq.) and the reaction mixture was stirred at 60 °C for 16 h. The reaction was monitored by TLC and LCMS. After completion, the reaction mixture was diluted with water (50 mL) and extracted by ethyl acetate (2 × 100 mL).

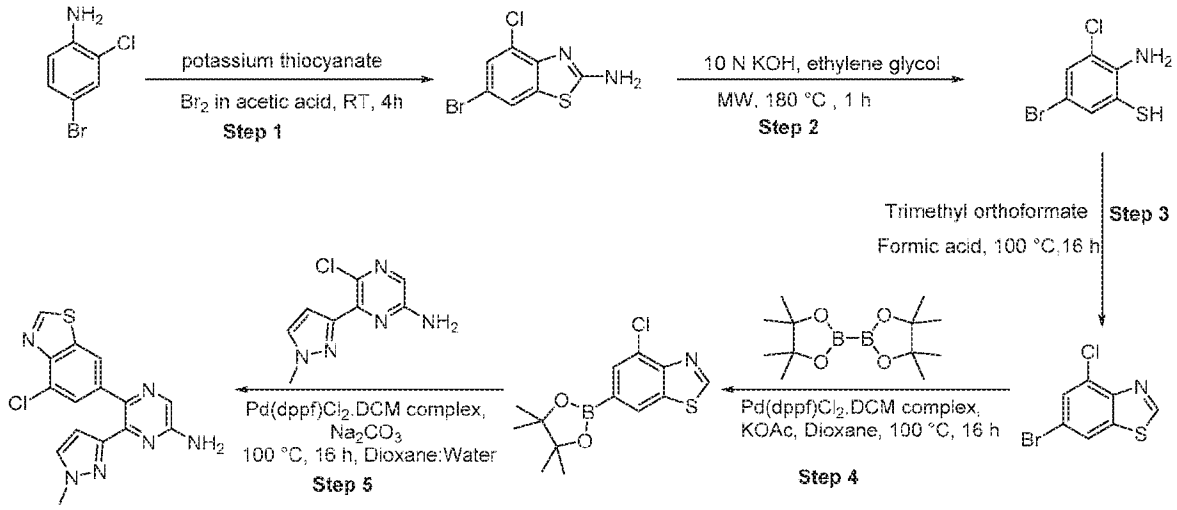
Combined organic layer was washed with water (5 × 30 mL) followed by brine and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to get the crude product which was purified by normal phase column chromatography to afford the desired product as yellow solid (165 mg, 36%).

LCMS: 210 $[M+1]^+$.

[0307] Step 3: Synthesis of 5-(7-chloro-1H-indazol-5-yl)-6-(1-methyl-1H-pyrazol-3-yl)pyrazin-2-amine: To a stirred solution of 5-chloro-6-(1-methyl-1H-pyrazol-3-yl)pyrazin-2-amine (0.125 g, 0.59 mmol, 1.0 eq.) and 7-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole (0.182 g, 0.65 mmol, 1.1 eq.) in dioxane (10 mL) was added Na_2CO_3 (0.126 g, 1.192 mmol, 2.0 eq.) and 2 mL water. The reaction mixture was purged with N_2 for about 5 min and $Pd(dppf)Cl_2$·DCM complex (0.024 g, 5 mol %) was added. Reaction mixture was re-purged with N_2 and heated at 100 °C for 16 h. Following this, reaction was allowed to cool to RT and extracted using ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum to obtain the solid residue which was purified by reversed phase column chromatography to afford the desired product as off white solid (0.039 g, 20%).

LCMS: 326 $[M+1]^+$. ^{1}H NMR: (400 MHz, DMSO-d_6) δ 13.53 (br. s., 1H), 8.14 (s, 1H), 7.90 (s, 1H), 7.65 (s, 1H), 7.59 (d, J = 2.19 Hz, 1H), 7.33 (s, 1H), 6.57 (s, 2H), 6.06 (d, J = 2.19 Hz, 1H), 3.73 (s, 3H).

Example S68. Synthesis of 5-(4-chlorobenzo[d]thiazol-6-yl)-6-(1-methyl-1H-pyrazol-3-yl)pyrazin-2-amine (Compound No. 1.305)



[0308] Step 1: Synthesis of 6-bromo-4-chlorobenzo[d]thiazol-2-amine: To a solution of 4-bromo-2-chloroaniline (2.5g, 12.11 mmol, 1 eq.) in acetic acid (25ml) was added at RT potassium thiocyanate (4.7g, 48.4 mmol, 4.0 eq). To this mixture was added a solution of bromine (1.25 ml, 24.22 mmol, 2 eq.) in acetic acid (5 ml) drop-wise for 15 min and allowed to stir at RT for 4h. The reaction mixture was neutralized with aqueous sodium hydroxide solution and product was precipitated out as solid and filtered to get residue. Residue was further purified using pentane and diethyl ether wash to get desired compound as pale yellow solid (2g, 62.6%).

LCMS: 263 $[M+1]^+$.

[0309] Step 2: synthesis of 2-amino-5-bromo-3-chlorobenzenethiol: To the stirred solution of 6-bromo-4-chlorobenzo[d]thiazol-2-amine (0.5 g ,1.89 mmol , 1 eq.) in ethylene glycol (3 ml) was added 10 N KOH solution (3.77 ml ,37.9 mmol , 20.0 eq.) and the reaction mixture was microwave irradiated at 180 °C for 1h. Reaction mixture was neutralized using 1N HCl solution and product was precipitated out as solid which was filtered to get residue. The obtained residue was further dissolved in methanol, filtered & concentrated under reduced pressure to get desired product as yellow viscous compound (350 mg, 77.4%).

LCMS: 238 $[M+1]^+$

[0310] Step 3: Synthesis of 6-bromo-4-chlorobenzo[d]thiazole: To the stirred solution of 2-amino-5-bromo-3-chlorobenzenethiol (0.250 g ,1.048 mmol , 1 eq.) in formic acid (5 ml) was

added trimethyl orthoformate (0.346 ml ,3.14 mmol , 3.0 eq.) and the reaction mixture was allowed to stir at 100 °C for 16 h. The reaction mixture was allowed to cool to RT, neutralized using 10% sodium hydroxide solution and extracted using ethyl acetate (3 x150 mL). The combined organic layers were washed (brine), dried (anhydrous Na_2SO_4) and concentrated under vacuum to get the solid residue which was purified by normal phase column chromatography to get the desired product as off white solid (0.110 g, 42.3%).

LCMS: 247 $[M+1]^+$

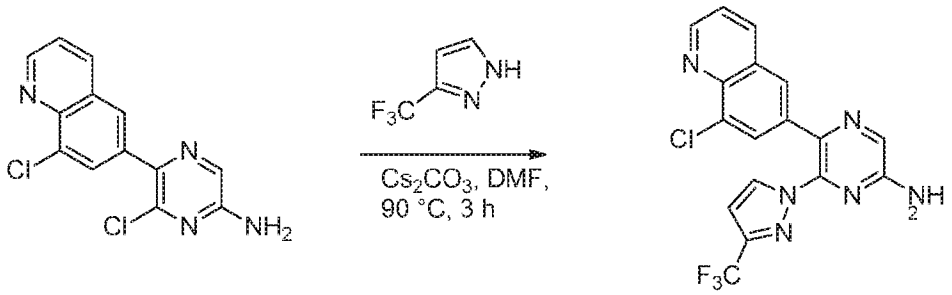
[0311] Step 4: 4-chloro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[d]thiazole: To the stirred solution of 6-bromo-4-chlorobenzo[d]thiazole (0.130g, 0.523mmol, 1 eq.) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (0.199g, 0.784mmol, 1.5 eq.) in 10 mL of dioxane was added potassium acetate (0.154g, 1.56 mmol, 3.0 eq.). The reaction mixture was purged with N_2 for about 5 min and $Pd(dppf)Cl_2$·DCM complex (0.021 g, 5 mol %) was added. Reaction mixture was re-purged with N_2 and heated at 100 °C for 16 h. Following this reaction mixture was allowed to cool to RT and filtered through celite bed and washed with ethyl acetate (200 mL).The obtained organic layer was concentrated under reduced pressure to get desired product which was used as such for next step without further purification.

LCMS: 296 $[M+1]^+$

[0312] Step 5 Synthesis of 5-(4-chlorobenzo[d]thiazol-6-yl)-6-(1-methyl-1H-pyrazol-3-yl)pyrazin-2-amine: To a stirred solution of 5-chloro-6-(1-methyl-1H-pyrazol-3-yl)pyrazin-2-amine (0.120 g, 0.572 mmol, 1.0 eq.) and 4-chloro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[d]thiazole (0.186 g, 0.629 mmol, 1.1 eq.) in dioxane (10 mL) was added Na_2CO_3 (0.121 g, 1.14 mmol, 2.0 eq.) and 2 mL water. Then reaction was purged with N_2 for about 5 min and $Pd(dppf)Cl_2$·DCM complex (0.0233 g, 5 mol %) was added. The reaction was re-purged again for another 5 min and was heated at 100 °C for 16 h. Following this, reaction mixture was allowed to cool to RT and extracted using ethyl acetate (3 × 50 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum to obtain the solid residue which was purified by reversed phase column chromatography to afford the desired product as pale yellow solid (0.020 g, 10%).

LCMS: 343 $[M+1]^+$. ^1H NMR: (400 MHz, DMSO-d_6) δ 9.43 (s, 1H), 8.08 (s, 1H), 7.93 (s, 1H), 7.64 (br. s., 1H), 7.47 (s, 1H), 6.70 (br. s., 2H), 6.21 (br. s., 1H), 3.71 (s, 3H).

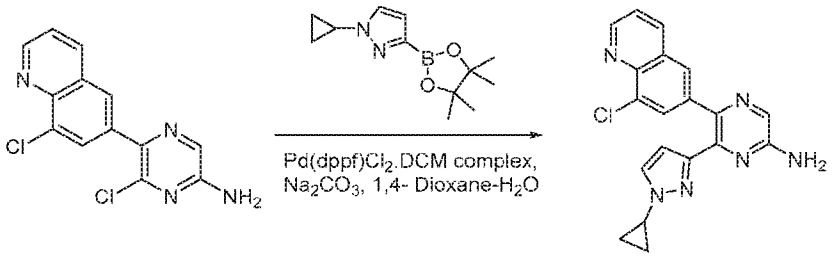
Example S69. Synthesis of 5-(8-chloroquinolin-6-yl)-6-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrazin-2-amine (Compound No1.306)



[0313] To a stirred solution of 3-(trifluoromethyl)-1H-pyrazole (0.154 g, 1.13 mmol, 2.2 eq.) in DMF (1mL) was added Cs_2CO_3 (0.504 g, 1.55 mmol, 3 eq.) and the mixture was stirred at RT for 30 min. To this mixture 6-chloro-5-(8-chloroquinolin-6-yl)pyrazin-2-amine (0.150, 0.52 mmol, 1.0 eq.) was added and the resultant mixture was heated at 90 °C for 3 h. The progress of the reaction was monitored by TLC. Upon completion, the mixture was diluted with water (40 mL), extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with water (40 mL), brine (40 mL), dried over Na_2SO_4, filtered & concentrated under reduced pressure to afford a crude residue which was purified by reversed phase chromatography to afford the desired product as an off-white solid (100 mg, 50 %).

LCMS : 391 $[M+1]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.91 (dd, J = 1.53, 4.17 Hz, 1H), 8.27 (dd, J = 1.75, 8.33 Hz, 1H), 8.15 - 8.21 (m, 2H), 7.68 (d, J = 1.75 Hz, 1H), 7.56 - 7.64 (m, 2H), 6.80 (d, J = 2.63 Hz, 1H).

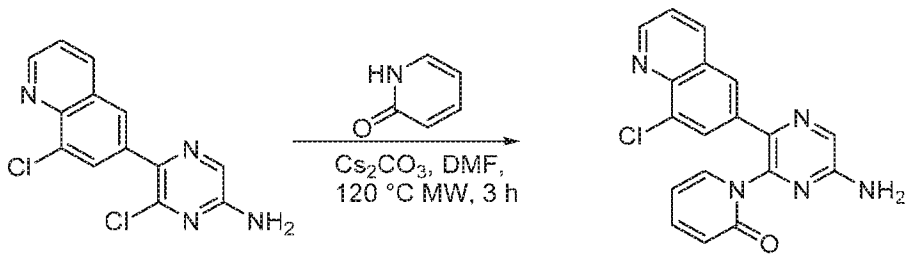
Example S70. Synthesis of 5-(8-chloroquinolin-6-yl)-6-(1-cyclopropyl-1H-pyrazol-3-yl)pyrazin-2-amine (Compound No. 1.307)



[0314] To a stirred solution of 6-chloro-5-(8-chloroquinolin-6-yl)pyrazin-2-amine (0.025 g, 0.086 mmol, 1.0 eq) in 1,4-Dioxane:Water (2:1, 1.5 mL) was added 1-cyclopropyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (0.030 g, 0.129 mmol, 1.5 eq), sodium carbonate (0.027 g, 0.258 mmol, 3.0 eq) at RT and the resulting mixture was degassed under nitrogen for 20 min. $Pd(dppf)Cl_2$.DCM complex (0.006 g, 0.0086 mmol, 0.1 eq) and then added to the mixture and the mixture was further degassed under nitrogen for 10 min. The resultant mixture was heated at 110 °C for 16 h. The progress of reaction was monitored by TLC. Upon completion, the reaction mixture was diluted with water (50 mL), extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with water (50 mL), brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford a crude residue which was purified by SFC to afford the desired product as an off- white solid (5 mg, 16%).

LCMS: 363 $[M+1]^+$. ^{1}H NMR: (400 MHz, MeOD) δ 8.92 (d, J = 2.63 Hz, 1H), 8.36 (d, J = 7.02 Hz, 1H), 8.02 (s, 1H), 7.92 (s, 1H), 7.76 (d, J = 1.75 Hz, 1H), 7.56 - 7.68 (m, 2H), 6.32 (d, J = 2.19 Hz, 1H), 3.56 (br. s., 1H), 0.78 - 0.93 (m, 4H).

Example S71. Synthesis of 1-(6-amino-3-(8-chloroquinolin-6-yl)pyrazin-2-yl)pyridin-2(1H)-one (Compound No. 1.308)

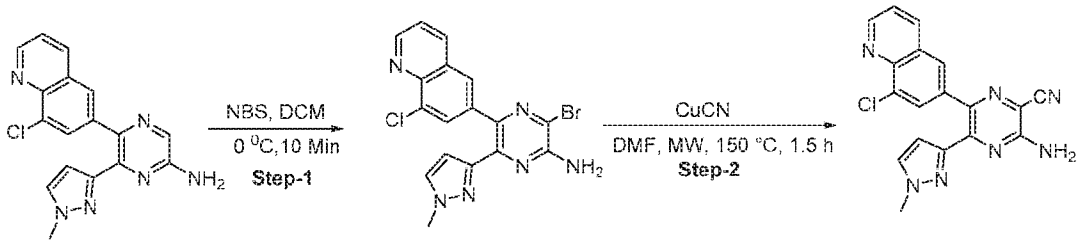


[0315] To a stirred solution of pyridin-2(1H)-one (0.122 g, 1.3 mmol, 2.2 eq.) in DMF (1 mL) was added Cs_2CO_3 (0.672 g, 2.06 mmol, 4 eq.) and the mixture was stirred at RT for 15 min. To

this mixture 6-chloro-5-(8-chloroquinolin-6-yl)pyrazin-2-amine (0.150, 0.517 mmol, 1.0 eq.) was added and the resultant mixture was irradiated under MW irradiation at 120 °C for 3 h. The progress of reaction was monitored by TLC. Upon completion, the mixture was diluted with water (40 mL), extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with water (40 mL), brine (40 mL), dried over Na_2SO_4, filtered & concentrated under reduced pressure to afford a crude residue which was purified by reversed phase chromatography to afford the desired product as an off-white solid (17 mg, 9 %).

LCMS: 350 $[M+1]^+$. ^1H NMR: (400 MHz, DMSO-d_6) δ 8.90 (dd, J = 1.53, 4.17 Hz, 1H), 8.55 (d, J = 1.75 Hz, 1H), 8.48 (d, J = 1.75 Hz, 1H), 8.41 (dd, J = 1.75, 8.33 Hz, 1H), 8.25 (d, J = 3.51 Hz, 1H), 7.88 - 7.92 (m, 2H), 7.60 (dd, J = 4.39, 8.33 Hz, 1H), 7.19 - 7.28 (m, 2H).

Example S72. Synthesis of 3-amino-6-(8-chloroquinolin-6-yl)-5-(1-methyl-1H-pyrazol-3-yl)pyrazine-2-carbonitrile (Compound No. 1.309)



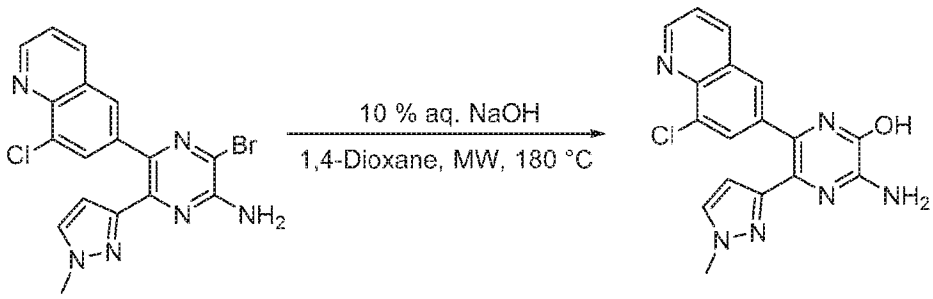
[0316] Step-1: Synthesis of 3-bromo-5-(8-chloroquinolin-6-yl)-6-(1-methyl-1H-pyrazol-3-yl)pyrazin-2-amine: To a stirred solution of 5-(8-chloroquinolin-6-yl)-6-(1-methyl-1H-pyrazol-3-yl)pyrazin-2-amine (0.350 g, 1.04 mmol, 1.0 eq.) in DCM (20 mL) was added *N*-Bromosuccinimide (0.194 g,1.09 mmol,1.05 eq.) portion wise at 0 °C and the mixture was allowed to stir at the same temperature for 10 min. The progress of reaction was monitored by TLC. Upon completion, the reaction mixture was diluted with water (15 mL), extracted with DCM (2 × 50 mL). The combined organic layers were washed with water (15 mL), brine (15 mL), dried over Na_2SO_4, filtered & concentrated under reduced pressure to afford the desired product as an off brown solid(0.400 g, 83 %).

LCMS: 415 $[M+1]^+$.

[0317] Step-2: Synthesis of 3-amino-6-(8-chloroquinolin-6-yl)-5-(1-methyl-1H-pyrazol-3-yl)pyrazine-2-carbonitrile: To ethyl 4-(2-(2-methoxyethyl)hydrazinyl)-2-(methylthio)pyrimidine-5-carboxylate (0.200 g, 0.48 mmol, 1 eq.) in DMF (4 mL) was added copper cyanide (0.129 g,1.44 mmol, 3 eq.) at RT and the resultant mixture was irradiated under MW irradiation at 150 °C for 90 min. The progress of reaction was monitored by TLC .Upon completion, ice cold water (15 mL) was added to the mixture to obtain a precipitate which was filtered over Büchner funnel to afford crude residue. The crude obtained was purified by reversed phase chromatography to afford the desired product as an off-white solid (0.005 g, 2.8 %).

LCMS: 362 $[M+H]^+$. ^{1}H NMR: (400 MHz, DMSO-d_6) δ 8.95 (br. s., 1H), 8.39 (d, J = 7.45 Hz, 1H), 7.99 (br. s., 1H), 7.87 (br. s., 1H), 7.63 (d, J = 4.38 Hz, 1H), 7.55 (br. s., 1H), 6.37 (br. s., 1H), 3.78 (br. s., 3H).

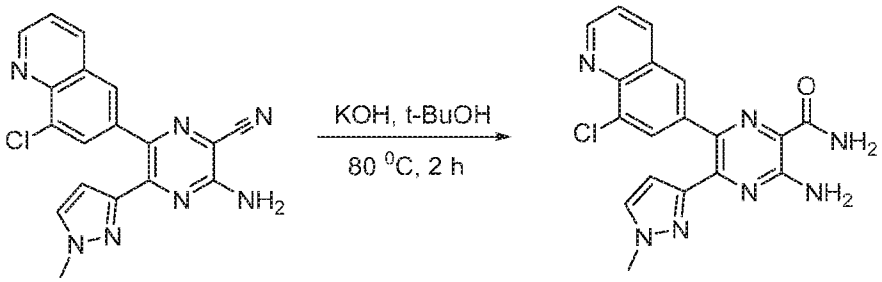
Example S73. Synthesis of 3-amino-6-(8-chloroquinolin-6-yl)-5-(1-methyl-1H-pyrazol-3-yl)pyrazin-2-ol (Compound No. 1.310)



[0318] To ethyl 4-(2-(2-methoxyethyl)hydrazinyl)-2-(methylthio)pyrimidine-5-carboxylate (0.070 g, 0.17 mmol, 1 eq) in 1,.4-Dioxane (1.2 mL) was added 10 % aq. NaOH solution (1.2 mL) and the mixture was irradiated under MW irradiation at 180 °C for 40 min. The progress of reaction was monitored by TLC. Upon completion, the mixture was concentrated under reduced pressure. To the residue obtained was added ice cold water (15 ml) to obtain a precipitate which was filtered over Büchner funnel to obtain a crude which was purified by reversed phase chromatography to afford desired product as an off-white solid (0.010 g, 17 %).

LCMS: 353 $[M+H]^+$. ^1H NMR: (400 MHz, DMSO-d_6) δ 8.96 (d, J = 3.51 Hz, 1H), 8.40 (d, J = 8.77 Hz, 1H), 7.92 (s, 1H), 7.74 (s, 1H), 7.64 (dd, J = 4.38, 8.33 Hz, 1H), 7.41 (s, 1H), 5.91 (d, J = 2.19 Hz, 1H), 3.78 (s, 3H).

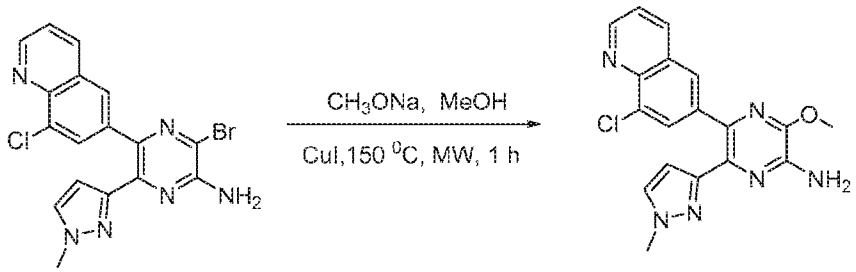
Example S74. Synthesis of 3-amino-6-(8-chloroquinolin-6-yl)-5-(1-methyl-1H-pyrazol-3-yl)pyrazine-2-carboxamide (Compound No. 1.311)



[0319] To a stirred solution of 3-amino-6-(8-chloroquinolin-6-yl)-5-(1-methyl-1H-pyrazol-3-yl)pyrazine-2-carbonitrile (0.120 g, 0.33 mmol, 1 eq) in *t*-BuOH (6 mL) was added potassium hydroxide (0.055 g, 0.99 mmol, 3 eq) and the mixture was heated at 80 °C for 2 h. The progress of reaction was monitored by TLC. Upon completion, the mixture was concentrated under reduced pressure. To the residue obtained was added ice cold water (15 mL) to obtain a precipitate which was filtered over Büchner funnel to obtain a crude which was purified by reversed phase chromatography to afford 3-amino-6-(8-chloroquinolin-6-yl)-5-(1-methyl-1H-pyrazol-3-yl)pyrazine-2-carboxamide (0.004 g, 3 %) as an off yellow solid.

LCMS: 380 $[M+H]^+$, ^1H NMR: (400 MHz, DMSO-d_6) δ 8.94 (d, J = 3.95 Hz, 1H), 8.40 (d, J = 8.33 Hz, 1H), 8.06 (s, 1H), 7.94 (s, 1H), 7.63 (d, J = 3.95 Hz, 1H), 7.56 (br. s., 1H), 6.32 (br. s., 1H), 3.81 (s, 3H).

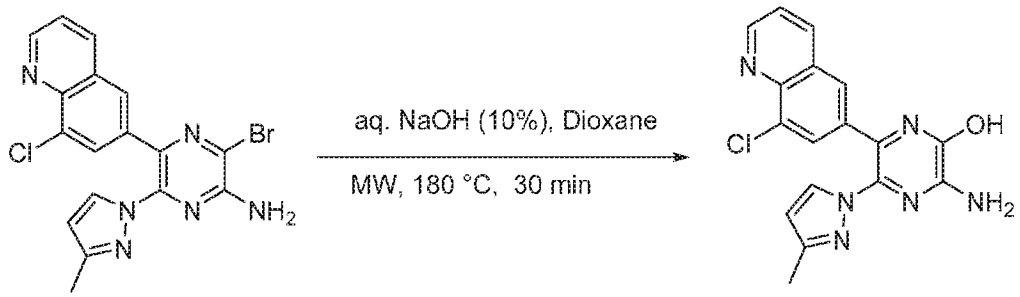
Example S75. Synthesis of 5-(8-chloroquinolin-6-yl)-3-methoxy-6-(1-methyl-1H-pyrazol-3-yl)pyrazin-2-amine (Compound No. 1.312)



[0320] To ethyl 4-(2-(2-methoxyethyl)hydrazinyl)-2-(methylthio)pyrimidine-5-carboxylate (0.15 g, 0.361 mmol, 1 eq) in methanol (4 mL) were successively added sodium methoxide (0.097 g, 1.80 mmol, 5 eq) and CuI (0.034 g,0.18 mmol,0.5 eq) at RT and the mixture was irradiated under MW irradiation at 150 °C for 60 min. The progress of reaction was monitored by TLC. Upon completion, the mixture was concentrated under reduced pressure. To the residue obtained was added ice cold water (15 mL) to obtain a precipitate which was filtered over Büchner funnel to obtain a crude which was purified by reversed phase chromatography to afford 5-(8-chloroquinolin-6-yl)-3-methoxy-6-(1-methyl-1H-pyrazol-3-yl)pyrazin-2-amine (0.009 g, 6.81 %) as an off- white solid.

LCMS: 367 $[M+H]^+$, ^{1}H NMR: (400 MHz, DMSO-d_6) δ 8.90 (br. s., 1H), 8.32 (d, J = 7.02 Hz, 1H), 7.95 (br. s., 1H), 7.90 (br. s., 1H), 7.52 - 7.62 (m, 2H), 6.10 (br. s., 1H), 4.13 (s, 3H), 3.84 (br. s., 3H).

Example S76. Synthesis of 3-amino-6-(8-chloroquinolin-6-yl)-5-(3-methyl-1H-pyrazol-1-yl)pyrazin-2-ol (Compound No. 1.313)

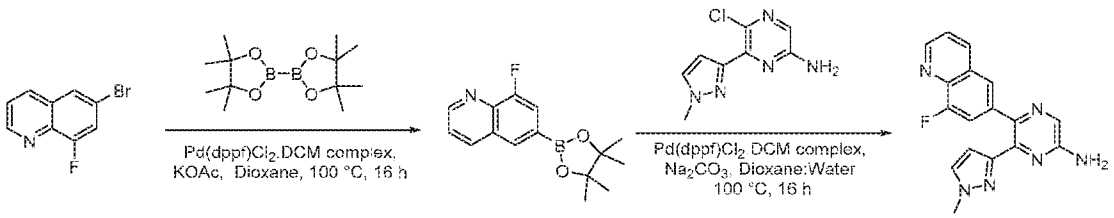


[0321] To a stirred solution of 3-bromo-5-(8-chloroquinolin-6-yl)-6-(3-methyl-1H-pyrazol-1-yl)pyrazin-2-amine (0.05 g, 0.12 mmol, 1.0 eq.) in dioxane (1 mL) was added aqueous NaOH solution (1 mL, 2.5 mmol, 20.0 eq.). Following this reaction mixture was microwave irradiated

for 30 min at 180 °C. The reaction was monitored by TLC and LCMS. After completion of reaction, reaction mixture was concentrated under reduced pressure to get desired product as solid residue which was purified by reversed phase column chromatography to get the desired product as off white solid (0.005 g, 12%).

LCMS: 353 $[M+1]^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.22 (br. s., 1H), 8.97 (d, J = 2.63 Hz, 1H), 8.31 (d, J = 7.45 Hz, 1H), 7.77 (br. s., 1H), 7.62 (dd, J = 4.17, 8.11 Hz, 1H), 7.55 (s, 1H), 7.33 (s, 1H), 7.10 (br. s., 2H), 6.09 (s, 1H), 2.12 (s, 3H)

Example S77. Synthesis of 5-(8-fluoroquinolin-6-yl)-6-(1-methyl-1H-pyrazol-3-yl)pyrazin-2-amine (Compound No. 1.314)



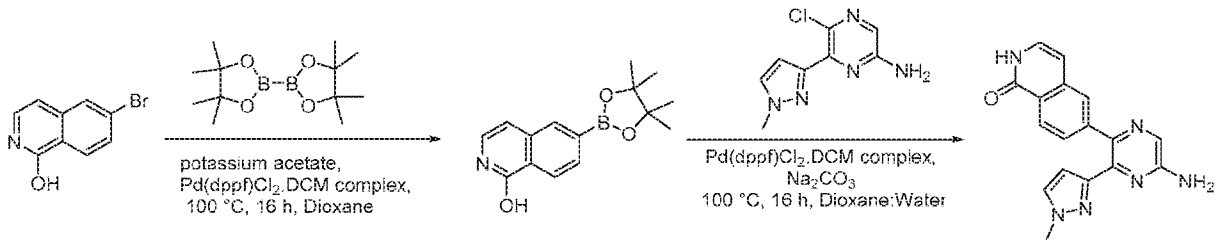
[0322] Step 1: Synthesis of 8-fluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline: To the stirred solution of 6-bromo-8-fluoroquinoline (0.2g, 0.88mmol, 1 eq.) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (0.336g, 1.327 mmol, 1.5 eq.) in 10 mL of dioxane was added potassium acetate (0.260g, 2.65 mmol, 3.0 eq.). The reaction mixture was purged with N_2 for about 5 min and $Pd(dppf)Cl_2$ DCM complex (0.036 g, 5 mol %) was added. Reaction mixture was re-purged with N_2 and heated at 100 °C for 16 h. Following this reaction mixture was allowed to cool to RT and filtered through celite bed and washed with ethyl acetate (200 mL). The organic layer was concentrated under reduced pressure to get desired product which was used as such for next step without further purification.
LCMS: 274 $[M+1]^+$

[0323] Step 2: Synthesis of 5-(8-fluoroquinolin-6-yl)-6-(1-methyl-1H-pyrazol-3-yl)pyrazin-2-amine: To a stirred solution of 5-chloro-6-(1-methyl-1H-pyrazol-3-yl)pyrazin-2-amine (0.120 g, 0.572 mmol, 1.0 eq.) and 8-fluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline (0.187 g, 0.686 mmol, 1.2 eq.) in dioxane (10 mL) was added Na_2CO_3 (0.121 g, 1.144 mmol, 2.0 eq.) and 2 mL water. The reaction was purged with N_2 for about 5 min and $Pd(dppf)Cl_2$·DCM complex (0.023 g, 5 mol %) was added. Reaction was purged with N_2 for another 5 min and was

heated at 100 °C for 16 h. Following this, reaction mixture was allowed to cool to RT and extracted using ethyl acetate (3 × 50 mL). The combined organic layers were washed (brine), dried (anhydrous Na_2SO_4) and concentrated under vacuum to get the solid residue which was purified by reversed phase column chromatography to get the desired product as off white solid (0.003 g, 1 %).

LCMS: 321 $[M+1]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.90 (dd, J = 1.53, 4.17 Hz, 1H), 8.38 (d, J = 8.33 Hz, 1H), 7.97 (s, 1H), 7.84 (s, 1H), 7.65 (d, J = 1.75 Hz, 1H), 7.60 (dd, J = 4.17, 8.55 Hz, 1H), 7.36 (dd, J = 1.53, 12.50 Hz, 1H), 6.76 (br. s., 2H), 6.22 (d, J = 2.19 Hz, 1H), 3.72 (s, 3H).

Example S78. Synthesis of 6-(5-amino-3-(1-methyl-1H-pyrazol-3-yl)pyrazin-2-yl)isoquinolin-1-ol (Compound No. 1.315)



[0324] Step 1: synthesis of 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoquinolin-1-ol: To the stirred solution of 6-bromoisoquinolin-1-ol (0.2g, 0.89mmol, 1 eq.) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (0.339g, 1.33 mmol, 1.5 eq.) in 10 mL of dioxane was added potassium acetate(0.26g, 2.67 mmol, 3.0 eq.). The reaction mixture was purged with N_2 for about 5 min and $Pd(dppf)Cl_2$·DCM complex (0.036 g, 5 mol %) was added. Reaction mixture was re-purged with N_2 and heated at 100 °C for 16 h. Following this reaction mixture was allowed to cool to RT and filtered through celite bed and washed with ethyl acetate (200 mL). The obtained organic layer was concentrated under reduced pressure to get desired product which was used as such for next step without further purification.

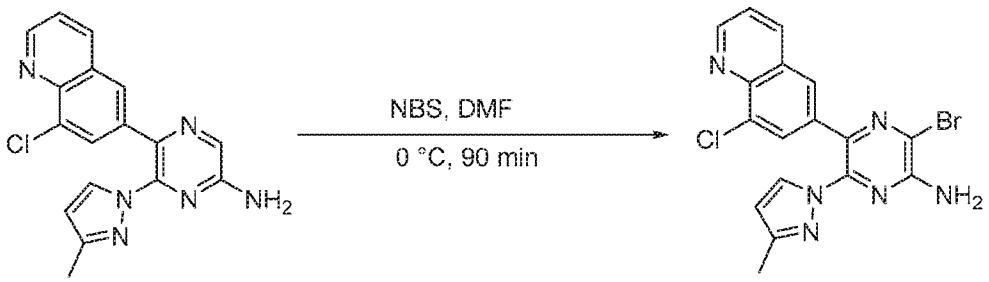
LCMS: 272 $[M+1]^+$,

[0325] Step 2: Synthesis of 6-(5-amino-3-(1-methyl-1H-pyrazol-3-yl)pyrazin-2-yl)isoquinolin-1-ol: To a stirred solution of 5-chloro-6-(1-methyl-1H-pyrazol-3-yl)pyrazin-2-amine (0.120 g, 0.572 mmol, 1.0 eq.) and 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoquinolin-1-ol (0.186

g, 0.686 mmol, 1.2 eq.) in dioxane (10 mL) was added Na_2CO_3 (0.121 g, 1.144 mmol, 2.0 eq.) and 2 mL water. The reaction was purged with N_2 for about 5 min and $Pd(dppf)Cl_2$·DCM complex (0.023 g, 5 mol %) was added. Reaction was purged with N_2 for another 5 min and was heated at 100 °C for 16 h. Following this, reaction mixture was allowed to cool to RT and extracted using ethyl acetate (3 × 50 mL). The combined organic layers were washed (brine), dried (anhydrous Na_2SO_4) and concentrated under vacuum to get the solid residue which was purified by reversed phase column chromatography to get the desired product as off white solid (0.002 g, 1%).

LCMS: 319 $[M+1]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 11.16 (br. s., 1H), 7.99 (d, J = 7.89 Hz, 1H), 7.93 (s, 1H), 7.64 (s, 1H), 7.60 (d, J = 2.19 Hz, 1H), 7.29 (d, J = 9.65 Hz, 1H), 7.11 (br. s., 1H), 6.68 (br. s., 2H), 6.48 (d, J = 7.45 Hz, 1H), 6.11 (d, J = 1.75 Hz, 1H), 3.72 (s, 3H).

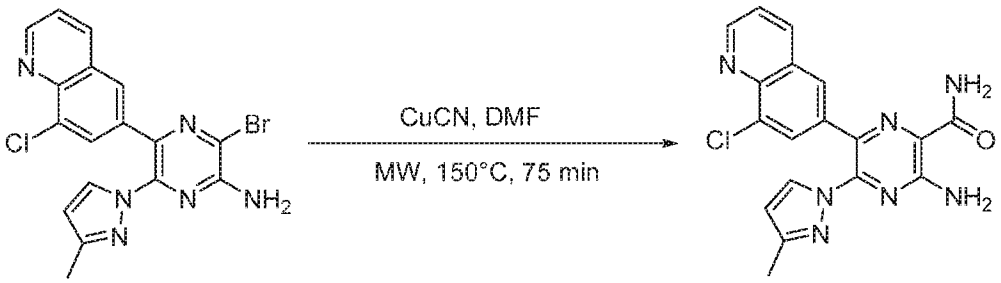
Example S79. Synthesis of 3-bromo-5-(8-chloroquinolin-6-yl)-6-(3-methyl-1H-pyrazol-1-yl)pyrazin-2-amine (Compound No. 1.316)



[0326] To a solution of 5-(8-chloroquinolin-6-yl)-6-(3-methyl-1H-pyrazol-1-yl)pyrazin-2-amine (0.38 g, 1.13 mmol, 1 eq.) in DMF (15 mL) was added N-bromosuccinimide (0.20 g, 1.13 mmol, 1 eq.) and the reaction mixture was stirred at 0 °C for 90 min. The reaction was monitored by TLC and LCMS. After completion of the reaction, ice was poured into reaction mixture to afford the precipitate which weas filtered and washed with water (100 mL). Further purification was done using normal phase column chromatography to afford desired product as off white solid (0.006 g, 1%).

LCMS: 415 $[M+1]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.98 (dd, J = 1.53, 4.17 Hz, 1H), 8.42 (d, J = 7.02 Hz, 1H), 7.95 (d, J = 2.19 Hz, 1H), 7.85 (d, J = 1.75 Hz, 1H), 7.63 (dd, J = 4.39, 8.33 Hz, 1H), 7.39 (br. s., 2H), 7.34 (d, J = 1.75 Hz, 1H), 6.33 (d, J = 2.19 Hz, 1H), 2.08 (s, 3H).

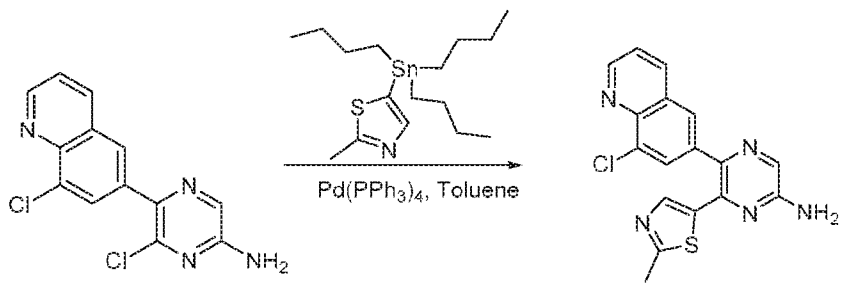
Example S80. Synthesis of 3-amino-6-(8-chloroquinolin-6-yl)-5-(3-methyl-1H-pyrazol-1-yl)pyrazine-2-carboxamide (Compound No. 1.317)



[0327] To a solution of 3-bromo-5-(8-chloroquinolin-6-yl)-6-(3-methyl-1H-pyrazol-1-yl)pyrazin-2-amine (0.42 g, 1.01 mmol, 1 eq.) in DMF (7 mL) was added copper cyanide (0.27 g, 3.03 mmol, 3 eq.). Following this reaction mixture was microwave irradiated for 75 min at 150 °C. Following this, reaction was allowed to cool to RT, and was diluted with water (5 mL) and extracted using ethyl acetate (3 x 30 mL) The combined organic layers were washed (brine), dried (anhydrous Na_2SO_4) and concentrated under vacuum to get solid residue which was purified by normal phase column chromatography to afford desired product as off white solid (0.003 g, 1%).

LCMS: 380 $[M+1]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.98 (d, J = 2.63 Hz, 1H), 8.30 - 8.35 (m, 2H), 8.07 (dd, J = 2.19, 6.58 Hz, 2H), 7.80 (br. s., 1H), 7.61 - 7.65 (m, 2H), 6.37 (d, J = 2.63 Hz, 1H), 2.05 (s, 3H).

Example S81. Synthesis of 5-(8-chloroquinolin-6-yl)-6-(2-methylthiazol-5-yl)pyrazin-2-amine (Compound No. 1.318)

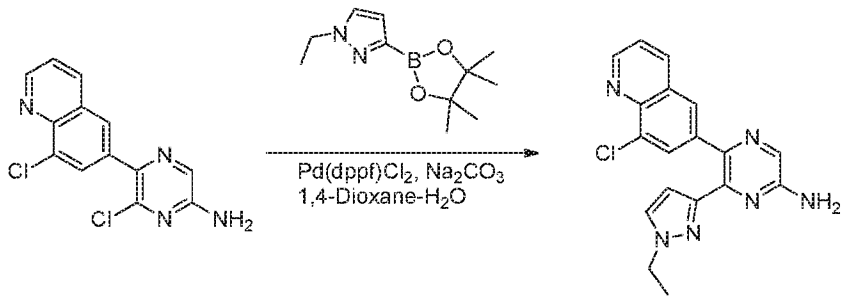


[0328] To a stirred solution of 6-chloro-5-(8-chloroquinolin-6-yl)pyrazin-2-amine (0.450 g, 1.55 mmol, 1.0 eq) in toluene (5 mL) was added 2-methyl-5-(tributylstannyl)thiazole (1.32 g, 3.41

mmol, 2.2 eq) at RT & the resulting mixture was degassed under nitrogen for 20 min. $Pd(PPh_3)_4$ (0.179 g, 0.55 mmol,0.1 eq.) and then added to the mixture and the mixture was further degassed under nitrogen for 10 min. The resultant mixture was heated at 110 °C for 16 h. The progress of reaction was monitored by TLC. Upon completion, the reaction mixture was diluted with water (200 mL), extracted with EtOAc (2 × 200 mL). The combined organic layers were washed with water (200 mL), brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford a crude residue which was purified by silica gel column chromatography (20 % KF / silica mixture) compound eluting at 3 % MeOH / DCM to obtain 0.350 g of the desired product (~ 90 % pure). 70 mg of the product obtained was further purified by SFC to afford the desired product as an off- white solid (0.021 g, 25 %).

LCMS: 354 $[M+H]^+$ ^{1}H NMR: (400 MHz, MeOD) δ 8.99 (d, *J* = 2.63 Hz, 1H), 8.42 (d, *J* = 8.33 Hz, 1H), 8.03 (d, *J* = 1.75 Hz, 1H), 7.97 (d, *J* = 1.75 Hz, 1H), 7.94 (s, 1H), 7.66 (dd, *J* = 3.95, 8.33 Hz, 1H), 7.26 (s, 1H), 2.61 (s, 3H).

Example S82. Synthesis of 5-(8-chloroquinolin-6-yl)-6-(1-ethyl-1H-pyrazol-3-yl)pyrazin-2-amine (Compound No. 1.319)

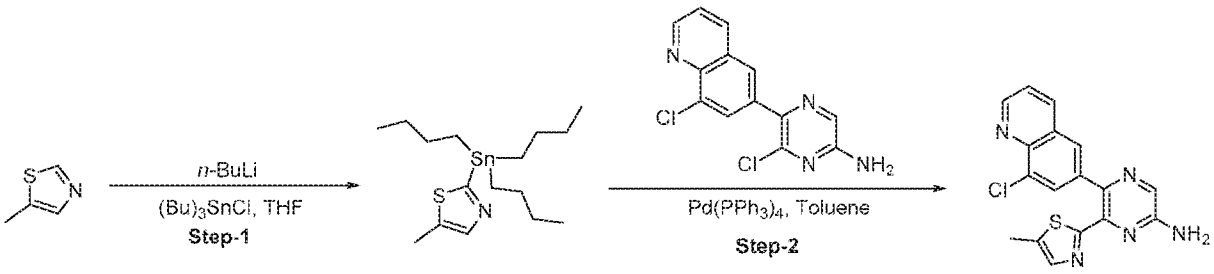


[0329] To a stirred solution of 6-chloro-5-(8-chloroquinolin-6-yl)pyrazin-2-amine (0.05 g, 0.172 mmol, 1.0 eq.) in 1,4-Dioxane:Water (4:1, 5 mL) was added 1-ethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (0.057 g, 0.258 mmol, 1.5 eq.), sodium carbonate (0.055 g, 0.517 mmol, 3.0 eq.) at RT and the resulting mixture was degassed under nitrogen for 20 min. $Pd(dppf)Cl_2$.DCM complex (0.013 g, 1.102 mmol, 0.017 eq.) and then added to the mixture and the mixture was further degassed under nitrogen for 10 min. The resultant mixture was heated at 110 °C for 16 h. The progress of reaction was monitored by TLC. Upon completion, the reaction mixture was diluted with water (50 mL), extracted with EtOAc (2 × 100 mL). The combined

organic layers were washed with water (50 mL), brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford a crude residue which was purified by SFC to afford the desired product (0.005 g, 8%) as an off- white solid.

LCMS: 351 $[M+1]^+$. ^{1}H NMR: (400 MHz, MeOD) δ 8.91 (d, J = 2.63 Hz, 1H), 8.34 (s, 1H), 8.03 (s, 1H), 7.93 (s, 1H), 7.80 (s, 1H), 7.54 - 7.65 (m, 2H), 6.30 (d, J = 1.75 Hz, 1H), 4.07 (d, J = 7.02 Hz, 2H), 1.26 (t, J = 7.45 Hz, 3H).

Example S83. Synthesis of 5-(8-chloroquinolin-6-yl)-6-(5-methylthiazol-2-yl)pyrazin-2-amine. (Compound 1.395)



[0330] Step-1: Synthesis of 5-(8-chloroquinolin-6-yl)-6-(5-methylthiazol-2-yl)pyrazin-2-amine: To a stirred solution of 5-methylthiazole (1.0 g, 10.0 mmol, 1.0 eq) in THF (10 mL) was added *n*-BuLi (7.0 mL, 11.0 mmol, 1.1 eq) at -78 °C and the mixture was stirred at -78 °C for 30 min. *tri*-Butyl tin chloride (4.0 ml, 12.0 mmol, and 1.2 eq) was then added to the mixture at -78°C and the resultant mixture was stirred at RT for 2 h. The progress of reaction was monitored by ^{1}H NMR. Upon completion, the reaction mixture was quenched with saturated ammonium chloride solution (100 mL), extracted with EtOAc (200 mL × 2). The combined organic layers were washed with water (200 mL), brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford 5-methyl-2-(tributylstannyl)thiazole (1.5 g, 38 %) as an viscous liquid which was taken to next step without further purification.

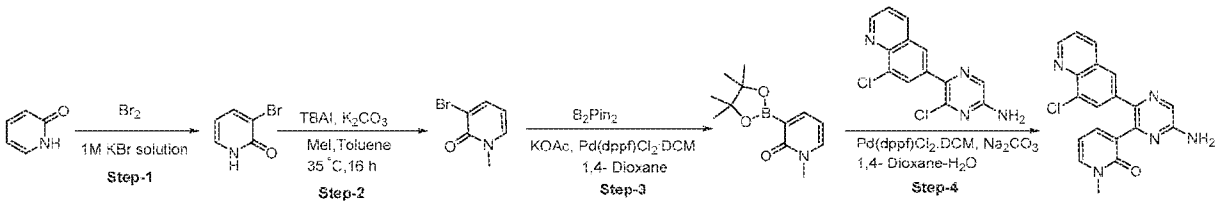
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (s, 1H), 2.49 (s, 3H), 1.48 - 1.64 (m, 9H), 1.25 - 1.37 (m, 12H), 1.10 - 1.21 (m, 6H).

[0331] Step-2: Synthesis of 5-(8-chloroquinolin-6-yl)-6-(5-methylthiazol-2-yl)pyrazin-2-amine: To a stirred solution of 6-chloro-5-(8-chloroquinolin-6-yl)pyrazin-2-amine (0.100 g, 0.34 mmol,

1.0 eq) in toluene (5 mL) was added 5-methyl-2-(tributylstannyl)thiazole (0.300 g, 0.75 mmol, 2.2 eq) at RT and the resulting mixture was degassed under nitrogen for 20 min. To this reaction mixture $Pd(PPh_3)_4$ (0.040 g, 0.034 mmol, 0.1 eq) was added and the mixture was further degassed under nitrogen for 10 min. The resultant mixture was heated at 110 °C for 16 h. The progress of reaction was monitored by TLC. Upon completion, the reaction mixture was diluted with water (60 mL), extracted with EtOAc (150 mL × 2). The combined organic layers were washed with water (50 mL), brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford a crude residue which was purified by reversed phase chromatography to afford 5-(8-chloroquinolin-6-yl)-6-(5-methylthiazol-2-yl)pyrazin-2-amine (8.5 mg, 7 %) as an off- white solid.

LCMS: 354 $[M+H]^+$. **^{1}H NMR** (400 MHz, MeOD) δ 8.93 (d, *J* = 3.07 Hz, 1H), 8.38 (d, *J* = 8.77 Hz, 1H), 8.04 (s, 1H), 7.96 (s, 1H), 7.91 (d, *J* = 1.75 Hz, 1H), 7.62 (dd, *J* = 4.17, 8.55 Hz, 1H), 7.30 (s, 1H), 2.49 (s, 3H).

Example S84. Synthesis of 3-(6-amino-3-(8-chloroquinolin-6-yl)pyrazin-2-yl)-1-methylpyridin-2(1H)-one (Compound No. 1.329)



[0332] Step-1: Synthesis of 3-bromopyridin-2(1H)-one: To a stirred solution of pyridin-2(1*H*)-one (1.0 g, 10 mmol, 1.0 eq.) in 1M aq. KBr solution (10 mL) was added bromine (0.840 g, 10 mmol,1 eq), 1M aq KBr (20 ml) at 0 °C dropwise and the mixture was stirred at RT for 16 h. The progress of reaction was monitored by TLC. Upon completion, the reaction mixture was diluted with water (100 mL), extracted with EtOAc (300 mL × 2). The combined organic layers were washed with water (50 mL), brine (50 mL), dried over Na_2SO_4, filtered & concentrated under reduced pressure to afford a crude residue which was purified by column chromatography (Eluent- 10 % MeOH / DCM) to afford 3-bromopyridin-2(1*H*)-one (0.700 g, 38%) as an off white solid.

LCMS: 174 $[M+H]^+$

[0333] Step-2: Synthesis of 3-bromo-1-methylpyridin-2(1*H*)-one**:** To a stirred solution of 3-bromopyridin-2(1*H*)-one (0.700 g, 7.36 mmol, 1.0 eq) in toluene (10 mL) were successively added potassium carbonate (2.5 g, 36.8 mmol, 2.5eq) and TBAI (0.272 g, 0.736 mmol, 0.05 eq) at RT and the mixture was stirred at RT for 15 min. Methyl iodide (2.50 mL, 73.60 mmol, 5.5 eq) was then added to the mixture and the resultant mixture was heated at 70 °C for 16 h. The progress of reaction was monitored by TLC. Upon completion, the mixture was diluted with water (80 mL) and extracted with EtOAc (200 mL × 2). The combined organic layers were washed with water (50 mL), brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford a crude residue which was purified by column chromatography over silica gel (elutent- 5 % MeOH / DCM) to afford 3-bromo-1-methylpyridin-2(1*H*)-one (0.300 g, 39.68 %) as a white solid.

LCMS 188 $[M+H]^+$

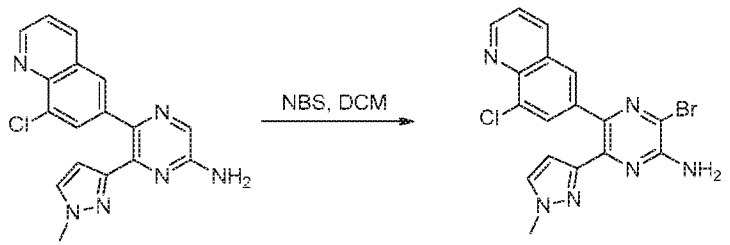
[0334] Step-3: Synthesis of 1-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1H)-one: To a stirred solution of 3-bromo-1-methylpyridin-2(1*H*)-one (0.300 g, 1.59 mmol, 1.0 eq) in 1, 4-Dioxane (150 mL) was added bis(pinacolato)diboron (0.670 g, 2.39 mmol, 1.5 eq), potassium acetate (0.470 g, 4.78 mmol, 3.0 eq) at RT and the resulting mixture was degassed under nitrogen for 30 min, Pd(dppf)Cl_2.DCM complex (0.065 g,0.079 mmole,0.05eq) was then added to the mixture and the mixture was further degassed under nitrogen for 15 min. The resultant mixture was then heated at 110 °C for 16 h. The progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was diluted with water (50 mL), extracted with EtOAc (250 mL × 2). The combined organic layers were washed with water (40 mL), brine (40 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford a crude residue which was purified by silica gel chromatography (Eluent- 30 % EtOAc/ Hexane) to afford 1-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1H)-one (0.250 g, 66 %) as a light brown viscous solid.

^{1}H NMR(400 MHz, CDCl3) δ 7.85 (s, 1H), 7.37 (dd, *J* = 2.41, 6.80 Hz, 1H), 6.13 (t, *J* = 6.58 Hz, 1H), 3.51 (s, 3H), 1.28 - 1.35 (m, 12H).

[0335] Step-4: Synthesis of 3-(6-amino-3-(8-chloroquinolin-6-yl)pyrazin-2-yl)-1-methylpyridin-2(1*H*)-one: To a stirred solution of 6-chloro-5-(8-chloroquinolin-6-yl)pyrazin-2-amine (0.050 g, 0.17 mmol, 1.0 eq) in 1,4-Dioxane-water (4:1, 6 mL) was added 1-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1H)-one (0.060 g, 0.25 mmol, 1.1 eq), sodium carbonate (0.054 g, 0.51 mmol, 3.0 eq) at RT and the resulting mixture was degassed under nitrogen for 30 min. $Pd(dppf)Cl_2$ .DCM (0.012 g,0.017 mmole,0.1 eq) was then added to the mixture and the mixture was further degassed under nitrogen for 15 min. The resultant mixture was heated at 110 °C for 16 h. The progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was diluted with water (25 mL), extracted with EtOAc (100 mL × 2). The combined organic layers were washed with water (25mL), brine (25 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford a crude residue which was purified by reversed phase column chromatography to afford 3-(6-amino-3-(8-chloroquinolin-6-yl)pyrazin-2-yl)-1-methylpyridin-2(1*H*)-one (6.6 mg, 10.6 %) as a white solid.

LCMS: 364 $[M+H]^+$. **^{1}H NMR** (400 MHz, MeOD) δ 8.89 (d, *J* = 3.07 Hz, 1H), 8.27 (d, *J* = 6.58 Hz, 1H), 8.07 (s, 1H), 8.00 (s, 1H), 7.85 (d, *J* = 1.75 Hz, 1H), 7.70 (d, *J* = 6.58 Hz, 1H), 7.51 - 7.61 (m, 2H), 6.44 (t, *J* = 6.80 Hz, 1H), 3.39 (s, 3H).

Example S85. Synthesis of 3-bromo-5-(8-chloroquinolin-6-yl)-6-(1-methyl-1H-pyrazol-3-yl)pyrazin-2-amine. (Compound No. 1.324)

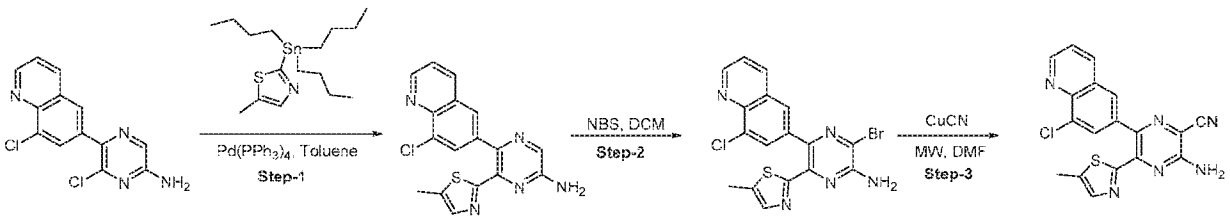


[0336] To a stirred solution of ethyl 4-(2-(tert-butoxycarbonyl)-2-(2-methoxyethyl)hydrazinyl)-2-(methylthio)pyrimidine-5-carboxylate (0.350 g, 1.041 mmol, 1.0 eq.) in 20 mL of DCM was successively added *N*-bromosuccinamide (0.194 g,1.093mmole,1.05 eq.) portion-wise at 0 °C and allowed to stir at same temperature for 10 min. The progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was diluted with water (15 mL), extracted with DCM (2×50 mL). The combined organic layers were washed with water (15 mL), with brine (15

mL), dried over Na_2SO_4, concentrated under reduced pressure afford ethyl 4-(2-(2-methoxyethyl)hydrazinyl)-2-(methylthio)pyrimidine-5-carboxylate (0.400 g, 82.99 %) as off brown solid.

LCMS 415 $[M+H]^+$. **^{1}H NMR** (400 MHz, MeOD) δ 8.92 (d, J = 2.63 Hz, 1H), 8.35 (d, J = 8.33 Hz, 1H), 7.95 (s, 1H), 7.84 (s, 1H), 7.61 (d, J = 4.38 Hz, 1H), 7.54 (s, 1H), 6.24 (d, J = 2.19 Hz, 1H), 3.82 (s, 3H).

Example S86. Synthesis of 3-amino-6-(8-chloroquinolin-6-yl)-5-(2-methylthiazol-5-yl)pyrazine-2-carbonitrile (Compound No. 1.402)



[0337] Step-1: Synthesis of 5-(8-chloroquinolin-6-yl)-6-(2-methylthiazol-5-yl)pyrazin-2-amine: To a stirred solution of 6-chloro-5-(8-chloroquinolin-6-yl)pyrazin-2-amine (0.450 g, 1.55 mmol, 1.0 eq) in toluene (5 mL) was added 5-methyl-2-(tributylstannyl)thiazole (1.32 g, 3.41 mmol, 2.2 eq) at RT and the mixture was degassed under nitrogen for 20 min. To this mixture $Pd(PPh_3)_4$ (0.179 g, 0.55 mmol,0.1 eq) was added and the mixture was further degassed under nitrogen for 10 min. The resultant mixture was heated at 110 °C for 16 h. The progress of reaction was monitored by TLC. Upon completion, the reaction mixture was diluted with water (200 mL), extracted with EtOAc (200 mL ×2). The combined organic layers were washed with water (200 mL), brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford a crude residue which was purified by silica gel column chromatography (20 % KF / silica mixture) (Eluent- 3 % MeOH / DCM) to obtain 5-(8-chloroquinolin-6-yl)-6-(2-methylthiazol-5-yl)pyrazin-2-amine (0.350 g, light brown solid, ~ 90 % pure).

LCMS 354 $[M+H]^+$

[0338] Step-2: Synthesis of 3-bromo-5-(8-chloroquinolin-6-yl)-6-(5-methylthiazol-2-yl)pyrazin-2-amine: To a stirred solution of 5-(8-chloroquinolin-6-yl)-6-(2-methylthiazol-5-yl)pyrazin-2-

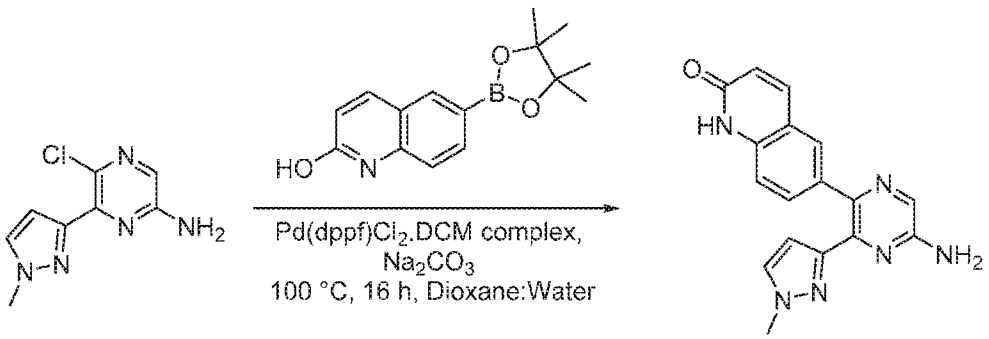
amine (0.450 g, 1.274 mmol, 1.0 eq.) in DCM (20 mL) was added *N*-Bromosuccinimide (0.239 g,1.338mmole,1.05 eq.) portion wise at 0 °C and the mixture was allowed to stir at the same temperature for 30 min. The progress of reaction was monitored by TLC. Upon completion, the reaction mixture was diluted with water (15 mL), extracted with DCM (50 mL × 2). The combined organic layers were washed with water (15 mL), brine (15 mL), dried over Na_2SO_4, filtered & concentrated under reduced pressure to afford 3-bromo-5-(8-chloroquinolin-6-yl)-6-(5-methylthiazol-2-yl)pyrazin-2-amine (0.430 g, 78.18 %) as a brown solid.

LCMS: 432 $[M+H]^+$

[0339] Step-3: Synthesis of 3-amino-6-(8-chloroquinolin-6-yl)-5-(2-methylthiazol-5-yl)pyrazine-2-carbonitrile: To stirred solution of 3-bromo-5-(8-chloroquinolin-6-yl)-6-(5-methylthiazol-2-yl)pyrazin-2-amine (0.150 g, 0.344 mmol, 1 eq) in DMF (4 mL) was added copper cyanide (0.093 g,1.040 mmol, 3 eq) at RT and the mixture was irradiated under MW irradiation at 150 °C for 90 min. The progress of the reaction was monitored by TLC. Upon completion, ice cold water (15 mL) was added to the mixture to obtain a precipitate which was filtered over Büchner funnel to afford crude residue. The crude obtained was purified by reversed phase column chromatography to afford 3-amino-6-(8-chloroquinolin-6-yl)-5-(2-methylthiazol-5-yl)pyrazine-2-carbonitrile (11.5 mg, 8 %) as an off white solid.

LCMS: 379 $[M+H]^+$. **^{1}H NMR** (400 MHz, MeOD) δ 8.52 (d, *J* = 7.89 Hz, 1H), 8.15 (s, 1H), 8.02 (s, 1H), 7.65 (br. s., 1H), 7.28 (s, 1H), 2.60 (s, 2H).

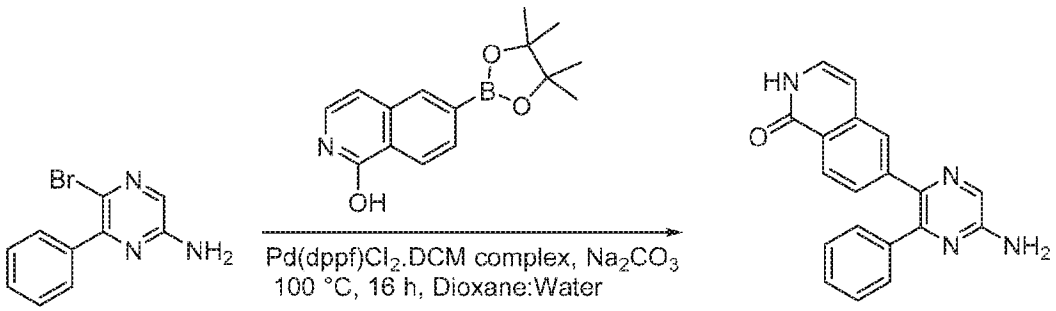
Example S87. Synthesis of 6-(5-amino-3-(1-methyl-1H-pyrazol-3-yl)pyrazin-2-yl)quinolin-2(1H)-one. (Compound No. 1.353)



[0340] To a stirred solution of 5-chloro-6-(1-methyl-1H-pyrazol-3-yl)pyrazin-2-amine (0.120 g, 0.572 mmol, 1.0 eq.) and 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoquinolin-1-ol (0.186 g, 0.686 mmol, 1.2 eq.) in dioxane (10 mL) was added Na_2CO_3 (0.121 g, 1.14 mmol, 2.0 eq.) and 2 mL water. Then reaction was purged with N_2 for about 5 min and $Pd(dppf)Cl_2$.DCM complex (0.023 g, 5 mol %) was added. The reaction was re-purged with N_2 for another 5 min and was allowed to heat at 100 °C for 16 h. Following this, reaction mixture was allowed to cool to RT and extracted using ethyl acetate (3 × 50 mL). The combined organic layers were washed (brine), dried (anhydrous Na_2SO_4) and concentrated under vacuum to get the solid residue which was purified by reversed phase column chromatography to get the desired product as off white solid (0.015 g, 8.24%).

LCMS : 319.2 $[M+1]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 11.74 (br. s., 1H), 7.90 (s, 1H), 7.85 (d, *J* = 9.65 Hz, 1H), 7.66 (d, *J* = 1.75 Hz, 1H), 7.59 (d, *J* = 1.75 Hz, 1H), 7.34 (d, *J* = 8.33 Hz, 1H), 7.14 (d, *J* = 8.33 Hz, 1H), 6.55 (s, 2H), 6.46 (d, *J* = 9.65 Hz, 1H), 6.04 (d, *J* = 2.19 Hz, 1H), 3.74 (s, 3H).

Example S88. Synthesis of 6-(5-amino-3-phenylpyrazin-2-yl)isoquinolin-1(2H)-one. (Compound No. 1.327)

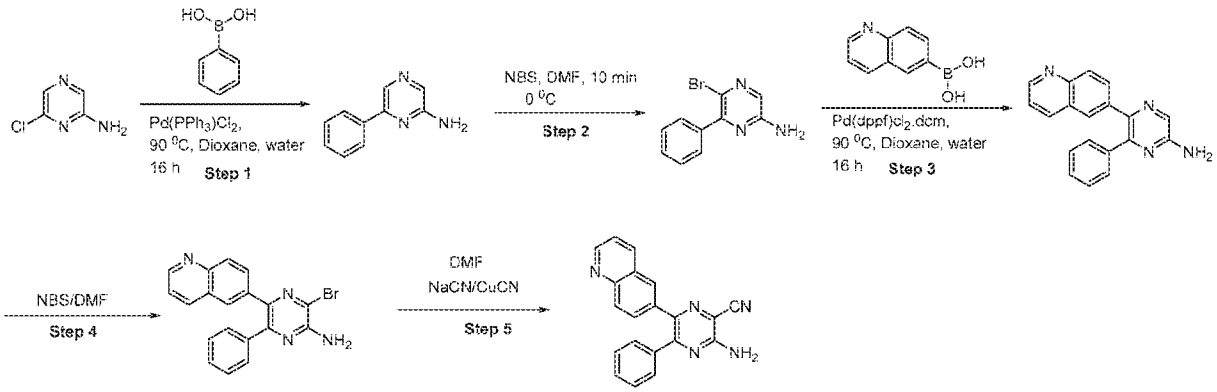


[0341] To a stirred solution of 5-bromo-6-phenylpyrazin-2-amine (0.120 g, 0.479 mmol, 1.0 eq.) and 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoquinolin-1-ol (0.156 g, 0.575 mmol, 1.2 eq.) in dioxane (10 mL) was added Na_2CO_3 (0.101 g, 0.958 mmol, 2.0 eq.) and 2 mL water. Then reaction was purged with N_2 for about 5 min and $Pd(dppf)Cl_2$.DCM complex (0.019 g, 5 mol %) was added. The reaction was re-purged with N_2 for another 5 min and was allowed to heat at 100 °C for 16 h. Following this, reaction mixture was allowed to cool to RT and extracted using ethyl

acetate (3 × 50 mL). The combined organic layer was washed (brine), dried (anhydrous Na_2SO_4) and concentrated under vacuum to get the solid residue which was purified by reversed phase column chromatography to get the desired product as off white solid (0.002 g, 1.33%).

LCMS: 315.3 $[M+1]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 11.18 (br. s., 1H), 7.99 (s, 1H), 7.93 (d, *J* = 8.33 Hz, 1H), 7.59 (s, 1H), 7.25 - 7.35 (m, 5H), 7.21 (d, *J* = 9.21 Hz, 1H), 7.08 - 7.12 (m, 1H), 6.76 (s, 2H), 6.40 (d, *J* = 7.45 Hz, 1H).

Example S89. Synthesis of 3-amino-5-phenyl-6-(quinolin-6-yl)pyrazine-2-carbonitrile. (Compound No. 1.19)



[0342] Step 1: Synthesis of 6-phenylpyrazin-2-amine: To a stirred solution of 6-chloropyrazin-2-amine (50g, 0.3861mol) in dioxane:water (400 mL;100mL) was added benzeneboronic acid (56.4 g,0.46 mol). The reaction mixture was purged with nitrogen for 20 min then charged Na_2CO_3 (70.6g, 0.57 mol) and $Pd(PPh_3)Cl_2$ (13.5g, 0.01930 mol). The reaction mixture was again purged with nitrogen .The reaction mixture was stirred at RT for 10 min followed by heating at 90 ^{0}C for 16 h. The reaction was monitored by TLC & LCMS. The reaction mixture was filter through celite and distilled. The reaction was diluted with water and extracted with ethyl acetate (3x 200 mL). The combined organic layers were washed (brine), dried (anhydrous Na_2SO_4) & concentrated under vacuum to get the solid which was purified by column chromatography over silica gel (100-200 mesh) [Ethyl acetate: Hexane (3:7) as eluent] to get the desired product (55 g, 83%).

LCMS: 172 $[M+1]^+$. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.38 (s, 1H), 7.83 - 7.99 (m, 3H), 7.40 - 7.49 (m, 3H), 4.82 (br. s., 2H)

[0343] Step 2: Synthesis of 5-bromo-6-phenylpyrazin-2-amine: To a stirred solution of 6-phenylpyrazin-2-amine (48g, 0.2803mol) in DMF was added NBS (49.9 g, 0.28 mol) at 0^0c under nitrogen atmosphere. The reaction mixture was stirred at RT for 16 h. The reaction was monitored by TLC & LCMS. The reaction was diluted with water and extracted with ethyl acetate (3x 100 mL). The combined organic layers were washed (brine), dried (anhydrous Na_2SO_4) & concentrated under vacuum to get the solid which was purified by column chromatography silica gel (100-200 mesh) [Ethyl acetate: Hexane (1:4) as eluent] to get the desired product (38 g, 55%).

LCMS: 252 $[M+2]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.68 (s, 1H), 7.55 - 7.64 (m, 2H), 7.40 - 7.51 (m, 3H), 6.75 (br. s., 2H)

[0344] Step 3: synthesis of 6-phenyl-5-(quinolin-6-yl)pyrazin-2-amine: To a stirred solution of 5-bromo-6-phenylpyrazin-2-amine (38g, 0.1519mol) in dioxane:water (320 mL; 80mL) was added quinolin-6-ylboronic acid (46.4g, 0.18 mol). The reaction mixture was purged with nitrogen for 20 min then charged with Na_2CO_3 (32.2g, 0.3038mol) and Pd(dppf)Cl_2 (6.19 g, 0.007 mol). The reaction mixture was again purged with nitrogen .The reaction mixture was stirred at RT for 10 min followed by heating at 90 ^{0}C for 16 h. The reaction was monitored by TLC & LCMS. The reaction mixture was filtered through celite and distilled. The reaction was diluted with water and extracted with ethyl acetate (3x 200 mL). The combined organic layers were washed (brine), dried (anhydrous Na_2SO_4) & concentrated under vacuum to get the solid which was purified by column chromatography over basic alumina [Ethyl acetate: Hexane (3:7) as eluent] to get the desired product (31 g, 68%).

LCMS: 299 $[M+1]^+$. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.83 (d, J = 3.07 Hz, 1H), 8.21 (d, J = 7.89 Hz, 1H), 8.02 (s, 1H), 7.93 (s, 1H), 7.80 (d, J = 8.33 Hz, 1H), 7.41 - 7.64 (m, 2H), 7.16 - 7.40 (m, 5H), 6.73 (s, 2H)

[0345] Step 4: synthesis of 3-bromo-6-phenyl-5-(quinolin-6-yl)pyrazin-2-amine**:** To a stirred solution of 6-phenyl-5-(quinolin-6-yl) pyrazin-2-amine (21g, 0.07 mol) in DMF was added NBS (12.5g, 0.07 mol) at 0^0c under nitrogen atmosphere. The reaction mixture was stir at RT for 16h. The reaction was monitored by TLC & LCMS. The reaction was diluted with water and extracted with ethyl acetate (3x 30 mL). The combined organic layers were washed (brine), dried (anhydrous Na_2SO_4) & concentrated under vacuum to get the solid which was purified by

column chromatography over basic alumina [Ethyl acetate: Hexane (3:7) as eluent] to get the desired product (18 g, 69%).

LCMS: 377 $[M+1]^+$. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.88 (br. s., 1H), 8.11-7.96 (m, 3H), 7.60-7.26(m, 7H), 5.23 (br. s., 2H).

[0346] Step 5: Synthesis of 3-amino-5-phenyl-6-(quinolin-6-yl)pyrazine-2-carbonitrile: To a stirred solution of NaCN (1.56g, 0.03 mol) and CuCN (5.7g, 0.06 mol) in dry DMF (150 mL) was added 3-bromo-6-phenyl-5-(quinolin-6-yl)pyrazin-2-amine (12.0 g, 0.03 mol) at 120^0 C. The reaction mixture was stirred at 145 ^{0}C for 12h. The reaction was monitored by TLC & LCMS. The reaction was distilled. The crude product was poured in ice-water the solid precipitate out. The reaction mixture pH was adjusted with aqueous ammonia and extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed (brine), dried (anhydrous Na_2SO_4) & concentrated under vacuum to get the solid which was purified by column chromatography using basic alumina [Ethyl acetate: Hexane (1:1) as eluent] to get the desired product (3.8 g, 34%).

[0347] LCMS: 354 $[M+1]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.88 (d, J = 2.63 Hz, 1H), 8.29 (d, J = 7.89 Hz, 1H), 7.99 (s, 1H), 7.84 (d, J = 8.77 Hz, 1H), 7.58 (br. s., 2H), 7.47 - 7.54 (m, 2H), 7.35 - 7.42 (m, 3H), 7.27 - 7.34 (m, 2H)

Biological Examples

Example B1. Radioligand binding competition assay

[0348] Binding of selected compounds to the adenosine A_{2A}, A_1, A_{2B}, and A_3 receptors was tested using a binding competition assay.

[0349] The general protocol for the radioligand binding competition assay was as follows. Competition binding was performed in duplicate in the wells of a 96 well plate (Master Block, Greiner, 786201) containing binding buffer (optimized for each receptor), membrane extracts (amount of protein/well optimized for each receptor), radiotracer (final concentration optimized for each receptor), and test compound. Nonspecific binding was determined by co-incubation with 200-fold excess of cold competitor. The samples were incubated in a final volume of 0.1 mL at 25°C for 60 minutes and then filtered over filter plates. Filters were washed six times with 0.5 mL of ice-cold washing buffer (optimized for each receptor) and 50 µL of Microscint 20

(Packard) were added on each filter. The filter plates were sealed, incubated 15 min on an orbital shaker and scintillation counted with a TopCount for 30sec/filter.

[0350] For the A_{2A} adenosine receptor radioligand binding assay, the following modifications were made to the general protocol. GF/C filters (Perkin Elmer, 6005174), presoaked in 0.01% Brij for 2h at room temperature were used. Filters were washed six times with 0.5 mL of ice-cold washing buffer (50 mM Tris pH 7.4) and 50 µL of Microscint 20 (Packard) was added in each well. The plates were then incubated for 15 min on an orbital shaker and then counted with a TopCount™ for 1 min/well. Another radioligand binding assay was used to evaluate the binding affinity for the adenosine A_{2A} receptor assay was performed in duplicate in the wells of a 384 plate. Assay buffer contained DPBS 500 mM, $MgCl_2$ 0.1 mM, and 1% DMSO. Membrane-bead suspension was prepared by mixing 25.98µL of human adenosine A_{2A} membrane preparation (Perkin Elmer, RBHA2AM400UA) at 33.4 µg/mL, 28 µL of ADA at 20 µg/mL, and 932 µL of SPA beads at 3.33 mg/mL) and incubated the mixture for 20 min at room temperature. Mixed 20 µL of radiotracer (^{3}H-SCH 58261) at 15 nM to each well containing test articles at various concentrations and centrifuge the plate at 1000 rpm for 1 minute. Added 30 µL of the membraine-bead suspension to each well. Sealed the plates and incubated for 1 hr at room temperature with vigorous mixing on a plate mixer. Plates were read on Microbeta^2 (Perkin Elmer, 2450-0010).

[0351] For the adenosine A_1 radioligand binding competition assay, a similar procedure was used except that the following reagents were used: CHO-K1-A1 cell membranes; binding buffer comprising HEPES 25 mM pH 7.4, $MgCl_2$ 5 mM, $CaCl_2$ 1mM, NaCl 100 mM, saponin 10 µg/mL; wash buffer comprising HEPES 25 mM pH 7.4, $MgCl_2$ 5 mM, $CaCl_2$ 1mM, NaCl 100 mM; Unifilter GF/B – treated for 2h with 0.5% PEI was the filter; and 1.6 nM of ^{3}H-DPCPX was the tracer.

[0352] Similarly, the following reagents were used for the adenosine A_{2B} radioligand binding competition assay: HEK-293-A_{2B} cell membranes, 20 µg/well, preincubated 30 min at RT with 25µg/mL Adenosine Deaminase; a binding buffer comprising HEPES 10 mM pH 7.4, EDTA 1 mM, 0.5% BSA; a wash buffer comprising HEPES 10 mM pH 7.4, EDTA 1 mM; a Unifilter GF/C – treated for 2h with 0.5% PEI; and 10 nM ^{3}H-DPCPX as the tracer.

[0353] For the adenosine A_3 radioligand binding competition assay, the following reagents were used:

CHO-K1-A3 cell membranes, 1.5µg/well; a binding buffer comprising HEPES 25 mM pH 7.4, $MgCl_2$ 5 mM, $CaCl_2$ 1mM, 0.5% BSA; a wash buffer comprising HEPES 25 mM pH 7.4, $MgCl_2$ 5 mM, $CaCl_2$ 1mM; a Unifilter GF/C – treated for 2h with 0.5% BS; and 0.4 nM of ^{125}I-AB-MECA as the tracer.

[0354] The results of the binding assay are shown in Tables B1-1 and B1-2 and are shown as percent residual binding at a given concentration. Percent of residual binding means binding of a compound in the presence of competitor normalized to the amount of binding in the absence of competitor. The compounds tested showed a range of binding to the adenosine receptors tested. For example, compound 1 strongly bound to adenosine A_{2A} receptor (30% residual binding at a concentration of 100 nM), A_1 receptor (-3% residual binding at 300nM) and A_{2B}, (-9% residual binding at 300 nM) but weakly bound to A_3 receptor (96% residual binding at 300 nM).

Table B1-1

Compound No.	A_{2A} radioligand binding competition assay % residual binding @ 3000/1000/300/100 nM	Radioligand binding competition assay % residual binding @ 300 nM (A_1/A_{2B}/A_3)	A_{2A} binding IC_{50} (nM)
1.1	ND/12/ND/30	-3/-9/96	57
1.2	ND/ND/ND/ 62	ND	ND
1.3	ND/ND/ND/ 57	ND	ND
1.7	ND/ND/100/ND	ND	ND
1.8	ND/ND/39/ ND	ND	ND
1.10	39/64/70/77	ND	ND
1.11	ND/ND/126/ND	ND	ND
1.12	12/12/66/ND	ND	ND
1.13	18/17/69/83	ND	ND

1.14	12/29/48/76	ND	ND
1.15	104/ND/ND/ND	ND	ND
1.16	80/ND/ND/ ND	ND	ND
1.17	8/ND/ND/ND	ND	ND
1.18	100/ND/ND/ ND	ND	ND
1.19	4/ND/ND/ND	ND	ND
1.20	3/ND/ND/ND	ND	ND
1.21	5/ND/ND/ND	ND	ND
1.22	39/ND/ND/ND	ND	ND

ND = Not determined

Table B1-2

Compound No.	A2a binding IC50 (nM)	A2a binding % inh @ 3000 nM	A2a binding % inh @ 1000/100/10/1 nM
1.241	ND	86	ND
1.45	ND	91	ND
1.185	ND	20	ND
1.270	ND	100	ND
1.271	2.1	ND	ND
1.210	ND	100	ND
1.238	ND	11	ND
1.272	ND	80	ND
1.273	ND	100	ND
1.274	ND	80	ND
1.275	ND	11	ND
1.276	ND	24	ND
1.25	ND	48	ND
1.192	ND	89	ND

1.277	ND	83	ND
1.278	ND	95	ND
1.193	ND	83	ND
1.35	ND	64	ND
1.279	ND	58	ND
1.186	ND	30	ND
1.280	ND	75	ND
1.36	ND	81	ND
1.281	ND	ND	80/88/78/ND
1.292	2.4	ND	ND/95/93/50
1.282	ND	ND	79/82/74/ND
1.283	ND	ND	95/83/63/ND
1.284	ND	ND	83/76/32/ND
1.285	ND	ND	90/76/56/ND
1.286	ND	ND	86/96/87/40
1.287	ND	ND	80/90/77/42
1.288	55.5	ND	84/86/83/42
1.289	ND	ND	95/87/75/41
1.290	3.3	ND	89/89/85/57
1.291	ND	ND	ND/0/0/0
1.293	ND	ND	ND/ 31/32/28
1.295	5.5	ND	ND
1.297	17	ND	ND
1.304	9	ND	ND
1.308	>10000	ND	ND
1.309	1.6	ND	ND
1.315	101	ND	ND
1.318	9.4	ND	ND

ND = Not determined

Example B2. cAMP assay

[0355] The functional activity of compounds was tested using one of the two assays to detect the present of cAMP. Activation of G-protein coupled receptors (such as A_{2A}) results in activation of adenylcyclase which converts ATP into cAMP which is used as a downstream signaling molecule. Therefore, molecules which act as GPCR (or specifically A_{2A} receptor) antagonists cause a decrease in intracellular cAMP concentration.

[0356] Both assays used HEK-293 cells expressing human recombinant adenosine A_{2A} receptor were grown prior to the test in media without antibiotic. Assay 1 (Table B2-1): The cells were detached by gentle flushing with PBS-EDTA (5 mM EDTA), recovered by centrifugation and suspended in assay buffer (KRH: 5 mM KCl, 1.25 mM $MgSO_4$, 124 mM NaCl, 25 mM HEPES, 13.3 mM Glucose, 1.25 mM KH_2PO_4, 1.45 mM $CaCl_2$, 0.5 g/L BSA, supplemented with Rolipram).

[0357] 12 µL of cells were mixed with 6 µL of the test compound at increasing concentrations and then incubated for 10 min. Thereafter 6 µL of the reference agonist was added at a final concentration corresponding to the historical EC_{80}. The plates were then incubated for 30 min at room temperature. After addition of the lysis buffer and 1 hour incubation, cAMP concentrations were estimated, according to the manufacturer specification, with the HTRF® kit.

[0358] Assay 2 (Table B2-2): 100 nL of test articles at 100× of final concentration were transferred to assay plate by Echo. Cells were washed twice with 5 mL of PBS 10 µL of cells were mixed with 5 mL PBS. After aspirating the PBS and adding 1.5 mL versine, cells were incubated at 37°C for 2-5 min. After centrifugation, 4 mL of medium was added and adjusted cell density to 5,000 cells/well with Stimulation Buffer. 10 µL of cells were aliquoted to the assay plate, centrifuged at 1000 rpm for 1 minute, and incubated for 60 minutes at room temperature. 5 µL 4× Eu-cAMP tracer solution and 5 µL 4× UlightTM-anti-cAMP solution were added to assay plate, followed by centrifugation and 60-minute incubation at room temperature. Plates were read on EnVision.

[0359] As shown in Tables B2-1 and B2-2, many of the compounds disclosed herein strongly reduced intracellular levels of cAMP. For example, compound 1.1 reduced cAMP levels by 97% compared to untreated cells.

Table B2-1

Compound No.	A2a cAMP (% inh @ 100 nM)	A2a cAMP IC_{50} (nM)
1.1	97	6
1.2	100	ND
1.3	100	ND
1.4	1.4	ND
1.6	47	ND
1.7	100	ND
1.8	100	ND
1.9	49	ND
1.10	100	ND
1.11	100	ND
1.12	94	ND
1.13	51	ND
1.14	100	ND
1.15	0	ND
1.16	0	ND
1.17	99	ND
1.18	14	ND
1.19	100	ND
1.20	81	ND
1.21	100	ND
1.22	24	ND

ND = Not determined

Table B2-2

Compound	A2a cAMP	A2a

No.	IC50 (nM)	cAMP % inh @ 100 nM
1.241	ND	80
1.45	ND	100
1.185	ND	9
1.270	ND	100
1.271	50	ND
1.210	ND	100
1.238	ND	7
1.272	ND	96
1.273	12	ND
1.274	ND	60
1.275	ND	0
1.276	ND	0
1.25	ND	6
1.192	ND	93
1.277	ND	44
1.278	303.8	ND
1.193	ND	87
1.35	ND	22
1.279	ND	9
1.186	ND	12
1.280	ND	51
1.36	ND	77
1.285	ND	34
1.286	ND	20
1.287	ND	16
1.288	1054	ND
1.290	35.7	ND

1.294	>10000	ND
1.295	33	ND
1.296	130	ND
1.297	47.9	ND
1.298	>10000	ND
1.299	1250	ND
1.300	119.9	ND
1.301	>10000	ND
1.302	867	ND
1.303	573	ND
1.304	40	ND
1.305	96	ND
1.306	120	ND
1.307	8477	ND
1.308	>10000	ND
1.309	13.1	ND
1.310	127	ND
1.311	279.3	ND
1.312	251	ND
1.313	1550	ND
1.314	1536	ND
1.315	1397	ND
1.316	40.1	ND
1.317	279.5	ND
1.318	199.6	ND
1.319	1927	ND
1.395	562.8	ND
1.329	>10000	ND
1.324	12.5	ND
1.402	260.1	ND

1.353	>10000	ND
1.327	172.6	ND

ND = Not determined

Example B3 GTPγ^{35}S scintillation proximity assay for A_{2A} receptor

[0360] A scintillation proximity assay (SPA) was used to determine the kinetic profile of the binding of candidate molecule compound 1.1 to the A_{2A} receptor.

[0361] For antagonist testing, membranes extracts were prepared from HEK-293 cells expressing recombinant human A_{2A} receptor, were mixed with GDP (volume:volume) and were incubated in assay buffer comprising 20mM HEPES pH 7.4; 100mM NaCl, 10μg/mL saponin, 5 mM $MgCl_2$ for at least 15 min on ice. In parallel, GTPγ[^{35}S] was mixed with the beads (volume:volume) just before starting the reaction. The following reagents were successively added in the wells of an Optiplate (Perkin Elmer): 25 μL of test compound or reference ligand, 25 μL of the membranes: GDP mix, 25 μL of reference agonist at historical EC_{80} and 25 μL of GTPγ[^{35}S] (PerkinElmer NEG030X), diluted in assay buffer to give 0.1 nM. The plate was incubated at room temperature for 1 hour. Then, 20 μL of IGEPAL was added for 30 minutes at room temperature. Following this incubation, 20 μL of beads (PVT-anti rabbit (PerkinElmer, RPNQ0016)), diluted in assay buffer at 50mg/mL (0.5mg/10μL) and 20 μL of an Anti-GαS/olf antibody were added for a final incubation of 3 hours at room temperature. Then, the plates were centrifuged for 10 min at 2000 rpm, incubated at room temperature for 1 hour and counted for 1 min/well with a PerkinElmer TopCount reader.

Table B3

Compound No.	A_{2A} γGTP assay (% Inh Avg) @ 100 nM
1.1	82

Example B4 Functional T Cell Assay

[0362] Human T Cell Activation Assay: Fresh human blood was diluted with the same volume of PBS and the buffy coat containing peripheral blood mononuclear cells (PBMCs) were prepared and resuspend in culture medium at a density of 2×10^6/mL. 2×10^5 PBMCs (in 100 μL) were plated to each well of 96-well flat bottom plate. 25 μL of 8x final concentration of 10-fold serial diluted compounds were added to indicated wells and incubate for 30 mins in 37 °C/5% CO2. Beads included in T cell activation/expansion kit (Miltenyi biotec Cat# 130-091-441) at a bead-to-cell ratio of 1:6 in 50 μL were added to all well with the final concentration of DMSO at 0.1% and final volume at 200 μL. 60 μL of supernatant post 24 hr and 48 hr incubation was collected for TNF-α and IFN-γ concentration evaluation using TNF-α ELISA ready-set-go kit (eBioscience, Cat# 88-7346-77) and IFN-γ ELISA ready-set-go kit (eBioscience, Cat# 88-7316-77), respectively. Figure 1 and Figure 2 show that the compounds of invention reversed NECA-mediated suppression of TNF-α and IFN-γ secretion in activated human T cells in vitro.

Example B5 cAMP Assay

[0363] In a 96-well plate coated with anti-CD3 antibody, $CD8^+$ T-cells (1×10^5) were cultured alone, with 3 μM of NECA, or in the presence of 1 μM of compound of the interest with or without 3 μM of NECA. The cells were incubated for 30 min at 37 °C and 5% CO2, and the reaction was stopped by addition of 200 μL, 0.1 M hydrochloric acid. cAMP levels were determined by an ELISA kit.

Example B6 Anti-tumor Activities in Immuno-oncology Mouse Models

[0364] The anti-tumor activities of test articles will be evaluated in selective mouse models (e.g., syngeneic model, xenograft model, or PDX) as a monotherapy or combination therapies. Using MC-38 syngeneic model as an example: female C57BL/6 mice are inoculated subcutaneously at right flank with MC-38 cells for tumor development. Five days after tumor inoculation, mice with tumor size ranging from 40-85 mm^3 are selected and assigned into sub-groups using stratified randomization with 10 mice per group based upon their tumor volumes. Mice receive pre-defined treatments include vehicle, test article at various doses alone, test article at various doses plus other anti-cancer therapy, and other anti-cancer therapy control. Body weight and tumor sizes are measured three times per week during the treatment. Tumor volume will be

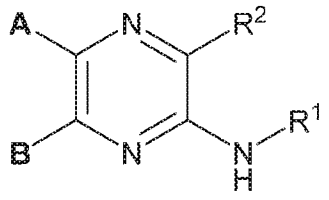
expressed in mm^3 using the formula: $V = 0.5\ a \times b^2$ where a and b are the long and short diameters of the tumor, respectively. The tumor sizes are used for the calculations of both tumor growth inhibition (TGI) and T/C values. When an individual animal reaches to the termination endpoint (e.g., with TV > 1000 mm^3), the mouse are euthanized. The time from inoculation to the termination are deemed as its survival time. Survival curve are plotted by Kaplan-Meier method. At the end of study, plasma and tumor samples are collected to explore biomarkers.

[0365] 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

What is claimed is:

1. A compound of the formula (I):



(I),

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

A is 4-hydroxyphenyl optionally further substituted by R^3, 4-hydroxy-2-pyridyl optionally further substituted by R^4, a naphthyl substituted by R^4, a 9- or 10- membered bicylic heterocylyl optionally substituted by R^4, or a 9- or 10-membered bicyclic heteroaryl optionally substituted by R^4;

B is a phenyl optionally substituted by R^3, C_3-C_6 cycloalkyl optionally substituted by R^4, 3- to 6-membered heterocyclyl optionally substituted by R^4 or a 5- to 10-membered heteroaryl optionally substituted by R^4;

R^1 is a 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, 5- to 10-membered heteroaryl, -(C_1-C_3 alkylene)(C_3-C_6 cycloalkyl), -(C_1-C_3 alkylene)(3-6-membered heterocyclyl), -(C_1-C_3 alkylene)(5-6-membered heteroaryl), -(C_1-C_3 alkylene)(C_6 aryl), -$C(O)R^{1a}$, -$C(O)OR^{1a}$, -$C(O)NR^{1b}R^{1c}$, -$NR^{1b}R^{1c}$, –$S(O)_2R^{1a}$, -(C_1-C_3 alkylene)$C(O)NR^{1b}R^{1c}$, -(C_1-C_3 alkylene)$C(O)R^{1a}$ or -(C_1-C_3 alkylene)$NR^{1b}R^{1c}$, wherein the 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, 5- to 10-membered heteroaryl, -(C_1-C_3 alkylene)(C_3-C_6 cycloalkyl), -(C_1-C_3 alkylene)(3-6-membered heterocyclyl), -(C_1-C_3 alkylene)(5-6-membered heteroaryl), and -(C_1-C_3 alkylene)(C_6 aryl) of R^1 are independently optionally substituted by R^4;

each R^{1a} is independently hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, 3-6-membered heterocyclyl, C_6 aryl, 5-6-membered heteroaryl, -(C_1-C_3 alkylene)(C_3-C_6 cycloalkyl), -(C_1-

C_3 alkylene)(3-6-membered heterocyclyl), -(C_1-C_3 alkylene)(C_6 aryl) or -(C_1-C_3 alkylene)(5-6-membered heteroaryl), wherein each of which is optionally substituted by methyl, ethyl, halogen, oxo, -CF_3, -OH, -OCH_3, -CN, -C(O)OCH_3, -C(O)OC_2H_5, -NH_2 or -$NHCH_3$;

each R^{1b} and R^{1c} is independently hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, 3-6-membered heterocyclyl, C_6 aryl, 5-6-membered heteroaryl, -(C_1-C_3 alkylene)(C_3-C_6 cycloalkyl), -(C_1-C_3 alkylene)(3-6-membered heterocyclyl), -(C_1-C_3 alkylene)(C_6 aryl) or -(C_1-C_3 alkylene)(5-6-membered heteroaryl), wherein each of which is optionally substituted by methyl, ethyl, halogen, oxo, -CF_3, -OH, -OCH_3, -CN, -C(O)OCH_3, -C(O)OC_2H_5, -NH_2 or -$NHCH_3$;

or R^{1b} and R^{1c} are taken together with the nitrogen atom to which they are attached to form a 3- to 6-membered heterocyclyl;

R^2 is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_6-C_{14} aryl, C_5-C_{14} heteroaryl, C_3-C_6 cycloalkyl, 3- to 6-membered heterocyclyl, -CN, halogen, -OR^{2a}, -SR^{2a}, -$NR^{2b}R^{2c}$, -C(O)R^{2a}, -NR^{2b}C(O)R^{2c}, -NR^{2a}C(O)$NR^{2b}R^{2c}$, -C(O)OR^{2a}, -C(O)$ONR^{2b}R^{2c}$ or -C(O)$NR^{2b}R^{2c}$, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_6-C_{14} aryl, C_3-C_6 cycloalkyl and 3- to 6-membered heterocyclyl of R^2 are independently optionally substituted by R^4;

each R^{2a} is independently hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, 3- to 6-membered heterocyclyl, C_6-aryl, 5- to 6-membered heteroaryl, -(C_1-C_3 alkylene)$N(C_2H_5)_2$, -(C_1-C_3 alkylene)(C_3-C_6 cycloalkyl), -(C_1-C_3 alkylene)(3-6-membered heterocyclyl), -(C_1-C_3 alkylene)(5-6-membered heteroaryl) or -(C_1-C_3 alkylene)(C_6 aryl), wherein each of which is optionally substituted by methyl, ethyl, halogen, oxo, -CF_3, -OH, -OCH_3, -CN, -C(O)OCH_3, -C(O)OC_2H_5, -NH_2 or -$NHCH_3$;

each R^{2b} and R^{2c} is independently hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, 3- to 6-membered heterocyclyl, C_6-aryl, 5- to 6-membered heteroaryl, -(C_1-C_3 alkylene)$N(C_2H_5)_2$, -(C_1-C_3 alkylene)(C_3-C_6 cycloalkyl), -(C_1-C_3 alkylene)(3-6-membered heterocyclyl), -(C_1-C_3 alkylene)(C_6 aryl) or -(C_1-C_3 alkylene)(5-6-membered heteroaryl), wherein each of which is optionally substituted by methyl, ethyl, halogen, oxo, -CF_3, -OH, -OCH_3, -CN, -C(O)OCH_3, -C(O)OC_2H_5, -NH_2 or -$NHCH_3$;

or R^{2b} and R^{2c} are taken together with the nitrogen atom to which they are attached to form a 3- to 6-membered heterocyclyl;

each R^3 is independently C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, -CN, -OR^5, -SR^5, -NR^6R^7, -NO_2, -C=NH(OR^5), -$C(O)R^5$, -$OC(O)R^5$, -$C(O)OR^5$, -$C(O)NR^6R^7$, -$OC(O)NR^6R^7$, -$NR^5C(O)R^6$, -$NR^5C(O)OR^6$, -$NR^5C(O)NR^6R^7$, -$S(O)R^5$, -$S(O)_2R^5$, -$NR^5S(O)R^6$, -$C(O)NR^5S(O)R^6$, -$NR^5S(O)_2R^6$, -$C(O)NR^5S(O)_2R^6$, -$S(O)NR^6R^7$, -$S(O)_2NR^6R^7$, -$P(O)(OR^6)(OR^7)$, C_3-C_6 cycloalkyl, 3-12-membered heterocyclyl, 5- to 10-membered heteroaryl, C_6-C_{14} aryl, -(C_1-C_3 alkylene)CN, -(C_1-C_3 alkylene)OR^5, -(C_1-C_3 alkylene)SR^5, -(C_1-C_3 alkylene)NR^6R^7, -(C_1-C_3 alkylene)CF_3, -(C_1-C_3 alkylene)NO_2, -C=NH(OR^5), -(C_1-C_3 alkylene)$C(O)R^5$, -(C_1-C_3 alkylene)$OC(O)R^5$, -(C_1-C_3 alkylene)$C(O)OR^5$, -(C_1-C_3 alkylene)$C(O)NR^6R^7$, -(C_1-C_3 alkylene)$OC(O)NR^6R^7$, -(C_1-C_3 alkylene)$NR^5C(O)R^6$, -(C_1-C_3 alkylene)$NR^5C(O)OR^6$, -(C_1-C_3 alkylene)$NR^5C(O)NR^6R^7$, -(C_1-C_3 alkylene)$S(O)R^5$, -(C_1-C_3 alkylene)$S(O)_2R^5$, -(C_1-C_3 alkylene)$NR^5S(O)R^6$, -$C(O)$(C_1-C_3 alkylene)$NR^5S(O)R^6$, -(C_1-C_3 alkylene)$NR^5S(O)_2R^6$, -(C_1-C_3 alkylene)$C(O)NR^5S(O)_2R^6$, -(C_1-C_3 alkylene)$S(O)NR^6R^7$, -(C_1-C_3 alkylene)$S(O)_2NR^6R^7$, -(C_1-C_3 alkylene)$P(O)(OR^6)(OR^7)$, -(C_1-C_3 alkylene)(C_3-C_6 cycloalkyl), -(C_1-C_3 alkylene)(3-12-membered heterocyclyl), -(C_1-C_3 alkylene)(5-10-membered heteroaryl) or -(C_1-C_3 alkylene)(C_6-C_{14} aryl), wherein each R^3 is independently optionally substituted by halogen, oxo, -OR^8, -NR^8R^9, -$C(O)R^8$, -CN, -$S(O)R^8$, -$S(O)_2R^8$, -$P(O)(OR^8)(OR^9)$, -(C_1-C_3 alkylene)OR^8, -(C_1-C_3 alkylene)NR^8R^9, -(C_1-C_3 alkylene)$C(O)R^8$, -(C_1-C_3 alkylene)$S(O)R^8$, -(C_1-C_3 alkylene)$S(O)_2R^8$, -(C_1-C_3 alkylene)$P(O)(OR^8)(OR^9)$, C_3-C_8 cycloalkyl, or C_1-C_6 alkyl optionally substituted by oxo, -OH or halogen;

each R^4 is independently oxo or R^3;

R^5 is independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{14} aryl, 5-6-membered heteroaryl or 3-6-membered heterocyclyl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{14} aryl, 5-6-membered heteroaryl and 3-6-membered heterocyclyl of R^5 are independently optionally substituted by halogen, oxo, -CN, -OR^9, -NR^9R^{10}, -$P(O)(OR^9)(OR^{10})$, phenyl optionally substituted by halogen, or C_1-C_6 alkyl optionally substituted by halogen, -OH or oxo;

R^6 and R^7 are each independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{14} aryl, 5-6-membered heteroaryl, -(C_1-C_3 alkylene)(C_6 aryl) or 3-6 membered heterocyclyl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{14} aryl, 5-6-membered heteroaryl, -(C_1-C_3 alkylene)(C_6 aryl) and 3-6 membered

heterocyclyl of R^6 and R^7 are independently optionally substituted by halogen, oxo, -CN, -OR^9, -NR^9R^{10} or C_1-C_6 alkyl optionally substituted by halogen, -OH or oxo;

or R^6 and R^7 are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo, -OR^9, -NR^9R^{10} or C_1-C_6 alkyl optionally substituted by halogen, oxo or -OH;

R^8 and R^9 in R^3 are each independently hydrogen, C_1-C_6 alkyl optionally substituted by halogen or oxo, C_2-C_6 alkenyl optionally substituted by halogen or oxo, or C_2-C_6 alkynyl optionally substituted by halogen or oxo;

or R^8 and R^9 in R^3 are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo or C_1-C_6 alkyl optionally substituted by halogen or oxo; and

R^9 and R^{10} in R^5, R^6 and R^7 are each independently hydrogen, C_1-C_6 alkyl optionally substituted by halogen or oxo, C_2-C_6 alkenyl optionally substituted by halogen or oxo, or C_2-C_6 alkynyl optionally substituted by halogen or oxo;

or R^9 and R^{10} in R^5, R^6 and R^7 are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo or C_1-C_6 alkyl optionally substituted by oxo or halogen.

2. The compound of claim 1, or a salt thereof, wherein:

A is 4-hydroxyphenyl optionally further substituted by R^3, 4-hydroxy-2-pyridyl optionally further substituted by R^4, an unsubstituted 9- or 10-membered bicyclic heteroaryl containing at least one annular nitrogen atom, a 9- or 10-membered bicyclic heteroaryl containing at least two annular nitrogen atoms and optionally substituted by R^4 which R^4 groups are connected to the parent structure via a carbon atom, or a 10-membered bicyclic heteroaryl optionally substituted by R^4;

B is a phenyl optionally substituted by R^3, or 5- to 6-membered heteroaryl optionally substituted by R^4;

R^1 is a 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, -$C(O)R^{1a}$, -$C(O)OR^{1a}$, -$C(O)NR^{1b}R^{1c}$, or -$NR^{1b}R^{1c}$, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl and 3- to 6-membered heterocyclyl of R^1 are independently optionally substituted by R^4;

each R^{1a} is independently hydrogen, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl;

each R^{1b} and R^{1c} is independently hydrogen, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl;

or R^{1b} and R^{1c} are taken together with the nitrogen atom to which they are attached to form a 3- to 6-membered heterocyclyl;

R^2 is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_6-C_{14} aryl, -CN, halogen, $-OR^{2a}$, $-NR^{2b}R^{2c}$, $-C(O)R^{2a}$, $-C(O)OR^{2a}$, or $-C(O)NR^{2b}R^{2c}$, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl and C_6-C_{14} aryl of R^2 are independently optionally substituted by R^4;

each R^{2a} is independently hydrogen, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl;

each R^{2b} and R^{2c} is independently hydrogen, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl;

or R^{2b} and R^{2c} are taken together with the nitrogen atom to which they are attached to form a 3- to 6-membered heterocyclyl;

each R^3 is independently C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, -CN, $-OR^5$, $-SR^5$, $-NR^6R^7$, $-NO_2$, $-C{=}NH(OR^5)$, $-C(O)R^5$, $-OC(O)R^5$, $-C(O)OR^5$, $-C(O)NR^6R^7$, $-OC(O)NR^6R^7$, $-NR^5C(O)R^6$, $-NR^5C(O)OR^6$, $-NR^5C(O)NR^6R^7$, $-S(O)R^5$, $-S(O)_2R^5$, $-NR^5S(O)R^6$, $-C(O)NR^5S(O)R^6$, $-NR^5S(O)_2R^6$, $-C(O)NR^5S(O)_2R^6$, $-S(O)NR^6R^7$, $-S(O)_2NR^6R^7$, $-P(O)(OR^6)(OR^7)$, C_3-C_6 cycloalkyl, 3-12-membered heterocyclyl, 5- to 10-membered heteroaryl, C_6-C_{14} aryl, -(C_1-C_3 alkylene)CN, -(C_1-C_3 alkylene)OR^5, -(C_1-C_3 alkylene)SR^5, -(C_1-C_3 alkylene)NR^6R^7, -(C_1-C_3 alkylene)CF_3, -(C_1-C_3 alkylene)NO_2, -C=NH(OR^5), -(C_1-C_3 alkylene)$C(O)R^5$, -(C_1-C_3 alkylene)$OC(O)R^5$, -(C_1-C_3 alkylene)$C(O)OR^5$, -(C_1-C_3 alkylene)$C(O)NR^6R^7$, -(C_1-C_3 alkylene)$OC(O)NR^6R^7$, -(C_1-C_3 alkylene)$NR^5C(O)R^6$, -(C_1-C_3 alkylene)$NR^5C(O)OR^6$, -(C_1-C_3 alkylene)$NR^5C(O)NR^6R^7$, -(C_1-C_3 alkylene)$S(O)R^5$, -(C_1-C_3 alkylene)$S(O)_2R^5$, -(C_1-C_3 alkylene)$NR^5S(O)R^6$, -$C(O)$(C_1-C_3 alkylene)$NR^5S(O)R^6$, -(C_1-C_3 alkylene)$NR^5S(O)_2R^6$, -(C_1-C_3 alkylene)$C(O)NR^5S(O)_2R^6$, -(C_1-C_3 alkylene)$S(O)NR^6R^7$, -(C_1-C_3 alkylene)$S(O)_2NR^6R^7$, -(C_1-C_3 alkylene)$P(O)(OR^6)(OR^7)$, -(C_1-C_3 alkylene)(C_3-C_6 cycloalkyl), -(C_1-C_3 alkylene)(3-12-membered heterocyclyl), -(C_1-C_3 alkylene)(5-10-membered heteroaryl) or -(C_1-C_3 alkylene)(C_6-C_{14} aryl), wherein each R^3 is independently optionally substituted by halogen, oxo, $-OR^8$, $-NR^8R^9$, $-C(O)R^8$, -CN, $-S(O)R^8$, $-S(O)_2R^8$, $-P(O)(OR^8)(OR^9)$, -(C_1-C_3 alkylene)OR^8, -(C_1-C_3 alkylene)NR^8R^9, -(C_1-C_3 alkylene)$C(O)R^8$, -(C_1-C_3 alkylene)$S(O)R^8$, -(C_1-C_3 alkylene)$S(O)_2R^8$, -(C_1-C_3 alkylene)$P(O)(OR^8)(OR^9)$, C_3-C_8 cycloalkyl, or C_1-C_6 alkyl optionally substituted by oxo, -OH or halogen;

each R^4 is independently oxo or R^3;

R^5 is independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{14} aryl, 5-6-membered heteroaryl or 3-6-membered heterocyclyl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{14} aryl, 5-6-membered heteroaryl and 3-6-membered heterocyclyl of R^5 are independently optionally substituted by halogen, oxo, -CN, -OR^9, -NR^9R^{10}, -$P(O)(OR^9)(OR^{10})$, phenyl optionally substituted by halogen, or C_1-C_6 alkyl optionally substituted by halogen, -OH or oxo;

R^6 and R^7 are each independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{14} aryl, 5-6-membered heteroaryl or 3-6 membered heterocyclyl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{14} aryl, 5-6-membered heteroaryl and 3-6 membered heterocyclyl of R^6 and R^7 are independently optionally substituted by halogen, oxo, -CN, -OR^9, -NR^9R^{10} or C_1-C_6 alkyl optionally substituted by halogen, -OH or oxo;

or R^6 and R^7 are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo, -OR^9, -NR^9R^{10} or C_1-C_6 alkyl optionally substituted by halogen, oxo or -OH;

R^8 and R^9 are each independently hydrogen, C_1-C_6 alkyl optionally substituted by halogen or oxo, C_2-C_6 alkenyl optionally substituted by halogen or oxo, or C_2-C_6 alkynyl optionally substituted by halogen or oxo;

or R^8 and R^9 are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo or C_1-C_6 alkyl optionally substituted by halogen or oxo; and

R^9 and R^{10} are each independently hydrogen, C_1-C_6 alkyl optionally substituted by halogen or oxo, C_2-C_6 alkenyl optionally substituted by halogen or oxo, or C_2-C_6 alkynyl optionally substituted by halogen or oxo;

or R^9 and R^{10} are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo or C_1-C_6 alkyl optionally substituted by oxo or halogen.

3. The compound of claim 1 or 2, or a salt thereof, wherein R^1 is hydrogen or -$C(O)R^{1a}$.

4. The compound of any one of claims 1-3, or a salt thereof, wherein R^1 is hydrogen.

5. The compound of any one of claims 1-3, or a salt thereof, wherein R^1 is $-C(O)R^{1a}$ and R^{1a} is C_1-C_6 alkyl.

6. The compound of any one of claims 1-5, or a salt thereof, wherein R^2 is hydrogen, C_1-C_6 alkyl, -CN, halogen, $-OR^{2a}$.

7. The compound of any one of claims 1-6, or a salt thereof, wherein R^2 is hydrogen.

8. The compound of any one of claims 1-6, or a salt thereof, wherein R^2 is C_1-C_6 alkyl.

9. The compound of any one of claims 1-6, or a salt thereof, wherein R^2 is –CN or halogen.

10. The compound of any one of claims 1-6, or a salt thereof, wherein R^2 is $-OR^{2a}$ and R^{2a} is C_1-C_6 alkyl.

11. The compound of any one of claims 1-10, or a salt thereof, wherein **A** is 4-hydroxyphenyl optionally further substituted by R^3 or 4-hydroxy-2-pyridyl optionally further substituted by R^4.

12. The compound of any one of claims 1-11, or a salt thereof, wherein **A** is 4-hydroxyphenyl optionally further substituted by R^3.

13. The compound of any one of claims 1-11, or a salt thereof, wherein **A** is 4-hydroxy-2-pyridyl optionally further substituted by R^4.

14. The compound of any one of claims 1-10, or a salt thereof, wherein **A** is a 9- or 10-membered bicyclic heteroaryl optionally substituted by R^4.

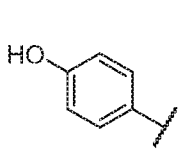
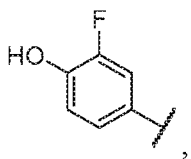
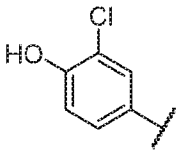
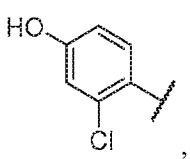
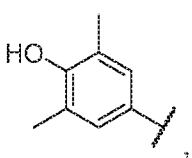
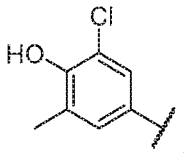
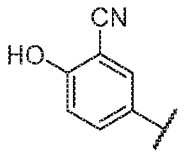
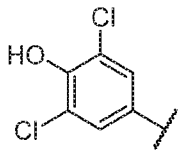
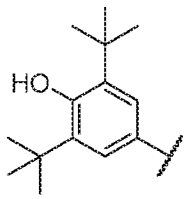
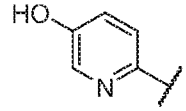
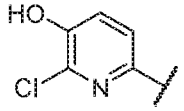
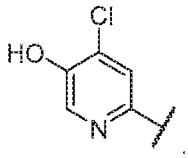
15. The compound of any one of claims 1-10, or a salt thereof, wherein the **A** is selected from the group consisting of benzimidazolyl, benzoxazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, indazolyl, quinoxalinyl, quinazolinyl, cinnolinyl, and naphthyridinyl, each of which is optionally substituted by R^4.

16. The compound of claim 15, or a salt thereof, wherein R^4 is R^3 and each R^3 is independently selected from the group consisting of halogen, -CN, $-OR^5$, $-SR^5$, $-NR^6R^7$, $-NO_2$, $-C(O)R^5$, $-C(O)OR^5$, $-C(O)NR^6R^7$, $-C(O)NR^5S(O)_2R^6$, $-OC(O)R^5$, $-OC(O)NR^6R^7$, $-NR^5C(O)R^6$,

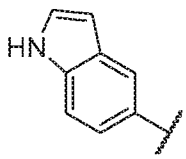
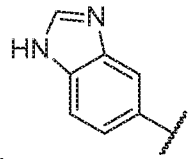
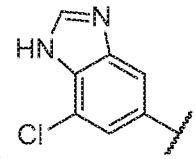
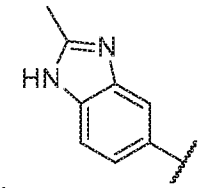
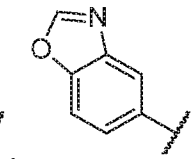
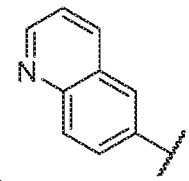
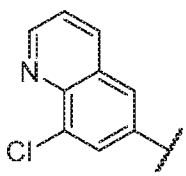
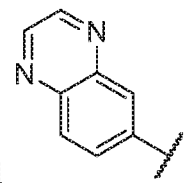
-$NR^5C(O)NR^6R^7$, -$S(O)R^5$, -$S(O)_2R^5$, C_3-C_6 cycloalkyl and C_1-C_6 alkyl optionally substituted by halogen.

17. The compound of claim 16, or a salt thereof, wherein each R^3 is independently selected from the group consisting of halogen, –OR^5 and C_1-C_6 alkyl optionally substituted by halogen.

18. The compound of any one of claims 1-12, or a salt thereof, wherein **A** is selected from the group consisting of:












, and

.

19. The compound of any one of claims 1-10, or a salt thereof, wherein **A** is selected from the group consisting of:








, and

.

20. The compound of any one of claims 1-19, or a salt thereof, wherein **B** is a phenyl optionally substituted by R^3.

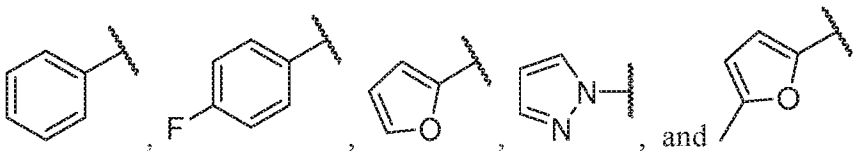
21. The compound of any one of claims 1-19, or a salt thereof, wherein **B** is a 5- to 6-membered heteroaryl optionally substituted by R^4.

22. The compound of any one of claims 1-19 and 21, or a salt thereof, wherein the **B** is a 5-membered heteroaryl selected from the group consisting of furanyl, oxazolyl, thiophenyl, pyrazolyl, isoxazolyl, 1,3,4-oxadiazolyl, imidazolyl, thiazolyl, isothiazolyl, triazolyl, 1,3,4-thiadiazolyl and tetrazolyl, which is optionally substituted by R^4.

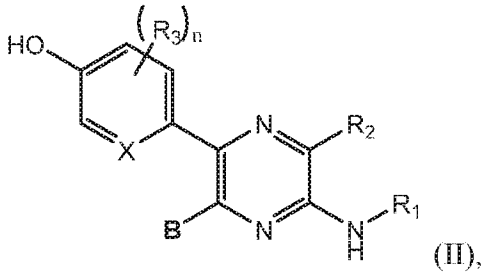
23. The compound of any one of claims 1-19 and 21, or a salt thereof, wherein the **B** is a 6-membered heteroaryl selected from the group consisting of pyridyl and pyrimidinyl, which is optionally substituted by R^4.

24. The compound of any one of claims 21-23, or a salt thereof, wherein R^4 is R^3 and R^3 is selected from the group consisting of halogen, $-OR^5$, $-NR^6R^7$, $-C(O)R^5$, C_3-C_6 cycloalkyl and C_1-C_6 alkyl optionally substituted by halogen.

25. The compound of claim 24, or a salt thereof, wherein R^3 is selected from the group consisting of halogen and C_1-C_6 alkyl optionally substituted by halogen (e.g., CF_3).

26. The compound of any one of claims 1-19, or a salt thereof, wherein **B** is selected from the group consisting of:  .

27. The compound of claim 1 or 2, wherein the compound is of the formula (II):



(II),

or a salt thereof, wherein R^1, R^2 and **B** are as defined for formula (I);

X is N or CH;

each R^3 is independently halogen, -CN, -OR^5, -SR^5, -NR^6R^7, -NO_2, -$C(O)R^5$, -$C(O)OR^5$, -$C(O)NR^6R^7$, -$C(O)NR^5S(O)_2R^6$, -$OC(O)R^5$, -$OC(O)NR^6R^7$, -$NR^5C(O)R^6$, -$NR^5C(O)NR^6R^7$, -$S(O)R^5$, -$S(O)_2R^5$, C_3-C_6 cycloalkyl, or C_1-C_6 alkyl optionally substituted by halogen;

each R^5 is independently hydrogen, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl;

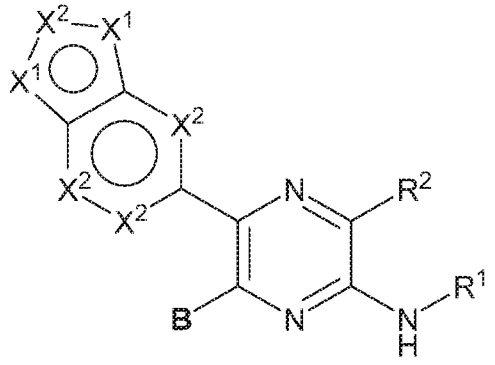
R^6 and R^7 are each independently hydrogen, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl;

or R^6 and R^7 are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl; and

n is 0, 1, 2 or 3.

28. The compound of claim 27, or a salt thereof, wherein R^3 is selected from the group consisting of halogen, –OR^5 and C_1-C_6 alkyl optionally substituted by halogen.

29. The compound of claim 1 or 2, wherein the compound is of the formula (IIIc):



(IIIc),

or a salt thereof, wherein R^1, R^2 and **B** are as defined for formula (I);

each X^1 is independently O, S, NH, NR^{4a}, CH_2, CHR^{4b}, $CR^{4b}R^{4b}$, N, CH or CR^{4b};

each X^2 is independently CH, CR^{4b} or N;

R^{4a} is C_1-C_6 alkyl;

each R^{4b} is independently halogen, -CN, -OR^5, -SR^5, -NR^6R^7, -NO_2, -$C(O)R^5$, -$C(O)OR^5$, -$C(O)NR^6R^7$, -$C(O)NR^5S(O)_2R^6$, -$OC(O)R^5$, -$OC(O)NR^6R^7$, -$NR^5C(O)R^6$, -$NR^5C(O)NR^6R^7$, -$S(O)R^5$, -$S(O)_2R^5$, C_3-C_6 cycloalkyl, or C_1-C_6 alkyl optionally substituted by halogen;

where each R^5 is independently hydrogen, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl; and

R^6 and R^7 are each independently hydrogen, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl;

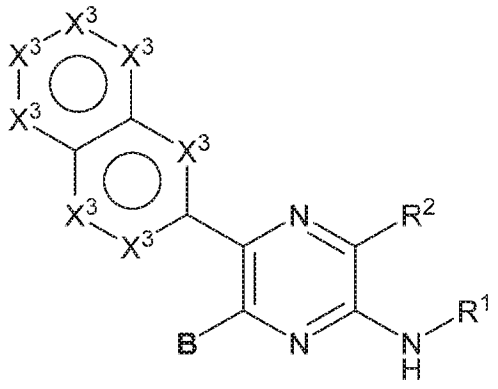
or R^6 and R^7 are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl.

30. The compound of claim 29, or a salt thereof, wherein R^{4b} is selected from the group consisting of halogen, $-OR^5$ and C_1-C_6 alkyl optionally substituted by halogen.

31. The compound of claim 29 or 30, or a salt thereof, wherein one of X^1 is N, and the other one of X^1 is NR^{4a}, and each X^2 is CR^{4b}.

32. The compound of claim 29 or 30, or a salt thereof, wherein one of X^1 is N, and the other one of X^1 is O or S, and each X^2 is CR^{4b}.

33. The compound of claim 1 or 2, wherein the compound is of the formula (IVc):



(IVc),

or a salt thereof, wherein R^1, R^2 and **B** are as defined for formula (I);

each X^3 is independently CR^4, CH or N;

each R^4 is independently halogen, -CN, $-OR^5$, $-SR^5$, $-NR^6R^7$, $-NO_2$, $-C(O)R^5$, $-C(O)OR^5$, $-C(O)NR^6R^7$, $-C(O)NR^5S(O)_2R^6$, $-OC(O)R^5$, $-OC(O)NR^6R^7$, $-NR^5C(O)R^6$, $-NR^5C(O)NR^6R^7$, $-S(O)R^5$, $-S(O)_2R^5$, C_3-C_6 cycloalkyl, or C_1-C_6 alkyl optionally substituted by halogen;

where each R^5 is independently hydrogen, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl; and

R^6 and R^7 are each independently hydrogen, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl;

or R^6 and R^7 are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl.

34. The compound of claim 33, or a salt thereof, wherein R^4 is selected from the group consisting of halogen, $-OR^5$ and C_1-C_6 alkyl optionally substituted by halogen.

35. The compound of claim 33 or 34, or a salt thereof, wherein one of X^3 is N, and the remaining X^3 are each CR^4.

36. The compound of claim 33 or 34, or a salt thereof, wherein two of X^3 are N, and the remaining X^3 are each CR^4.

37. A compound selected from Compound Nos. 1.1-1.179, 1.186-1.999, and 2.000-2.899 in Table 2 or a salt thereof.

38. The compound of claim 37, wherein the compound is selected from Compound Nos. 1.1-1.269 in Table 2 or a salt thereof.

39. The compound of claim 37, wherein the compound is selected from Compound Nos. 1.1-1.22, 1.45, 1.210 and 1.241 in Table 2 or a salt thereof.

40. A pharmaceutical composition comprising a compound of any one of claims 1-39, or a salt thereof, and a pharmaceutically acceptable carrier.

41. A method of treating disease mediated by an adenosine signaling pathway in an individual in need thereof comprising administering to the individual a therapeutically effective amount of a compound of any one of claims 1-39, or a pharmaceutically acceptable salt thereof.

42. A method of treating cancer in an individual in need thereof comprising administering to the individual a therapeutically effective amount of a compound of any one of claims 1-39, or a pharmaceutically acceptable salt thereof.

43. A method of inhibiting an adenosine receptor of subtype A_{2A}, A_{2B} or A_3 in a cell, comprising administering a compound of any one of claims 1-39, or a pharmaceutically acceptable salt thereof, to the cell.

44. The method of claim 43, wherein the adenosine receptor is of subtype A_{2A}.

45. Use of a compound of any one of claims 1-39, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for treatment of a disease mediated by an adenosine signaling pathway.

46. A kit comprising a compound of any one of claims 1-39, or a pharmaceutically acceptable salt thereof.

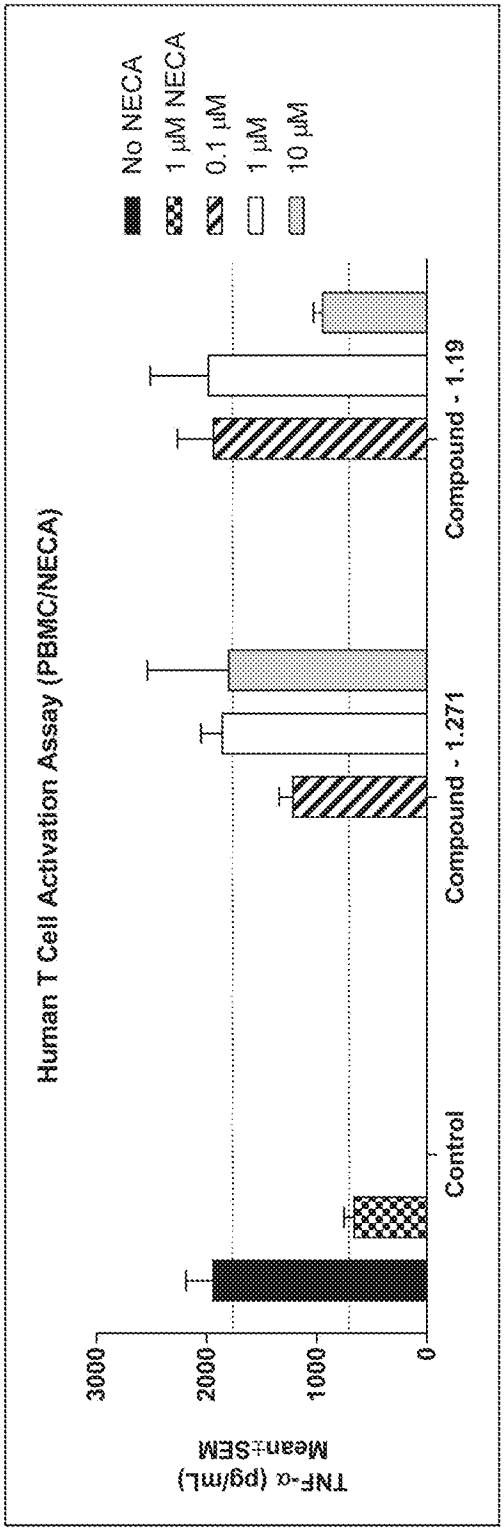

Human T Cell Activation Assay (PBMC/NECA)
TNF-α (pg/mL)
Mean+SEM
3000
2000
1000
0
No NECA
1 μM NECA
0.1 μM
1 μM
10 μM
Control
Compound - 1.271
Compound - 1.19

Figure 1

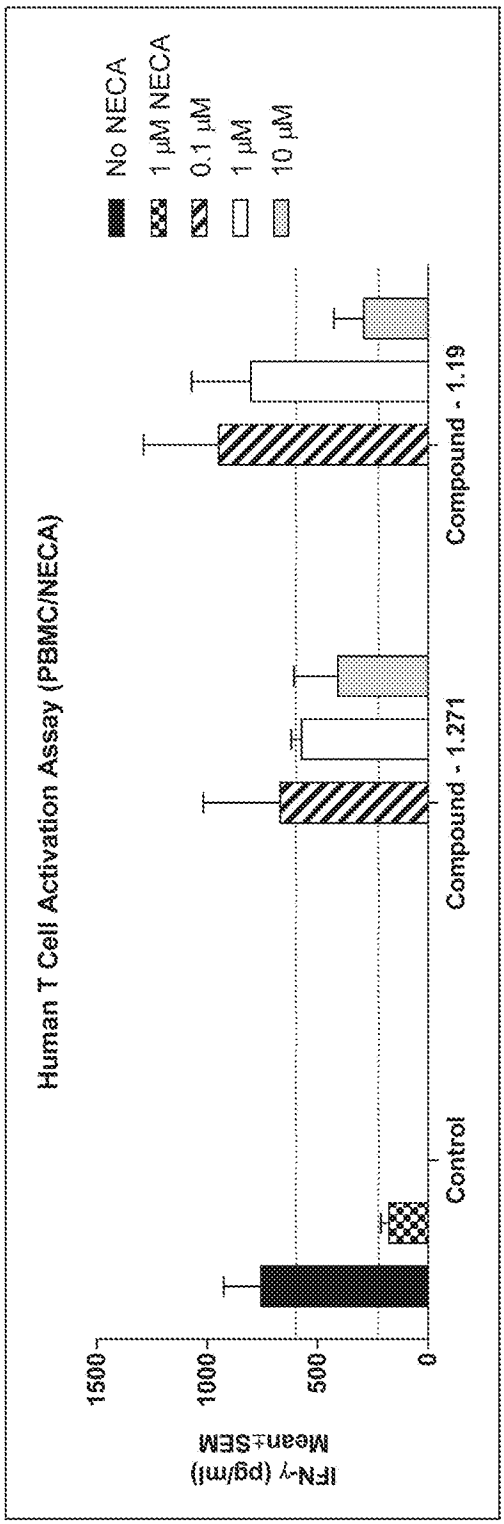

Human T Cell Activation Assay (PBMC/NECA)
No NECA
1 μM NECA
0.1 μM
1 μM
10 μM
IFN-γ (pg/ml)
Mean+SEM
1500
1000
500
0
Control
Compound - 1.271
Compound - 1.19

Figure 2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US18/42777

A. CLASSIFICATION OF SUBJECT MATTER
IPC - A61K 31/495; C07D 241/10 (2018.01)
CPC - A61K 31/495; C07D 241/10

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2016/0311784 A1 (UNIVERSITY OF GREENWICH) 27 October 2016; paragraphs [0018]-[0023], [0025]-[0026], [0030]	1-2, 3/1-2, 27/1-2
Y	US 2006/0293339 A1 (CHAKRAVARTY, PK et al.) 28 December 2006; paragraphs [0010], [0012], [0029]-[0030], [0049]-[0050], [0055]	1-2, 3/1-2, 27/1-2

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
03 September 2018 (03.09.2018)	01 NOV 2018
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US18/42777

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

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

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

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

3. ☒ Claims Nos.: 4-26, 31-32, 35-36, 40-46
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

-***-Continued Within the Next Supplemental Box-***-

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

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

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

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-2, 3/1-2, 27/1-2

Remark on Protest

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

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

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US18/42777

-***-Continued from Box No. III Observations where unity of invention is lacking -***-

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Groups I+, Claims 1-3 (in-part), 27-30 (in-part), 33-34 (in-part), 37-39 (in-part); compound of Formula (I), wherein A is 4-hydroxyphenyl; B is unsubstituted phenyl; R1 is hydrogen; and R2 is hydrogen (first exemplary compound structure).

The compound, compositions and methods will be searched to the extent the compound encompasses a compound of Formula (I), wherein A is 4-hydroxyphenyl; B is unsubstituted phenyl; R1 is hydrogen; and R2 is hydrogen (first exemplary compound structure). Applicant is invited to elect additional compound(s), with fully specified structure (e.g. no optional or variable atoms or substituents) for each, to be searched. Additional compound(s) will be searched upon the payment of additional fees. It is believed that claims 1-3 (in-part) and 27 (in-part) encompass this first named invention and thus these claims will be searched without fee to the extent that they encompass a compound of Formula (I), wherein A is 4-hydroxyphenyl; B is unsubstituted phenyl; R1 is hydrogen; and R2 is hydrogen (first exemplary compound structure). Applicants must specify the claims that encompass any additionally elected compound structure (s). Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined. An exemplary election would be a compound of Formula (I), wherein A is 4-hydroxyphenyl; B is phenyl substituted by R3 wherein R3 is C1-C6 alkyl; R1 is hydrogen; and R2 is hydrogen (first exemplary elected compound structure).

Groups I+ share the technical features including: a compound of Formula (I), wherein A is 4-hydroxyphenyl; B is unsubstituted phenyl; R1 is hydrogen; and R2 is hydrogen.

However, these shared technical features are previously disclosed by US 2016/0311784 A1 (UNIVERSITY OF GREENWICH) (hereinafter 'Greenwich') in view of US 2006/0293339 A1 to Chakravarty, et al. (hereinafter 'Chakravarty').

Greenwich discloses a compound of Formula (I): as shown, wherein B is unsubstituted phenyl; R1 is hydrogen; and R2 is hydrogen (compound of formula I wherein X is N, Y is C, N* is NRaRb wherein Ra and Rb are each H, Z is a single bond, A is phenyl, R1 is hydrogen, and R2 is a substituent group wherein said substituent group is phenyl; paragraphs [0018]-[0023], [0025]-[0026], [0030]), but Greenwich does not disclose wherein A is 4-hydroxyphenyl. However, Chakravarty discloses wherein A is 4-hydroxyphenyl (compound of formula II wherein Het-2 is third recited moiety, R6 and R8 are H, and R7 is –ORa wherein Ra is H (4-hydroxyphenyl); paragraphs [0010], [0012], [0029]-[0030], [0049]-[0050], [0055]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the compound, as previously disclosed by Greenwich, in order to have provided wherein A is 4-hydroxyphenyl, as previously disclosed by Chakravarty, for providing pyrazine-based heterocyclic compounds useful as sodium channel blockers for the treatment of disorders such as pain (Chakravarty; paragraphs [0009]-[0010], [0012]; Greenwich; paragraphs [0007], [0018]).

Since none of the special technical features of the Groups I+ inventions is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by the Greenwich and Chakravarty references, unity of invention is lacking.